

Cost-consequences analysis of switching from oral antipsychotics to long-acting risperidone in the treatment of schizophrenia

Analisi costo-conseguenze dello switch terapeutico da antipsicotici orali a risperidone a rilascio prolungato nel trattamento farmacologico della schizofrenia

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Summary

Objectives

Lack of treatment adherence in schizophrenia often leads to an increase in relapses and, consequentially, to an increase in direct healthcare costs (e.g., hospitalizations). The aim of the SMART study (Schizophrenia Medications Adherence: long-acting Risperidone versus other Therapies) was to assess the variation in total direct health-related costs among schizophrenic patients switching from oral antipsychotics to long-acting injectable risperidone (LA-risperidone).

Materials and methods

A multicentre, retrospective, observational cohort study based on administrative databases from 4 local health units was conducted. Patients with a diagnosis of schizophrenia with a first prescription of LA-risperidone between January 1, 2007 and December 31, 2008 and a previous treatment with oral antipsychotics were enrolled. Direct medical costs (drugs, hospitalizations, Department of Mental Health services, outpatient specialist services) were evaluated during the 12 months preceding and following the date of inclusion (Fig. 1).

Results

A total of 157 patients were enrolled, 85 males and 72 females, aged 46 ± 14 years (Table I). Total mean disease-related costs

per patient were € 5942.54 during the period preceding LA-risperidone and € 5385.88 after switching (-€ 556.66, -9.4%) (Table III). The cost increase for antipsychotic drugs (from € 401.78 to € 2356.30, $p < 0.001$) was offset by a cost reduction for assisted-living (from € 287.61 to € 236.49, $p = 0.573$), congregate housing (from € 2113.38 to € 1132.48, $p = 0.007$), Department of Mental Health services (from € 300.30 to € 278.33, $p = 0.555$) and hospitalizations (from € 2767.26 to € 1313.30, $p < 0.001$); we registered a decrease in hospital mean length of stay (from 10.6 days to 4.6, $p < 0.001$) and the number of hospitalizations per patient (from 0.70 to 0.37, $p < 0.001$); 44% patients were hospitalized during the period preceding LA-risperidone and 20% after switching (Table II). The costs for services unrelated to schizophrenia showed no significant differences (from € 439.54 to € 518.28). The level of treatment adherence increased from $36.4\% \pm 30.5\%$ to $61.4\% \pm 30.1\%$ (Fig. 2).

Conclusions

Therapy with LA-risperidone appears to be cost saving, especially considering the reduction in costs of hospitalizations due to increased adherence.

Key words

Antipsychotics • Real-life practice • Cost-efficacy • Long-acting risperidone • Schizophrenia • Switching

Introduction

Schizophrenia is a chronic mental disorder with a prevalence between 0.5-1% in the adult population^{1,2}. Schizophrenia is characterized by the presence of complex symptoms that can lead to dysfunction in interpersonal relations, work and self-care, with frequent exacerbations that often necessitate hospitalization, and a progressive worsening of the personality of the patient and social abilities. Even if oral atypical antipsychotics have a better tolerability profile than typical antipsychotics, about 20-

50% of patients are affected by frequent recurrences after an initial improvement of symptoms. The greatest risk of relapse is due to partial or no adherence to therapy^{3,4}. Non-adherence to therapy in schizophrenia is mainly associated with poor response to treatment, and brings about an increased risk of recurrence, rehospitalization and increased use of emergency psychiatric structures⁵⁻⁷. Long-term management of schizophrenia thus requires an integrated approach including several therapeutic modalities, based on appropriate principles in several dimensions, and aims to improve the effectiveness of

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therapy by adopting parallel behavioural and pharmacological measures to increase adherence to treatment⁸. The guidelines of the National Institute for Health and Clinical Excellence (UK) from 2009⁹ suggest that long-acting injectable antipsychotic therapy can reduce both intentional and non-intentional non-adherence to pharmacological antipsychotic therapy when this becomes a clinical priority.

Diverse pharmacological therapies, including fluphenazine, haloperidol, risperidone, olanzapine and paliperidone, are available in long-acting injectable formulations. Among these, risperidone was the first second-generation antipsychotic (atypical) available in this formulation. The advantages of a long-acting injectable include a reduction in non-adherence, and consequently, a decrease in acute clinical recurrence and the immediate awareness of non-adherence when a dose is missed¹⁰. Moreover, the results of meta-analyses have suggested the superiority of a long-acting injectable compared to oral formulations in reducing the percentage of both recurrences and rehospitalizations¹¹.

For the above reasons, it is of interest to evaluate if, considering the immediate and inevitable increases of direct costs of pharmacological treatment, extended release formulations of antipsychotics are also associated with differences in direct costs (hospitalizations, visits, access to mental health services) in the short- to long-term period¹²⁻¹⁸.

Study objectives

The main objective of the present study was to quantify, from an economical standpoint, based on the direct costs of the National Health Service, the costs of a patient affected with schizophrenia. In particular, cost differences were evaluated in patients switching from an oral antipsychotic to LA-risperidone; all direct costs were considered (pharmacological treatment, diagnostic tests, specialist visits and hospitalizations). Eventual changes in adherence level to therapy before and after switching were also assessed.

Materials and methods

Data

The data used for the analyses were obtained from administrative databases from 4 Local Health Units in Italy relating to the regions Emilia-Romagna, Toscana and Lazio, with about 1,480,000 beneficiaries. The following data was retrieved: demographics; prescribing history, with information relative to individual prescriptions including the ATC (Anatomical-Therapeutic-Chemical) code of the drug prescribed,

number of boxes, number of pills per box, dose, units costs and the date of prescription; hospital discharge records, containing clinical information at discharge after each hospitalization, and in particular date of admission and discharge, main and secondary diagnoses, coded according to the International Classification of Diseases, Revision IX, Clinical Modification (ICD-9-CM); data on mental health status (code ICD-10-CM), services offered by the Department of Mental Health (DMH) along with the date; specialist outpatient assistance (visits, laboratory exams, diagnostic tests) provided to the patient along with the date and number of individual services provided.

Linkage between various databases was kept anonymous, and personal data that could allow identification of the patient was not disclosed. The ethics committees of the individual Local Health Units approved the study.

Identification of patients

This was a retrospective cohort analysis that evaluated information relative to prescriptions, ambulatory services and hospitalizations during the period under study for subjects with a diagnosis of schizophrenia (code ICD10 F20-F29) and treated with LA-risperidone [code ATC N05AX08] with an age ≥ 18 years. Patients were included in the analysis if, during the period from 1 Jan 2007 – 31 Dec 2008 (enrolment period), they had at least one prescription for LA-risperidone and if they were treated with an oral antipsychotic in the 12 months preceding the date of inclusion (pre-switch period).

The date of enrolment of individual subjects was defined as the date during the period of enrolment in which the patient received the first prescription of LA-risperidone; patients were excluded if they were already treated with LA-risperidone at the date of enrolment. Patients transferred to other Local Health Units or who died during the follow-up period (one year starting from the date of enrolment) were excluded from the analysis.

All analyses were carried out by comparing the 12 months preceding the date of enrolment (pre-switch) with the 12 months after enrolment (post-switch period), without considering the first 2 months of the post-switch period in order to correct for protopathic bias. This was necessary to exclude eventual uncontrolled bias such as the absence of a specific indicator on the severity of the patient; the design was based on a previous study with the same objectives².

Diagnosis

A diagnosis of schizophrenia was obtained from available databases: a database specific for mental health was firstly considered; following a diagnosis of schizophrenia,

the diagnosis at hospital discharge was added (primary or secondary) which was obtained from discharge forms during the period of the analysis; this choice was dictated by the need to identify patients that did not access local mental health units, but who developed recurrence and were thus hospitalized in other Psychiatric Departments.

Protopathic bias

In order to ensure that the costs associated with the two different therapies were correctly attributed to the relative period, an interval of two months was introduced between the two sub-periods, with the objective of minimizing protopathic bias, or the probability of attributing an event to the drug (and subsequent hospitalization) that occurred immediately after the introduction of the new antipsychotic ¹⁹. All analyses were thus carried out by comparing the previous year with respect to the date of enrolment and the period between 2 and 14 months following that date (Fig. 1).

Costs

Costs retrieved from archives were divided into inherent and non-inherent costs. For the former, all services provided by the Department of Mental Health were considered; among these, particular attention was paid to access at residential structures with various levels of care (from community therapy to assisted-living in apartments) and to semi-residential structures (rehabilitation day centres and other projects aimed at acquiring social and employment skills).

The following services carried out in an outpatient setting were also considered inherent: functional evaluation (global, segmental, monofunctional) with psycho-behavioural scales, visits with clinical psychologists, psychiatric visits and follow-up, psychotherapy (individual, family, group) and psychodiagnostic exams. Additional inherent costs were antipsychotics (code ATC N05A) and other drugs acting on the central nervous system (code ATC N).

Concerning hospitalization, admission to Psychiatric Services was also considered an inherent cost as was a primary diagnosis of schizophrenia or related disorders (codes ICD9 295, 297, 298) at discharge, or psychosis (DRG 430); all hospitalizations for psychiatric reasons were also considered as inherent costs (code ICD9 from 290.X to 319.X), in agreement with the methodology proposed by Weiden et al. ²⁰.

For treatment, the price of the drug considered was that at the time of acquisition; outpatient services were evaluated using a regional price list; costs of individual admissions were derived directly from the Diagnosis Related Group (DRG) and increased as appropriate if hospitalization was longer than that expected from the DRG code.

Adherence to treatment

Adherence to treatment was calculated using the method of Catalan ²¹. Using this criteria, the period in which the drug was used was divided into sub-periods identified on the basis of the date of acquisition (presumed to be the date of prescription of the drug). Therapeutic coverage during the sub-period was calculated by adding the number of days of treatment covered by the drug prescribed to the date of acquisition plus a period of tolerance. A prescription close to the end of follow-up contributes only the days in which the patient was within the period of study. Coverage was calculated by adding the sub-periods that were correctly covered and dividing by the duration of follow-up.

Statistical analyses

Continuous variables are reported as mean \pm standard deviation and compared using a paired Student's T test; categorical variables are reported as absolute values and percentages, and compared with a McNemar test. A p value < 0.05 was considered statistically significant. All analyses were carried using SPSS-Windows version 18.0.

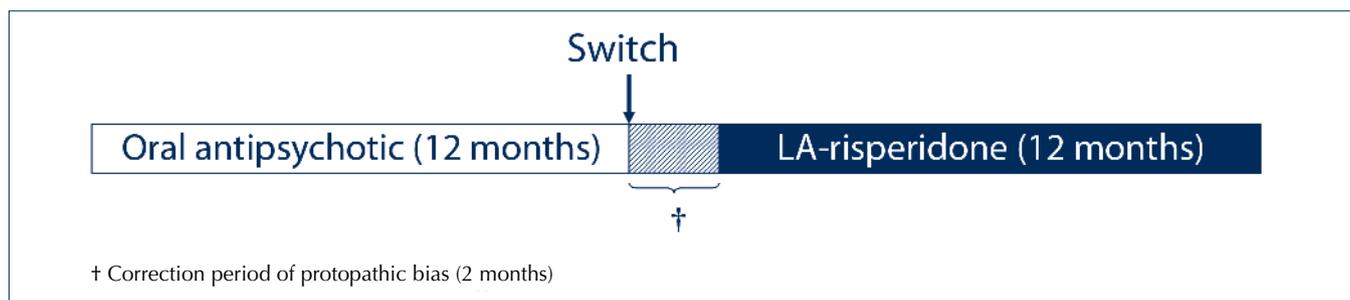


FIGURE 1.

Study design. *Disegno dello studio.*

Results

A total of 157 patients were included in the study, 85 males (54%) and 68 females (46%), with a mean age of 46.0 ± 14.3 years (Table I), who switched to LA-risperidone in the period under investigation, as registered by the Italian Department of Mental Health. There were 110 hospitalizations in the 12 months before the switch to LA-risperidone (with mean of 0.70/patient) and 58 hospitalizations after switching (mean of 0.37/patient) ($p = 0.001$). A total of 1,664 hospital days were recorded in the pre-switch period (mean of 10.6 days/patient) and 719 days after switching to LA-risperidone (mean 4.6 days/patient) ($p = 0.001$). In the period before switching, 69 patients (43.9%) were hospitalized compared to 32 (20.4%) after switching ($p < 0.001$). The mean length of stay was 15 and 12 days before and after the switch, respectively ($p < 0.001$).

Regarding access to local mental health units, considering all patients, there were 422 days in assisted living (mean 2.7 days/patient) before switching and 347 (mean 2.2 days/patient) following the switch ($p = 0.573$); for congregate housing or group homes, there were a total of 2,370 days registered in the pre-switch period (mean 15.1 days/patient) and 1,270 (mean 8.1 days/patient) in the post-switch period ($p = 0.007$) (Table II). Considering only those patients who accessed local mental health units, a mean of 28.1 days were spent in assisted living (15 patients) before switching compared to 26.7 days after switching (13 patients). Regarding congregate housing, there were 74.1 days in the pre-switch period (32 patients) and 79.4 days after the switch to LA-risperidone (16 patients).

Mean adherence to therapy in the two periods revealed an increase of 25.0 percentage points, from $36.4\% \pm 30.5\%$ to $61.4\% \pm 30.1\%$ ($p < 0.001$, Fig. 2).

Costs

The mean total costs per patient for inherent services were € 5942.54 and € 5385.88, respectively, before and after therapy with LA-risperidone, for a decrease

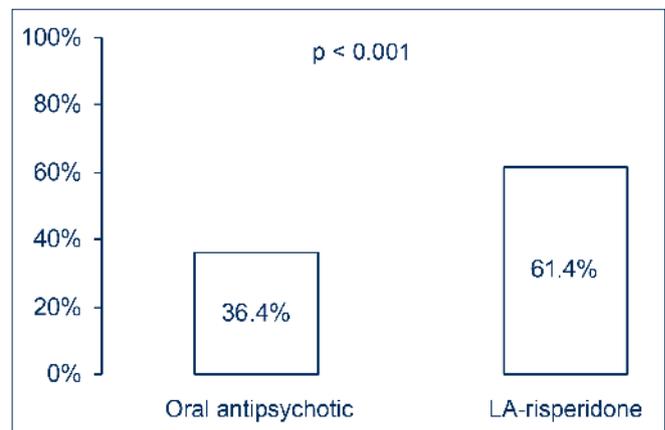


FIGURE 2. Adherence to therapy. *Aderenza al trattamento.*

of € 556.66 (-9.4%). Considering individual costs, an increase was seen in mean annual costs for antipsychotic drugs (from € 401.78 to € 2356.30, $p < 0.001$), which was however accompanied by a reduction in costs for assisted living (from € 287.61 to € 236.49, $p = 0.573$), congregate housing (from € 2113.38 to € 1132.48, $p = 0.007$), all other services offered by the Mental Health Units or as an outpatient (from € 300.00 to € 278.33, $p = 0.555$), and for hospital admissions (from € 2767.26 to € 1313.30, $p < 0.001$). The costs for other drugs acting on the central nervous system, which represented about 1% of the total costs, did not significantly change (from € 72.21 to € 68.98, $p = 0.893$). Taken together, in the pre-switch period, 87.0% of inherent costs were due to hospitalization or admission to congregate housing or assisting living; in the post-switch period, this percentage decreased to 49.8%, also because the cost of antipsychotic drugs was 43.7% of total costs.

The non-inherent costs of schizophrenia showed no significant differences (from € 439.54 to € 518.28); in particular, "other drugs" increased from € 98.23 to € 111.11 ($p = 0.453$), outpatient services from € 163.83 to € 182.33 ($p = 0.525$), and other admissions from € 177.48 to € 224.84 ($p = 0.946$) (Table III).

It was also observed that for patients who did not show an increased level of adherence (19 subjects, 12%), total costs increased from € 5099 to € 6464; this was due to the increased cost of treatment as, for these patients, the costs of hospitalization and access to mental healthcare structures did not change during the study period (€ 3268 pre-switch vs. € 3312 post-switch); these patients, moreover, had a cost of disease in the pre-switch period that was lower than the cost for patients that showed better adherence; these latter pa-

TABLE I. Demographic characteristics of patients. *Caratteristiche demografiche dei pazienti in analisi.*

Patients	N.	157
Age (mean \pm SD)		46.0 ± 14.3
Male	N. (%)	85 (54.1%)
	Age (mean \pm SD)	43.1 ± 14.3
Female	N. (%)	72 (45.9%)
	Age (mean \pm SD)	49.3 ± 13.7

TABLE II.
Hospitalizations and Mental Health Service admissions. *Accessi ospedalieri e al DSM.*

		Oral antipsychotic	LA-risperidone
Patients	N.	157	157
Hospitalizations	N.	110	58
	Mean per patient*	0.70	0.37
Length of stay	Total days	1664	719
	Mean per patient*	10.6	4.6
Hospitalized patients	N.	69	32
	%*	43.9%	20.4%
Mean length of stay (days)*		15	12
Assisted living	Total days	422	347
	Mean per patient*	2.69	2.21
Congregate housing	Total days	2370	1270
	Mean per patient*	15.10	8.09

* p < 0.05.

tients, in fact, decreased from € 6559 to € 5827 (in particular, costs relative to hospitalization and access to mental healthcare structures decreased from € 5430

to € 2596). It is thus possible that patients who did not show increased adherence may have less severe disease.

TABLE III.
Costs of disease before and after switching. *Costo di malattia, differenze pre-post switch.*

Related costs	12 months before oral antipsychotic (n = 157)		12 months after LA-risperidone (n = 157)		Difference	p-value
	Mean ± SD	%	Mean ± SD	%		
Drugs (N05A)	401.78 ± 601.34	6.8%	2356.30 ± 1524.49	43.7%	1954.52	< 0.001
Other drugs	72.21 ± 349.61	1.2%	68.98 ± 157.02	1.3%	-3.23	0.893
Outpatient visits	300.30 ± 484.28	5.1%	278.33 ± 455.83	5.2%	-21.97	0.555
Hospitalizations	2767.26 ± 4666.25	46.6%	1313.30 ± 3508.54	24.4%	-1453.96	< 0.001
Assisted living	287.61 ± 1523.74	4.8%	236.49 ± 1479.27	4.4%	-51.12	0.573
Congregate housing	2113.38 ± 7271.43	35.6%	1132.48 ± 6191.60	21.0%	-980.90	0.007
Total related	5942.54	93.1%	5385.88	91.2%	-556.66	
Non-related						
Other drugs	98.23 ± 275.66	22.3%	111.11 ± 362.10	21.4%	12.88	0.453
Other outpatient visits	163.83 ± 261.14	37.3%	182.33 ± 373.84	35.2%	18.50	0.525
Other hospitalizations	177.48 ± 1270.94	40.4%	224.84 ± 944.79	43.4%	47.36	0.946
Total non-related	439.54	6.9%	518.28	8.8%	78.74	
Total general costs	6382.08	100.0%	5904.16	100.0%	-477.92	

Discussion

Non-adherence to antipsychotic therapy is believed to be responsible for a large proportion of treatment costs in hospitalized patients with schizophrenia; improving the continuity of antipsychotic therapy can thus lead to cost savings by reducing the frequency and duration of hospital stay²². The need for early diagnosis and treatment in patients with psychotic spectrum disorders has become increasingly evident in clinical practice, and in particular for schizophrenic disturbances. Several lines of evidence have confirmed that early intervention – especially at the appearance of clinical symptoms – significantly improves both pharmacological and rehabilitative treatment outcomes. Such results are possible only with continuity of pharmacological therapy.

The present study highlights how switching from an oral antipsychotic to LA-risperidone is associated with a decrease in the inherent direct costs of treatment of schizophrenia, and in particular to those costs related to residential care. In the period after switching, in the patients analyzed, there was a decrease in the number of hospitalizations and in the duration of hospitalization; this trend was also confirmed by the data relative to access to local mental health units (group homes or daytime centres), both in assisted living and congregate housing. The increase in mean costs of antipsychotic drugs was balanced by a reduction in the mean costs for assisted living and congregate housing, as well as for all other services offered by the Department of Mental Health including outpatient visits and hospital admissions. In the pre-switch period, the majority of inherent costs of schizophrenia (87.0%) were due to hospitalization and access to regional structures, which decreased to 49.8% after switching to LA-risperidone. The mean total costs per patient decreased by 9.4% compared to the pre-switch period. This is possibly due to an increase in adherence to treatment, which during the period analyzed rose from 36% to 61%. Thus, real-life practice in Italy confirms literature data suggesting that greater adherence to pharmacological therapy is associated with better outcomes and lower costs.

From a clinic-therapeutic viewpoint, and especially in major psychiatric disturbances, psychiatrists must firstly consider control of symptoms and continuity of treatment (adherence to therapy, discontinuity or interruption up to drop-out). However, new formulations offer a more complete monitoring of therapy, and offer new possibilities to the patient for improving family and social relationships as the overall clinical picture may be more stable. In this light, the patient and his/her family must all participate in treatment, and should have realistic expectations about improvement and therapeutic goals. It should be kept in mind that the patient's quality of life is related to the quality and appropriateness of treatment.

The results of the present study confirm several previous investigations in Europe. A French study (CGS) evaluated 1,859 patients at psychiatric centres from 15 different regions, and demonstrated that the use of LA-risperidone was associated with a 34% reduction in the risk of hospitalization compared to non-use, and by 47% compared to first-generation depot antipsychotics. The percentages for the risk of hospitalization also decreased when LA-risperidone was compared with any first- or second-generation oral antipsychotic¹⁹. Several studies from different countries have shown that recurrence in schizophrenia leads to a greater use of healthcare resources and higher costs²³. In the SOHO study, the costs for recurrence (observation period of 3 years) were 4-times higher than those without recurrence²⁴. The costs of treatment take into consideration hospitalization, social assistance, psychiatric consultations and drug therapy. The largest costs are due to hospital stay²⁵.

A cost-efficacy analysis was also carried out using the eSTAR database in Spain, which derives from an observational study in patients with schizophrenia who, in normal clinical practice, started new treatment with LA-risperidone, switching from a typical oral or depot antipsychotic or an atypical oral antipsychotic. It was found that LA-risperidone showed the best results both in efficacy measured as the number of patients without hospitalization for an acute episode (89.1% vs. 67.0%) and in cost-efficacy per patient per month of treatment (€ 539.82 vs. € 982.13)²⁶.

In Italy, in the regional healthcare system of Lombardy, a study was carried out to evaluate the direct healthcare costs and efficacy related to adherence to therapy with antipsychotics in patients with schizophrenia. Efficacy and costs in the 12 months preceding the initiation of therapy with LA-risperidone were compared to those in the successive 12 months. From this study, LA-risperidone seemed to be a better strategy compared to oral treatment since it was associated with higher efficacy (percentage of patients without hospitalization: 67.9% vs. 28.6%) and lower costs (mean total costs per patient: € 9191.45 vs. € 10125.57)².

The main limitations of the present study are due to the geographic area under consideration, which may not be representative of the situation on a national level. Another limitation is the duration of the observational period of 12 months; for evaluation of long-term costs and efficacy, such as those used to treat schizophrenia, it would be desirable to have a longer time interval and a larger number of patients.

Conclusions

Therapy with LA-risperidone for the treatment of schizophrenia appears to be, when clinically-indicated, an

economically-acceptable, cost-saving treatment, and in particular is associated with a reduction in the number of hospitalizations and the costs of both assisted and congregate housing. This is presumably due to increased adherence to antipsychotic therapy. The present data confirm the importance of clinical research and durability of treatment from both pharmacoeconomic and clinical standpoints.

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