Validation of an early relapse and readmission prediction scale in patients with schizophrenia

(PRECOG STUDY)

Protocol RISSCH4075

CLINICAL REPORT SYNOPSIS

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1 SUMMARY

1.1 TYPE OF APPLICATION

A multicentre, open-label, cross-sectional, prospective, epidemiological study.

1.2 STUDY TITLE

Validation of an early relapse and readmission prediction scale in patients with schizophrenia (PRECOG Study).

1.3 PROTOCOL CODE

Study PRECOG (RISSCH4075)

1.4 STUDY SITES

This study was performed in short-stay psychiatric hospitalization units or acute case units.

1.5 PRIMARY OBJECTIVE

To establish and validate a model/scale for the prediction, based on risk factors, of the time to early relapse of patients discharged from a short stay unit, within the framework of the clinical profile of patients with schizophrenia or schizoaffective or schizophreniform disorders suffering readmission/relapses in short stay psychiatric hospital units or acute case units in Spain.

1.6 DESIGN:

Epidemiological, multicentre, observational, cross-sectional, prospective study

1.7 STUDY DISEASE OR DISORDER

Schizophrenia and schizoaffective/schizophreniform disorder according to the DSM-IV criteria.

1.8 STUDY POPULATION

Patients seen in short-stay psychiatric hospitalization units or acute case units.

2 STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVES

To establish and validate a model/scale that predicts, based on risk factors, time to early relapse of patients discharged from a short-stay psychiatric hospitalisation unit or acute case unit in Spain.
To determine the factors carrying greatest weight with regard to the number of admissions.
To recognise and evaluate the impact of the clinical profile of patients with schizophrenia and schizoaffective/schizophreniform disorders suffering relapse (predictive model in a cross-sectional, prospective evaluation).

2.2 SECONDARY OBJECTIVES

To describe the clinical decisions taken by psychiatrists regarding the therapeutic approach, according to the prior characteristics of the patient.

3 STUDY DESIGN

3.1 TYPE OF STUDY

Analytical observational study of concurrent cases to assess the validity of a model/predictive scale of time to patient relapse using clinical/epidemiological characteristics of interest.

This study was conducted under standard clinical practice conditions.

All information was adequately documented in the electronic case report form (eCRF).

3.2 SELECTION CRITERIA:

3.2.1 Inclusion criteria

1. Patients with schizophrenia or schizoaffective/schizophreniform disorder for more than 2 years admitted to a short-stay psychiatric hospitalization unit or acute case unit.
2. Patients whose clinical records from the past 3 years may be accessed.
3. The patient (or his/her legal representative) has signed informed consent, stating that he/she understands the study purpose and requirements and wishes to participate in the study.

3.2.2 Exclusion criteria

1. Patients with psychiatric disease other than schizophrenia or schizoaffective/schizopheniform disorder.

2. Patients with schizophrenia or s chizoaffective/schizophreniform disorder with onset < 2 years previously.
3. Patients under the age of 18, and pregnant or, nursing patients or those who plan to become pregnant in the next 12 months.
4. Patients who are actively participating in any clinical trial/study.

4 ENDPOINTS

4.1 PRIMARY ENDPOINTS

For assessment of the primary objective, the following variables will be recorded:

Variables included in the model:

1. Number of different medications (antipsychotics) previously used
2. Years since onset of disease
3. CGI (Clinical Global Impression)
4. Age
5. Gender
6. Maximum level of studies
7. Family support
8. Assessment of compliance with drug treatment
9. Heroin user
10. Cocaine user
11. Cannabis user
12. Life event stressors
13. Patient's diagnosis (schizophrenia/schizoaffective disorder/schizophreniform disorder)
14. Number of previous admissions*

* only psychiatric admissions due to disease exacerbation are included.

Clinical progress recorded at 6 and 12 months using a qualitative criterion of readmission occurring during this period (Yes(t)/No). If yes, the date of admission will be collected.

5 STATISTICAL ANALYSIS

Grupo Infociencia S.L. performed the statistical analysis using SAS software (Statistical Analysis System) version 9.1.3.

All tables, figures, or graphs were calculated from the number of valid cases (N), and this was the number considered for calculation of percentages or other statistical considerations.

Continuous variables were summarized as the number of valid cases (N), mean, standard deviation (SD), median, and extreme values. Meanwhile, the categorical variables were described using the

number of valid cases and the % o f each category. Variables showing asymmetric frequency distributions were described using medians and their 25^{th}-75^{th} percentiles. A sta tistical significance level of 0.05 was considered for all comparisons.

All patients who signed the Informed Consent and met all the inclusion criteria/exclusion were considered enrolled.

Of the total patients enrolled, all patients from whom data were available during the 12 months of follow-up were considered as evaluable; otherwise, the patient was considered as excluded (since the investigator could not carry out the patient follow-up).

5.1 DESCRIPTION OF THE STUDY POPULATION

- Most patients were aged between 30 and 45 years, with a c lear predominance of me n (67.6%) compared to women.
- Of all the patients, 77.3**%** were diagnosed with schizophrenia, while schizoaffective/schizofreniform disorders were represented to a lesser extent.
- The years since onset of the disease until the date of in clusion indicated that approximately 60% of cases had had the disease course for over 10 years.
- As regards the current assessment of the clinical global impression of the severity of the disease (CGI-S), the most prevalent categories were moderately ill (37.0%) and markedly ill (33.9%).
- With regard to the evaluation of tr eatment adherence during the previous 3 years, 40.6% of patients demonstrated average adherence, followed by t he low (36.1%) and the maximum (23.3%) adherence groups. When values of 1 to 9 were allocated to adherence, with 1 representing “poor adherence” and 9 “very good adherence”, the mean compliance of patients in the study was 4.62 which would correspond to average adherence.
- In the overall study population, mean admissions within the previous 3 years was 2.74 years.
- Most patients had only one previous admission (38.2%). 21.7% had two admissions, while few had 4 or more previous admissions.
- The description of prior treatments was performed calculating the percentage over total treatments evaluated (N=2963).
- As regards the number of dif ferent medications previously used, the most represented categories were one single antipsychotic (34.1%), two antipsychotics (34.9%) and three different antipsychotics (15.5%). The mean for the study population was 2.03 different antipsychotics.

- 31.3% of the patients presented low treatment adherence, approximately 40.7% had average adherence and 28.0% maximum adherence.
- Of the 1,646 evaluable patients, 25.0% suffered a relapse in the 6 months since their last admission. 13.3% patients had switched treatment after 6 months.
- Of all the 1,646 patients evaluated in the study, 38.6% had at least one relapse/hospitalization within 12 months. 20.8% patients had switched treatment within 12 months after medical discharge.
- Of the total evaluable patients, 38.6% suffered at least one relapse/readmission within 12 months.
- Regarding the clinical global assessment of disease in patients suffering relapses, the groups most represented were moderately ill (33.9%), markedly ill (36.3%) and severely ill patients (18.5%).
- Most patients with relapse showed low family support (32.4%) during the time since their last admission. 18.9% of the patients had high family support.
- For the mean assessment of treatment adherence in patients who experienced relapse since the last hospitalisation, 34.7% presented low adherence, 38.3% average adherence and 27.0% maximum adherence.

5.2 ANALYSIS OF THE FIRST PRIMARY OBJECTIVE

5.2.1 Univariate analysis

A univariate logistic regression was performed for each risk factor with the presence of relapse as response variable. With regard to the importance of the degree of family support in the risk of relapse, both low support and high support were a protective factor compared to no support. (p=0.0089).

Patients with a diagnosis of schizophrenia or schizoaffective disorder, had more likelihood of relapse than patients with a diagnosis of schizophreniform disorder (p=0.0074).

The number of years since onset of the disease were also associated with a higher probability of relapse. The groups with more than 5 years since onset had an increased risk of relapse compared to patients with onset between 2 and 5 years previously. (p=0.0445).

The number of hospitalisations within the previous 3 years was also a predictor associated with a higher probability of relapse. Thus, the more the previous admissions, the higher the likelihood of readmission within the following year. (p<0.0001)

No use of cannabis in the previous 3 years was a protective factor compared to the use of this substance (p <0.0001), as was also the case with the use of cocaine. (p=0.0058).

The greater the number of different drug substances previously taken, the greater the risk of readmission. (p <0.0001).

Variables, such as age, the GSI (at time of inclusion), treatment adherence (in the last 3 years), or the presence of life event stressors were not found in this study to be significantly associated with the occurrence of relapses.

5.2.2 Multivariate analysis

Variables statistically significant (<0.01) in the univariate analysis were introduced as explanatory variables in the multivariate logistic model, with the presence of relapse being the response variable in the model.

To estimate the multivariate logistic model, all statistically non-significant variables were excluded from the model, one by one.

In multivariate analysis, the variables a) previous admissions (OR 1.28, 95% IC 1.21 - 1.35), b) use of cannabis (no vs yes, OR 0.72, 95% CI 0.58 - 0.89) and c) number of different antipsychotics previously taken (OR 1.13, 95% CI 1.03 - 1.24) remained significant in the probability of a relapse.

5.3 ANALYSIS OF THE SECOND PRIMARY OBJECTIVE

A statistical evaluation of the power of the intrinsic validity of the scale/model prediction of the time to relapse/readmission in patients with schizophrenia or schizoaffective/schizophreniform disorder was performed.

The model presented a sensitivity of 81.9%. This suggests that if the patient is going to have the next relapse within one year, the model will be accurate in more than 8 of every 10 cases.

Its specificity was 28.0%. For every 100 people who will not relapse in one year, the model will predict approximately 28 patients as non-relapsers. It will only be correct in fewer than 3 of 10 patients.

The precision of the model in the prediction of absence/presence of relapses was 48.8%. This means that, knowing the values assigned to the variables included in the model, it will correctly predict if there will be a readmission or not during the following year in approximately 5 of every 10 cases.

The positive predictive value (PPV) was 42%. This means that of every 100 patients with a positive prediction of relapse, 42 will relapse and the other 58 will be false positives, indicating that there is not a great chance of relapse even though the model predicts it.

The negative predictive value (NPV) of the model was 71%. This means that of every 100 subjects with a negative prediction of relapse, 71 will not be readmitted, and the remaining 29 will be false negatives (they will relapse, although the model predicts they will not).

With regard to the confusion matrix of the time to relapse, the precision of the model was 25.64%. The model will correctly predict time to admission in only 25 of every 100 cases.

5.4 ANALYSIS OF SECONDARY OBJECTIVE

To describe the clinical decisions taken by psychiatrists regarding management approach, according to the prior characteristics of the patient.

The prior characteristics of the patients were described according to their type of treatment at the baseline visit.

Of the patients who were receiving injectable atypical antipsychotics at baseline, most of them had average family support, followed by the group with high family support. The percentages are very similar to those receiving oral atypical antipsychotics. Among patients receiving injectable typical antipsychotics, the most represented group had a low family support and for patients receiving oral typical antipsychotics, family support was high.

Patients on injectable and oral atypical antipsychotics were distributed in a more or less balanced manner between the different ranges of years since disease onset but of the patients who took a typical antipsychotic, the majority had had the disease for more than 20 years.

There were more patients receiving treatment with oral typical antipsychotics in the "markedly ill" group (47.1%), while a higher percentage of patients receiving other treatments were represented in the category "moderately ill."

Of the patients receiving injectable atypical antipsychotics, 44.3% had low adherence; of those taking oral atypical and injectable typical antipsychotics, there was a higher percentage of patients in the category of average adherence; while 45.1% of the patients on oral typical antipsychotics were in the category of maximum adherence. However, it must be remembered that these percentages refer to the average adherence of each patient over the three years prior to inclusion in the study, so many patients had not been taking the same type of antipsychotic they were receiving at the baseline visit for this whole period, and many of them had taken more than one different type of drug during the three previous years.

Of the patients who were taking oral typical antipsychotics at baseline, 52.9% were admitted for a psychotic exacerbation due to lack of efficacy; in the remaining 3 groups, most were admitted for lack of treatment compliance.

In all patients, the categories most represented with regard to the number of different antipsychotics previously taken were one and two antipsychotics, with a higher percentage of a single antipsychotic in patients taking an oral atypical antipsychotic at the baseline visit.

5.5 SAFETY ANALYSIS

Adverse events and serious adverse events were listed. Each adverse event was assigned to a system organ class (SOC) and a preferred term (PT) according to the MedDRA v .11 available to Grupo Infociencia.

A total of 18 patients in this study (1% of the population studied) experienced one or more adverse events. Nervous system disorders were the most common and were recorded in 9 patients, of whom 4 had an extrapyramidal disorder.

A total of 11 patients experienced a serious adverse event, with nervous system disorders (ataxia, tremor and sedation) being the most common. Three subjects died during the study.

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