Electronic Schizophrenia Treatment Adherence Registry (e-STAR) in Latin America:
Clinical outcomes of long-acting injectable risperidone in a 2-year follow-up

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Original article

SUMMARY

Schizophrenia involves high healthcare costs. Lack of adherence to treatment for this illness is one of the main reasons for relapse and hospitalization. The foregoing leads to poor prognosis and global functional impairment of patients. Risperidone Long-Acting Injection (RLAI) has demonstrated its efficacy in treating schizophrenia and offers the possibility that patients have a better therapeutic adherence.

Objective

To determine efficacy and effect on the functionality and use of RLAI hospital resources in a 2-year follow-up Latin-American sample of patients with schizophrenia.

Method

The Electronic Schizophrenia Treatment Adherence Registry (e-STAR) in Latin America is an observational study of the RLAI use in schizophrenia. Patients from Mexico, Colombia and Brazil were recruited. Clinical information from patients was collected one year prior to RLAI treatment and prospectively every three months for a 24-month follow-up. Hospitalizations and the RLAI treatment scheme were registered. Efficacy was assessed using the Clinical Global Impression of Illness-Severity Scale (CGI-S), while the Global Assessment of Functioning (GAF) and the Personal and Social Performance (PSP) were used for the evaluation of functioning.

Results

Seventy-three patients completed the two-year follow-up. The proportion of patients hospitalized declined from 16.4% before treatment to 4.1% after 2 years of treatment with RLAI. 2.7% discontinued the treatment due to lack of efficacy. Significant improvements were reported regarding illness severity and global functioning.

Discussion

In daily clinical practice RLAI offers an effective long-term treatment for patients with schizophrenia, with a lower use of healthcare resources.

Key words: Risperidone long-acting injection, schizophrenia, Latin America, treatment adherence.

RESUMEN

La esquizofrenia genera elevados costos al sistema de salud. La falta de adherencia al tratamiento es una de las principales causas de recaídas y hospitalizaciones en la esquizofrenia. Lo anterior conduce a un pobre pronóstico y deterioro funcional de los pacientes. La risperidona inyectable de liberación prolongada (RILP) ha demostrado su eficacia en el tratamiento de la esquizofrenia, ofreciendo la posibilidad de que los pacientes tengan una mayor adherencia terapéutica.

Objetivo

Determinar la eficacia y efecto sobre la funcionalidad y el uso de recursos hospitalarios de la RILP en una muestra de pacientes con esquizofrenia de América Latina a dos años de seguimiento.

Método

El Registro Electrónico de Adherencia al Tratamiento de Esquizofrenia en Latinoamérica (e-STAR) es un estudio observacional del uso de la RILP en la esquizofrenia. Se reclutaron pacientes de México, Colombia y Brasil. Se registró la información clínica del paciente un año previo al inicio del tratamiento con la RILP y de forma prospectiva cada tres meses hasta cumplir los 24 meses de seguimiento. Se registraron las hospitalizaciones y el esquema de tratamiento con la RILP. La escala de Impresión Clínica Global-Gravedad (CGI-S) se utilizó como indicador de eficacia mientras que la Escala Global de Funcionamiento (GAF) y la Escala de Desempeño Personal y Social (PSP) se utilizaron para evaluar el funcionamiento.

Resultados

Setenta y tres pacientes completaron los dos años de seguimiento. La proporción de pacientes hospitalizados disminuyó del 16.4 al 4.1% después de dos años de tratamiento con la RILP. El 2.7% descontinuó el tratamiento debido a falta de eficacia. Se observó una mejoría significativa en cuanto a la gravedad del padecimiento y el funcionamiento global.

Discusión

En la práctica clínica cotidiana, la RILP resulta ser un tratamiento a largo plazo efectivo para la esquizofrenia con el beneficio adicional de una menor utilización de recursos del sistema de salud.

Palabras clave: Risperidona inyectable de liberación prolongada, esquizofrenia, América Latina, adherencia al tratamiento.

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INTRODUCTION

The mental illness treatment not only has an impact within the health sector, but also in other affected areas that generate high economic costs for society, such as the reduction or lack of labor productivity and absenteeism, among others. It has been reported that schizophrenia is one of the mental illnesses that generates higher healthcare costs.[1] Total annual schizophrenia costs incurred by Latin-American countries and the Caribbean are assumed to be $1.81 million dollars per million of persons.[2,3]

Direct costs of schizophrenia care mainly come from hospitalizations and health care institutions. Only medication costs range between 1.1% and 9% of the direct cost of the illness.[4,5] Nevertheless, the increase in psychiatric hospitalizations, as well as a greater use of the general healthcare resources, are usually attributable to the lack of patient adherence to the long-term treatment.[6-8]

At least between 40 and 50% of patients with schizophrenia show poor antipsychotic treatment adherence.[7,9-11] Forgetting to take the medicine, thinking that the medicine is not necessary, subjective perception of inefficiency or intolerance of side effects are some of the reasons patients quit the antipsychotic treatment.[12-14]

The lack of adherence rate is particularly high when the treatment is with oral antipsychotics,[7] even over 70% during the first 18 months of treatment,[15] which leads to restate the handling of the long-term schizophrenia treatment. Some studies report that patients with low oral medication adherence show a better adherence to long-acting injection medication.[16,17] Particularly, the role of atypical long-acting antipsychotics is highlighted because they offer appropriate efficacy and safety parameters, as well as the benefit of a better adherence due to their acting mechanism.[12,18]

The first long-acting atypical injectable antipsychotic was the risperidone (RLAI).[19] The RLAI has shown its efficacy and tolerability in several clinical trials,[20-23] also with a lower number of hospitalizations and a higher treatment adherence by patients.[24-28]

Most of the data published in relation to the antipsychotics efficacy comes from controlled clinical trials. The methodological inflexibility of these studies allows obtaining rigorous evidence regarding the medication, but limits the applicability of results within daily clinical practice.[27,29,30] Therefore, it has been proposed to perform observational studies, with the appropriate methodological designs, aimed at valuing the efficacy of such medication within daily clinical practice.

The Electronic Schizophrenia Treatment Adherence Registry (e-STAR)[31] is an observational-type international registration used by the Risperidone Long-Acting Injection (RLAI) within daily clinical practice at a 24-month follow-up. Additionally, the information is recorded one year before the start of the RLAI. The primary goal of this study is assessing the efficacy and effect of the long-term treatment with the RLAI on the functionality and use of hospital resources in a sample of patients with schizophrenia treated in a daily clinical context.

This study is part of the e-STAR and shows the results of those patients who started their treatment with RLAI. After two years of follow-up, there was information available from the three Latin-American countries: Mexico, Colombia and Brazil.

MATERIALS AND METHODS

The study was approved by the Ethics and Research Committees of the participating institutions from each country. All patients, including the responsible relative or legal representative, were verbally informed about the procedures to be made and their written approval was requested for their inclusion in the study, ensuring confidentiality and approval for results reporting. In the case of patients who —due to the severity of the symptoms of the disease— could not duly understand the study conditions, the responsible relative or legal representative's informed consent was requested.

Patients

Patients with diagnosis of schizophrenia and schizoaffective disorder were included in accordance with the diagnostic criteria of the DSM-IV.[32] Patients were recruited from the services of hospitalization, outpatient care and emergency rooms from public and private institutions of Mexico, Colombia and Brazil. Patients over 18 years of age suffering from active psychotic symptoms and who could benefit from the use of RLAI were included in accordance with the researcher's clinical criteria. Patients with an intolerance background or poor clinical response to risperidone not associated to the lack of adherence and women of reproductive age planning to become pregnant during the follow-up period of the study were excluded.

In accordance with these criteria, there were a total of 151 patients from Mexico, Colombia and Brazil. However, the electronic recording of baseline and follow-up data of 78 patients was incomplete, but this was not associated with dropouts from the study or limited efficacy of the RLAI. For this study, only those patients who started their treatment with the RLAI and had information on its use as of 24 months of follow-up were included in the analysis.

Instruments

- *Clinical Global Impression-Severity (CGI-S).* The CGI-S consists of a single question in which the clinician as-

signs a global rating with a scale ranging from 0 to 6, grading the global severity of the patient's illness. The validity of the instrument is given by the assumed clinical capacity of the evaluator to determine the patient's condition.[33]

- *Global Assessment of Functioning (GAF).* The GAF is one of the forms of global evaluation most widely used in psychiatry. It is a continuous scale ranging between 1 to 100 points, where the clinician evaluates in general the patient's condition within the psychological, social and occupational functioning areas. The maximum grade indicates the lack of symptoms and a high functioning, while the minimum grade implies that there is a danger to harm oneself or others, and/or a persistent inability to maintain the minimum personal hygiene.[32,34]

- *Personal and Social Performance Scale (PSP).* The PSP is a short one-question instrument evaluating, from 1 to 100, the patient's social functioning in accordance with four main indicators: 1. socially useful activity, 2. personal and social relations, 3. self-care and 4. disruptive and aggressive behaviors. Each of these is graded on a 6-point Likert scale with varying degrees of severity (absent-very severe). The results of this assessment are transformed in the overall score of the instrument.[35,36]

Procedure

In order that the design of the study did not interfere with the procedures made in daily clinical practice, the management of patients was only performed by the treating physician. Once the physician and the patient or his/her legal representative agreed starting the handling of the illness with the RLAI, the patient's medical history was obtained as well as his/her progress with the RLAI, which was documented and recorded in the e-STAR electronic system.

In the baseline stage of the study the following information was gathered: demographic data, main diagnosis, duration of the illness, reasons to start the RLAI treatment and initial dose, global severity of illness (CGI-S) and functionality level (GAF and PSP). Subsequently, quarterly assessments were made until a 24-month follow-up. The CGI-S, the GAF and the PSP were used in each assessment as indicators of the RLAI's efficacy. Additionally, the use of psychiatric hospitalization services was recorded during the follow-up period, which was compared with the number of hospitalizations reported in the e-STAR's retrospective period.

The RLAI dose was adjusted during the follow-up and according to the treating doctor's clinical criterion. Likewise, both the use of concomitant treatments and the RLAI treatment adherence were recorded, the latter in accordance with the treating doctor's general appreciation.

Statistical Analysis

The description of the variables included in the study was made with frequencies and percentages in the case of categorical variables; and with means and standard deviations (SD) for continuous variables. McNemar's test was used to compare follow-up assessments vs. retrospective assessments as for hospitalizations and the use of concomitant medication. To determine the efficacy, Student's t-tests were conducted for paired samples (follow-up vs. baseline assessments) with the scores in the CGI, GAF and PSP scales. The statistical significance level was fixed with a $p \leq 0.05$, with confidence intervals of 95%.

RESULTS

a) *Demographic and clinical characteristics of patients.* From the 73 patients who received RLAI in the baseline stage and who had information of its usage as of a 24-month follow-up, 61 were recruited in Mexico, eight in Colombia and four in Brazil. 68.5% were men, with an average age of 33.2 (SD=9.3) years old. At the start of the study, 85% (n=62) of the patients did not have an economically paid employment.

Most of the patients had a diagnosis of schizophrenia (n=69, 93.2%) and the remaining patients (n=4, 5.5%) were diagnosed with schizoaffective disorder. The illness' average time of evolution was 9.7 (SD=8.3) years. The three main reasons to start the RLAI treatment were: lack of response to previous treatment (n=27, 37%), lack of adherence (n=22, 30.1%) and to be used as maintenance treatment (n=10, 13.7%).

b) *Adherence to RLAI treatment.* From the 73 patients included, one patient discontinued the RLAI treatment within the 2-year follow-up. The time RLAI was discontinued lasted 368 days. The reason of the RLAI discontinuity was the lack of clinical response according to the treating doctor's criterion.

In the baseline assessment, 82.2% (n=60) received a 25mg-dose of RLAI and 17.8% (n=13) a 37.5mg-dose; at two years of follow up 35 patients (48.6%) had 25mg, 18 (25%) had 37.5mg and 19 (26.4%) had 50mg.

The RLAI treatment adherence in both assessments was reported as excellent (from 81 to 100% of compliance) according to the treating doctor's general appreciation in all patients. Also, at a two-year follow-up, 96.4% of patients reported being very satisfied with the RLAI treatment; whereas in the baseline stage of the study only 35.7% were satisfied with the treatment prior to the RLAI.

c) *Use of resources – Hospitalization and concomitant medication.* In contrast with the retrospective assessment period (12 months), a significant reduction was observed

Table 1. Hospitalized patients at least once per assessed period and inpatient hospital care (*n*=73)

Period	Hospitalized Patients (n=73) n (%)			Total Hospital Care (days) Mean (SD)		
	Retrospective	Prospective	*p* Value*	Retrospective	Prospective	*p* Value*
3 months	11 (15.1)	0.0	<0.001	3.9 (11.6)	0.0	0.005
6 months	15 (20.5)	1.0 (1.4)	<0.001	8.2 (22.9)	0.7 (6.3)	0.006
12 months	20 (27.4)	3.0 (4.1)	<0.001	16.2 (48.9)	1.1 (6.7)	0.010
18 months	NA	4.0 (5.5)	–	NA	1.5 (7.4)	–
24 months	NA	5.0 (6.8)	–	NA	1.5 (7.4)	–

NA Retrospective assessments not included in the study's methodology.
 * Values obtained with a McNemar's test.
 ** Values obtained with a Student's *t*-test for paired samples.

in the number of hospitalized patients as well as in the average total time of inpatient hospital care once the patients were treated with RLAI. The proportion of patients decreased from 16.4 to 4.1% (*p*<0.02), and the total time of inpatient hospital care showed an average reduction of 11.2 days (*p*=0.03). These results are shown in Table 1.

As for the use of concomitant medication, there was a record of information of 56 patients both in the baseline assessment and as of a two-year follow-up. A greater number of patients with no additional medication at the end of the follow-up was observed. Specifically, there was a reduction in the use of anticholinergics (Table 2).

d) *Symptomatic severity and functionality.* In the baseline stage of the study, 77.7% of patients had moderate/severe symptoms (CGI-S of 4-6 points), a percentage reduced to 23.8% at the two-year follow-up. A global improvement in the severity of the symptoms throughout the study was observed, an improvement that occurred from the third month of RLAI treatment, remaining stable up to month 24 (Figure 1).

From the third month of follow-up an improvement was reported in the functionality of patients. The foregoing was evidenced by the obtaining of higher scores in the GAF and PSP scales (Figure 2) from the third month of follow-up; the functional recovery remained stable throughout the follow-up.

An additional indicator of the functionality improvement was the employment situation. There was information of 56 patients both in the baseline assessment and as of a two-year follow-up. At the start of the study, only 10 patients had an economically paid employment, whereas as of a two-year follow-up this percentage increased to 39.3% (*n*=22).

DISCUSSION

The objective of this study was reporting the efficacy and the effect over the functionality and the use of RLAI hospital resources in a 2-year follow up Latin-American sample of patients with schizophrenia.

The study supports and maintains those results described in the e-STAR preliminary report in Latin America,[37] in which the RLAI shows an appropriate efficacy upon the control of symptoms of the schizophrenia and the global functionality of the patient. At the start of the study with RLAI, patients had moderate/severe psychotic symptoms and difficulties in the global psychosocial functioning. Once

Table 2. Concomitant treatment

	Baseline (n=56)		Month 6 (n=44)		Month 12 (n=45)		Month 18 (n=44)		Month 24 (n=56)		
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	*p* Value*
No medication	16	(28.6)	19	(43.2)	21	(46.7)	21	(47.7)	29	(51.8)	0.02
Anticholinergics	18	(32.1)	10	(22.7)	8	(17.8)	7	(15.9)	6	(10.7)	0.01
Antidepressants	4	(7.1)	4	(9.1)	3	(6.7)	2	(4.5)	4	(7.1)	1.00
Mood stabilizers	13	(23.2)	7	(15.9)	8	(17.8)	10	(22.7)	13	(23.2)	1.00
Benzodiazepines	20	(35.7)	7	(15.9)	11	(24.4)	11	(25.0)	12	(21.4)	0.09
Somatic medications	6	(10.7)	6	(13.6)	7	(15.6)	7	(15.9)	7	(12.5)	1.00

Nota[1] Only patients having the baseline and the 2-year follow-up assessments were included.
Nota[2] Each patient was found with more than one concomitant medication during the assessed periods.
 * Values obtained with the McNemar's test between the 24th month *vs.* Baseline.
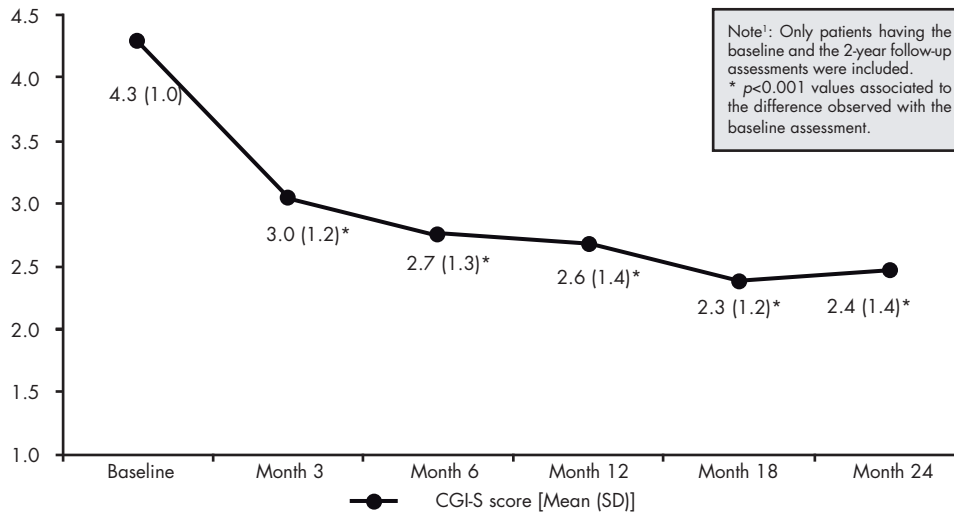
**Figure 1.** Evolution of the symptomatic severity throughout the study (CGI-S).

the RLAI treatment started a clear symptomatic and functional improvement was detected from the third month of treatment, an improvement maintained throughout the two-year follow-up. Even though the efficacy of the RLAI in the control of schizophrenia symptoms has been previously proved in controlled clinical trials, the reports of their efficacy in an observational study made in daily clinical practice give a better support for their use in the maintenance treatment required by patients with schizophrenia.

The lack of efficacy with previous treatments was one of the main reasons for the RLAI prescription to patients of this study. In Latin America, the use of injectable antipsychotics must be limited to those patients with very severe symptoms of the illness or with a poor treatment adherence.[37] It seems that the RLAI prescription for critically ill patients is

associated with a higher-therapeutic perception. However, this same perception may involve some misconceptions on the specific criteria for the RLAI prescription, an antipsychotic that may be even used in patients who have not been previously treated with antipsychotics.[37-40]

Furthermore, these results show that the RLAI is an effective medication for the long-term treatment. The CAT-IE (*Clinical Antipsychotic Trials of Intervention Effectiveness*) study reported that 74% of patients discontinue the use of antipsychotics during the first 18 months of treatment,[41,42] while this study found a low ratio of patients who discontinued the treatment due to the lack of efficacy.

The second cause to start the RLAI treatment in this study was the lack of adherence to the previous treatment. The lack of adherence to the pharmacological treatment in
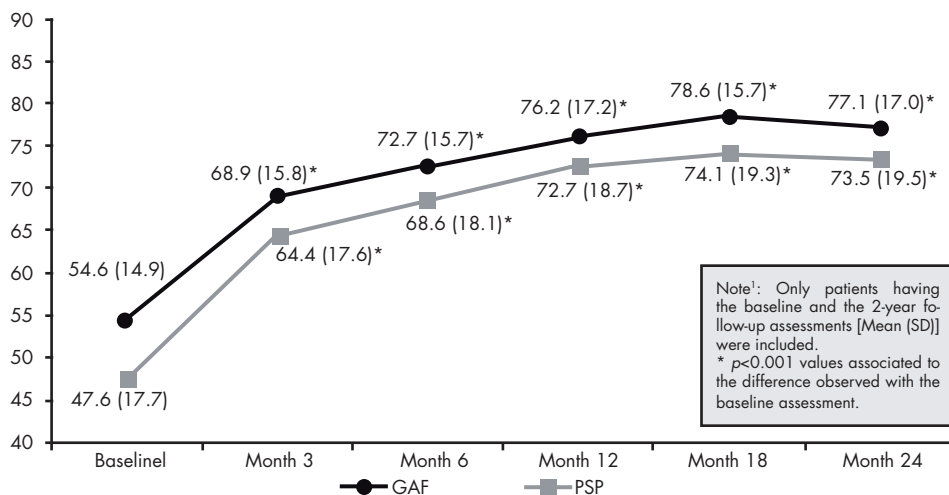
Figure 2. Evolution of the functionality throughout the study.

schizophrenia is associated to a higher global deterioration, secondary to a higher number of relapses, exacerbation of psychotic symptoms and a higher number of psychiatric hospitalizations throughout the illness.[12,26,43-46] Lack of treatment adherence not only impacts the control of illness, but also a higher number of hospitalizations implying higher costs for the patient and his/her relatives at specialist care centers, as well as a higher use of healthcare resources in terms of the use of hospital facilities and more concomitant medication.[47-50]

In the control of schizophrenia not only is important to consider the efficacy of medicine for controlling psychotic symptoms. Although the atypical antipsychotics represented a great advance in the treatment of schizophrenia, the necessity to have new medicines with the purpose to increase adherence, prevent relapses and diminish the use of concomitant medication and the use of services of the health system[5] became a challenge for the mental health specialists. Thus, the introduction of long-acting atypical injectable antipsychotics opened the possibility to have an efficient treatment reducing the direct costs of the illness in connection with the use of hospital resources. The results obtained with the use of the RLAI in Latin-American patients are consistent with those previously reported by other countries. The RLAI is a treatment that besides being efficient in the control of symptoms of the illness, it allows a proper treatment adherence by patients, which diminishes the number of hospitalizations and time of inpatient hospital care.[5,19,23,27,31,37,51-53]

One of the main implications of these results is addressed to the conceptions concerning the use of injectable antipsychotics as the first-choice treatment option for schizophrenia, even in clinical situations not related to difficulties in the treatment adherence. With the use of the RLAI, the patients would be benefited by an antipsychotic efficient for the treatment of the symptoms, which do not have to be taken daily, a fact that increases the chance of a proper adherence and reduces the chance of relapse and an eventual hospitalization. Therefore, the global functioning of the patients could be kept in an appropriate level, allowing them a better social and labor integration within their environment.

This study has several slants and limitations. In addition to the possible slants of selection and observation appropriate for an open study, the main limitation of the study is focused on the slant of recording of baseline and follow-up data. 48.3% of patients initially included in the study could not be analyzed due to this slant, which limits importantly the generalization of the obtained data. This point should be monitored and controlled in other studies made in daily clinical practice, firstly through strengthening interaction between medical care and research, and a closer surveillance of the electronically record of data.

Nevertheless, our results provide information that is relevant for the control of schizophrenia in daily clinical practice, with appropriate data on the efficacy and benefits associated to the use of resources with the treatment based on the RLAI, replying findings made by other international studies. On the other hand, although the quantification of the economic benefit is not part of the study's objective, our results are a basis for the development of studies aimed at considering the cost-benefit relationship of the RLAI for the patient and the Latin-American systems.

ACKNOWLEDGEMENTS

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