ORIGINAL RESEARCH

Key Words: Long-acting injectable risperidone, outpatients, effectiveness, naturalistic conditions

The Effectiveness of Long-Acting Injectable Risperidone in a Population of Psychiatric Out-Patients: 1-Year Naturalistic Study

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ABSTRACT ~ Objective: *A naturalistic, prospective study analyzed the effectiveness of long-acting injectable risperidone (LAIR) in psychotic outpatients.* ***Methods:*** *All outpatients (n = 53), affected by Schizophrenia and other Psychotic Disorders, who have begun LAIR at the Mental Health Service of Modena from December 1, 2005 to December 1, 2006, were collected. Exclusion criteria: concomitant oral antipsychotic therapy at the 12th weeks (n = 16 patients) and treatment discontinuation (n = 12). The reasons of drop-out were analyzed. Clinical and demographic characteristics of outpatients (n = 25), motivations, implementation and adverse effects of LAIR treatment were evaluated. Main outcome: the improvement of symptoms (25% reduction of BPRS and CGI-S scale score from baseline) and functioning level (50% increase of GAF scale score from baseline) at 6th (T6) and 12th (T12) month of LAIR therapy. Secondary outcome: reduction of the hospitalization days during the 1-year LAIR treatment in comparison to the previous year ones of the same patients.* ***Results:*** *The final BPRS, CGI-S and GAF scores both at T6 and T12 showed a statistically significant difference from baseline ($p < 0.0001$, t-test). The frequency of improved patients in BPRS, CGI-S and GAF scales were 60%, 68%, 52% at T6, and 72%, 54%, 56% at T12, respectively. Side effects were represented by weight increase (4%), orthostatic hypotension (8%) and EPS (4%). The hospitalization days were statistically significant reduced during the 1-year LAIR treatment in comparison to the previous year ones ($p < 0.05$, t-test).* ***Conclusion:*** *Our data, limited by the small sample and the naturalistic methodology, suggest that 1-year LAIR treatment may be effective and safe.* Psychopharmacology Bulletin. *2010;43(1):39–52.*

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INTRODUCTION

Schizophrenia is characterized by positive (delusions and hallucinations) and negative symptoms (anhedonia, affective flattening, alogia, avolition, etc.), as well as disorganized behaviour and thought. It also involves dysfunction in many areas, such as interpersonal relations, work, and self-care,[1–2] with frequent exacerbations that often require hospital admission, and a progressive deterioration of the patient's personality and social skills. Schizophrenia constitutes an economic burden for society due to both the patient's inability to work and the need for assistance.[3] To date, antipsychotic medication remains the cornerstone of current therapeutic interventions for schizophrenia.

The traditional neuroleptics or typical antipsychotic medications are antidopaminergic drugs with a high affinity for D_2 receptors, resulting in both efficacy on positive symptoms and significant neurological (extrapyramidal symptoms) and endocrinological (hyperprolactinemia) side effects. Moreover, these drugs are ineffective on negative symptoms. Approximately one third of schizophrenic patients are treatment-resistant and about 50% of patients are non-compliant with typical antipsychotic treatment.[4–5] During the past ten years, new antipsychotic drugs, known as atypical antipsychotic agent, have been introduced.

The first atypical antipsychotic agent, clozapine, was recently reintroduced due to its efficacy on psychotic symptoms, especially negative ones, despite its haematological risk of agranulocytosis, so to be considered the drug of choice for treatment-resistant schizophrenia, according to most therapeutic guidelines.[6] The group of the atypical antipsychotics is heterogeneous, but is characterized by low cataleptic activity in the animal tests, fast release from dopamine D_2 receptors[7] and low risk of extrapyramidal symptoms (EPS) in human, high ratio of affinity for 5-HT2A serotonin receptors to that for D_2 dopamine receptors (5-HT2A/D_2 > 1) and efficacy on both negative and cognitive symptoms of schizophrenia.[8–9]

Although the atypical antipsychotic drugs have ameliorated the treatment compliance, due to the more tolerable adverse effect profile, about 20–50% of treated schizophrenic patients suffer frequent relapses after an initial symptom improvement.[10] An absent or non constant adherence to treatment may represent the major risk of relapse,[11] which could be improved by a long-acting antipsychotic therapy, as literature data show.[12]

The first long-acting antipsychotic agents were developed in the 1960s in order to assure a constant delivery of the drug and an enhance of therapeutic compliance. Anyway, conventional long-acting agents are associated to similar side effects to the equivalent oral doses of typical antipsychotic drugs. In 1997, the guidelines for the treatment of

patients with schizophrenia of American Psychiatric Association's highlighted the need for a long-acting formulation of atypical antipsychotic drugs and indicated three primary goals in the treatment of schizophrenia: 1) sustained relief from psychotic symptoms, 2) reduce relapse rates, 3) improve functioning and quality of life.[13]

Using an atypical long-acting antipsychotic may improve patient outcome by offering the good efficacy and tolerability of an atypical antipsychotic combined with improved therapeutic compliance since depot administration provides the opportunity of regular contacts between patient and treatment teams. Besides, long-acting drug is not associated with a "first-pass metabolism" and reduces the haematic peaks, so to permit the prescription of the lowest effective doses. Many data from clinical trials and meta-analyses evidence that long-acting antipsychotics reduce relapses and rehospitalizations and favour the rehabilitation and psychosocial programs.[14] There is considerable evidence for the value of treatment programs that combine medications with a range of psychosocial services in exerting positive influences on such clinical outcomes as medication compliance, and symptom and relapse reduction.[15]

Long-acting injectable risperidone (LAIR) is the only currently available long-acting atypical antipsychotic drug. In comparison to other antipsychotics, risperidone, a benzoisoxazole compound, and its active metabolite, 9-OH-risperidone, show a very high affinity for D_2 receptors (similar to haloperidol and ziprasidone) and higher affinity for serotonin 5-HT2α receptors (similar to ziprasidone) with 5-HT2 to D_2 ratio greater than one, high antagonism to α2-adrenergic and histamine H1 receptors but negligible antagonism to muscarinc receptors.[16]

Risperidone has a safety profile which resembles that of typical neuroleptics at the highest dose range (> 6 mg/day), regarding liability to induce EPS and prolactin serum level elevation with associated sexual dysfunction (risperidone is the only atypical agent which may cause serum elevation of prolactin, because of its higher affinity and lower specificity for dopamine receptors).[17] Risperidone presents lower risk of bodyweight gain than clozapine and olanzapine, but superior than haloperidol or placebo, as evidenced by a number of studies.[18]

The novel formulation of LAIR, constituted by biodegradable polymers, permits a constant and slow delivery of the medication with:

- reduced fluctuations in plasma concentrations of risperidone plus 9-OH-risperidone, which has been determined in about 18 ng/ml and 35 ng/ml for 25 mg and 50 mg injectable doses respectively;[19–20]
- reduced drug haematic peaks of 25–32% in comparison to the oral prescription;[21]

- D_2-receptor occupancy of 54% for 25 mg and 74% for 50 mg doses of LAIR, as PET studies have been evidenced,[22] which is sufficient for an antipsychotic action but is below the threshold for extrapyramidal side effects (EPS) (80%).[23–24]

Firstly, the benefits of LAIR were explored by three pivotal clinical trials: two short-term studies of 12 weeks[25] and 24 weeks,[17] and one long-term and open label trial of 1-year.[19] A randomized, double-blind study has evidenced a similar efficacy and tolerability of both LAIR and oral risperidone at equivalent doses in a 20 week treatment.[26] The LAIR treatment efficacy and safety appeared similar to other long-acting antipsychotic therapies in two open label studies: the first one vs zuclopenthixol in schizophrenic and substance abuser patients for 6 month treatment[27] and the second one vs other conventional long-acting antipsychotic drugs for a period of 12 months.[28] Two trials have evidenced the effectiveness of LAIR switches from other antipsychotic agents: a short-term study of 4 weeks in stabilized psychotic patients[29] and a long-term treatment of 1-year in non-compliant or treatment-resistant psychotic patients.[17]

Only one study has analyzed the effectiveness of LAIR in comparison to oral atypical antipsychotic agents in young adults with recent onset of Schizophrenia, Schizophreniform and Schizoaffective Disorders.[30] A sub analyse of Kane 12-week study[25] measured the quality of life (HRQoL) by means Medical Outcome Study Short-Form 36-item (SF-36) and pointed out that the quality of life (HRQoL) of patients treated with LAIR was similar to normal population.[31] Finally, other studies have shown that LAIR directly decreased healthcare costs due to reducing hospitalizations.[32]

On the basis of the results of the studies up to date conducted long acting injectable risperidone generally appeared to be well tolerated, with a low incidence of adverse affects.[33] In particular, the frequency of withdrawn due to adverse effects was ranged from 1.2% to 16%, the most common adverse effects were represented by headache, insomnia, anxiety, with a low incidence, similar to other antipsychotic treatments, of EPS.[17,19,25–26,29,34–36] The iperprolactine serum was analyzed by three studies,[26,29,34] which reported rates of 1.3–7%. In short term 12-week studies, a weight gain of 0.5–2 kg was evidenced, which could increase up to 3 kg after 1-year of treatment, without a further increase after 4-year therapy of LAIR.[35,37]

In order to verify the effectiveness and the risk of long acting injectable risperidone treatment in a psychiatric outpatient populations, we conducted a prospective, open label, non-randomized study of all patients affected by Schizophrenia and other Psychotic Disorders

treated with long acting injectable risperidone for 12 months, from December 1, 2005 to December 31, 2007, in the Mental Health Service of Modena (Centro Salute Mentale-Modena Centro).

MATERIALS AND METHODS

This study was conducted in accordance with the principles of the Declaration of Helsinki and good clinical practice, and was not sponsored by any pharmaceutical company. It was approved by the Institutional Review Board.

Inclusion criteria: all patients (n = 53) affected by Schizophrenia and other psychotic disorders treated with long-acting injectable risperidone (LAIR) for 12 months from December 1, 2005 to December 31, 2007, in Mental Health Service (outpatient settings) of Modena Centro. All patients signed an informed consent form before being treated with LAIR.

Exclusion criteria: the patients (n = 16) treated with concomitant oral antipsychotic therapy up to the 12th weeks and the drop-out cases (n = 12) were excluded, in order to select a homogeneous sample for therapy (only LAIR as antipsychotic drug from to 13th to 52th weeks) and period of treatment (12 months).

The drop-cases represented the 23% of all patients treated with LAIR, who interrupted the treatment after 9,75 prescriptions on average at the mean dose of 37.90 mg/14 days, largely due to absent compliance (83%), while side effects (EPS and sexual impotence) represented the reasons of discontinuation only in the 17% of patients.

As shown in Table 1, the study group consisted of 25 outpatients affected by Schizophrenia, Schizoaffective Disorder, Delusional Disorder, Schizoid Personality Disorder, and Schizotypal Personality Disorder (according to DSM-IV-TR).[2] The sample was small and inclusive of heterogeneous diagnoses, which were set in the same "schizophrenic-paranoid spectrum." In particular, schizoid and schizotypal personality disorders were considered to be the so-called schizophrenia *simplex* before DSM-III.[38] The sample included severe and chronic patients with many years of illness and several hospital admissions, as shown in Table 1, where the demographic and psychopathological characteristics of the sample are summarized.

The main reasons for prescription LAIR treatment were represented by intolerance to other drugs (50%) and absence of compliance (42%), followed by lack of efficacy of previous treatments (8%).

The mean dose of LAIR was 37.35 mg prescribed twice a month. The implementation of treatment was represented by the following procedures: switch from previous long-acting drug (56%), switch from oral risperidone (40%) or augmentation to other oral antipsychotic drugs (4%).

TABLE 1

BASELINE DEMOGRAPHIC AND PSYCHOPATHOLOGICAL CHARACTERISTICS OF PATIENTS TREATED WITH LAIR

	NO PATIENTS (%)
Gender	11 F (44%) 14 M (56%)
Age 49.92 years old (mean) 51 years old (median)	≤ 51 years: 8 (56%) > 51 years: 17 (44%)
Diagnosis (DSM-IV-TR)	13 (52%) Schizophrenia 6 (24%) Schizoaffective Disorder 3 (12%) Delusional Disorder 3 (12%) Paranoid and Schizotypal Personality Disorder
Years of disease 16.3 years (mean) 10 years (median)	≤ 10 years: 8 (32%) > 10 years: 17 (68%)
Number of previous admissions 5 (mean)	0 admission: 2 (8%) 1–5 admissions: 18 (72%) 6–10 admissions: 5 (20%)

TABLE 2

DRUGS ASSOCIATED TO LAIR AT BASELINE (T0), AFTER 6 MONTHS (T6), AFTER 12 MONTHS (T12)

ASSOCIATED DRUGS	T0	T6	T12
LAIR monotherapy	24%	44%	60%
Oral antipsychotic drugs	40%	8% (only oral risperidone)	4% (only oral risperidone)
Benzodiazepines or promethazine	12%	12%	8%
Anticholinergic drugs	8%	12%	4%
Antidepressant drugs	4%	8%	8%
Mood stabilizer drugs	12%	16%	16%

In the Table 2 are shown the frequency of LAIR as monotherapy or associated to the other psychiatric therapies (oral antipsychotics, benzodiazepines and promethazine, anticholinergic, antidepressant and mood stabilizer drugs) at the beginning of treatment (T0), at the 6th month (T6) and at the 12th month (T12). We have to specify that the concomitant oral antipsychotic therapy shown in Table 2 consisted of only oral risperidone after the 12th week of treatment, according to our exclusion criteria above mentioned. At the 6th month the frequency of LAIR monotherapy was 44%, which increased to 60% at the 12th month (T12) of treatment, while the frequency of associated treatment decreased to 40% at the end of the observation period (T12).

At the beginning of the treatment and again at the 6th (T6) and at the 12th month, each patient's physician applied the Brief Psychiatric Rating Scale-24 items (BPRS),[39] Clinical Global Impression-Serverity (CGI-S)[40] and the Global Assessment of Functioning (GAF) scale.[41]

The main outcome consisted of the improvement of symptoms (reduction at least of 25% from the initial score in BPRS and CGI-S)[42] and functioning level (increase at least of 50% from the initial GAF scale score).[43] We performed statistical analysis of the differences between the rating scale scores from baseline to T6 and T12 (t-test).[44] Besides we analyzed what items of BPRS ameliorated at T6 and T12.

The secondary outcome concerned the reduction of hospitalization days during the 1-year risperidone RP treatment which were compared to the previous year ones of the same patients by means a statistical analysis (t-test).[44]

For safety, adverse effects and their impact on treatment course were also evaluated. Data are expressed as mean ± SD.

RESULTS

As shown in the Table 3, at T6 the frequency of improved patients in BPRS, CGI-S (reduction of at least 25% from the initial score) and in GAF (increase of at least 50% from the initial score) was represented by 60%, 68% and 52% respectively, with a quite similar percentage of improvement at T12 (72%, 54%, 56% in BPRS, CGI-S and GAF respectively).

The scores of evaluation scales both at T6 and T12 showed a statistically significant difference from the beginning treatment (T0) scores [$BPRS_{T0}$

TABLE 3

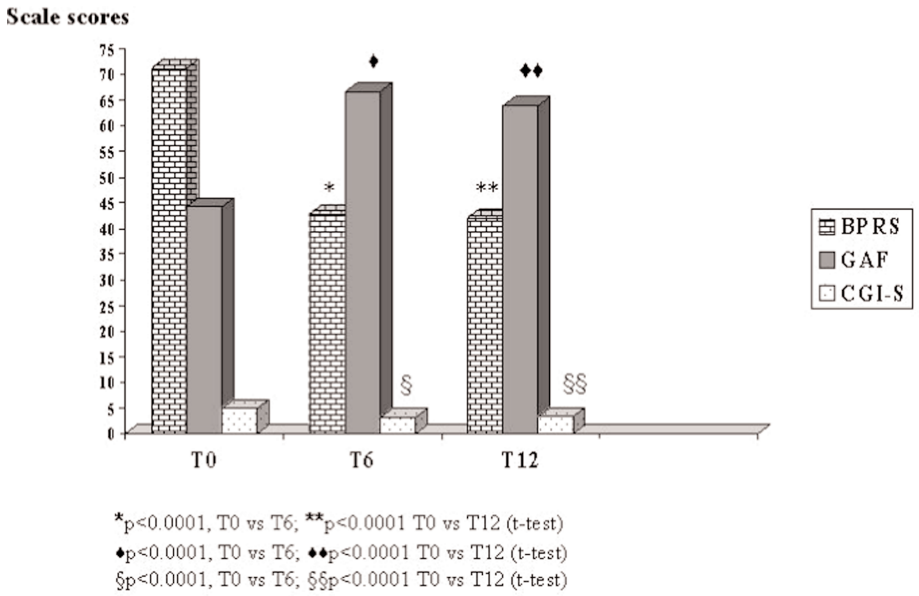
FREQUENCY OF IMPROVED PATIENTS ACCORDING TO SCALE SCORES AT 6TH MONTH (T6) AND AT 12TH MONTH (T12) OF LAIR TREATMENT IN COMPARISON TO BASELINE SCORE

RANGE OF SYMPTOMATIC IMPROVEMENT	FREQUENCY OF AMELIORATED PATIENTS AT T6	FREQUENCY OF AMELIORATED PATIENTS AT T12
BPRS-24 Reduction at least of 25% from the initial score	60%	72%
CGI-S Reduction at least of 25% from the initial score	68%	64%
GAF Increase at least of 50% from baseline score	52%	56%

(71.28 ± 27.72) vs. BPRS $_{T6}$ (42.80 ± 17.35), t = 6.66, df = 24, p < 0.0001; $BPRS_{T0}$ (71.28 ± 27.72) vs. BPRS $_{T12}$ (42.08 ± 15.38), t = 6.63, df = 24, p < 0.0001; GAF_{T0} (42.28 ± 18.82) vs. GAF_{T6} (64 ± 15.75), t = 9.15, df = 24, p < 0.0001; GAF_{T0} (42.28 ± 18.82) vs. GAF_{T12} (66.76 ± 14.26), t = 6.44, df = 24, p < 0.0001; CGI-S_{T0} (5 ± 2.70) vs. CGI-S_{T6} (3.2 ± 1.26), t = 7.15, df = 24, p < 0.0001; CGI-S_{T0} (5 ± 2.70) vs. CGI-S_{T12} (3.44 ± 1.00), t = 6.03, df = 24, p < 0.0001; (t-test)] (Fig. 1), with any statistically significant difference between T6 and T12 scores of the three evaluation scales (Fig. 1).

FIGURE 1

THE SCORE OF THE EVALUATION SCALES (BPRS, GAF, CGI-S) AT THE BEGINNING OF THE TREATMENT WITH LAIR (T0) AND AT THE 6TH (T6) AND 12TH MONTH (T12)



*p<0.0001, T0 vs T6; **p<0.0001 T0 vs T12 (t-test)
♦p<0.0001, T0 vs T6; ♦♦p<0.0001 T0 vs T12 (t-test)
§p<0.0001, T0 vs T6; §§p<0.0001 T0 vs T12 (t-test)

Total score of BPRS at the beginning of treatment $BPRS_{T0}$, at the 6th month of treatment $BPRS_{T6}$ and at the 12th month of treatment $BPRS_{T12}$.
$BPRS_{T0}$ (71.28 ± 27.72) vs. $BPRS_{T6}$ (42.80 ± 17.35); $BPRS_{T0}$ (71.28 ± 27.72) vs. $BPRS_{T12}$ (42.08 ± 15.38).
Data are expressed as mean ± SD: *p < 0.0001, t = 6.66, df = 24 (t-test); **p < 0.0001, t = 6.63, df = 24 (t-test).

The score of GAF scale at the beginning of treatment GAF_{T0} and at the 6th month of treatment GAF_{T6} and at the 12th month of treatment GAF_{T12}.
GAF_{T0} (42.28 ± 18.82) vs. GAF_{T6} (64 ± 15.75); GAF_{T0} (42.28 ± 18.82) vs. GAF_{T12} (66.76 ± 14.26).
Data are expressed as mean ± SD: ♦p < 0.0001, t = 9.15, df = 24 (t-test): ♦♦p < 0.0001, t = 6.44, df = 24 (t-test).

The score of CGI-S scale at the beginning of treatment CGI-S_{T0} and at the 6th month of treatment CGI-S_{T6} and at the 12th month of treatment CGI-S_{T12}.
CGI-S_{T0} (5 ± 2.70) vs. CGI-S_{T6} (3.2 ± 1.26); CGI-S_{T0} (5 ± 2.70) vs. CGI-S_{T12} (3.44 ± 1.00).
Data are expressed as mean ± SD: §p < 0.0001, t = 7.15, df = 24 (t-test); §§p < 0.0001, t = 6.03, df = 24 (t-test).

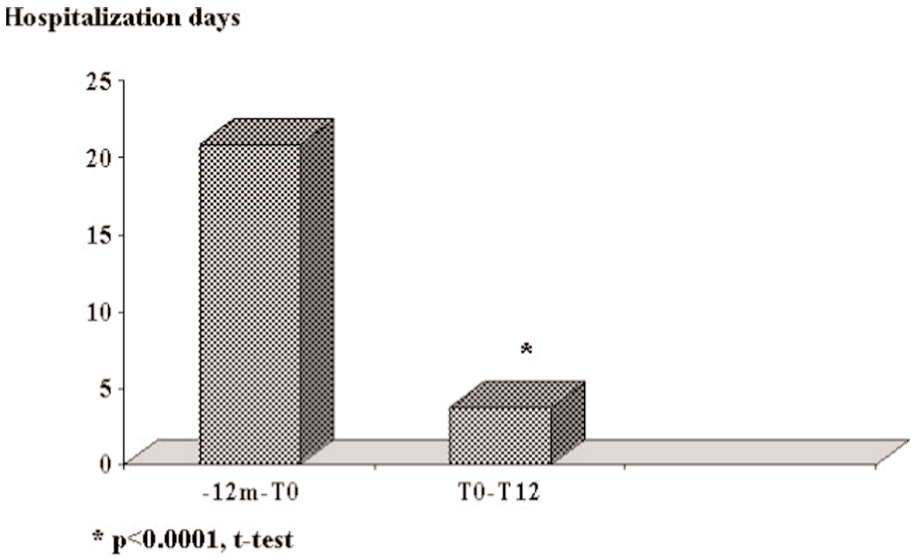
The following items of BPRS both at the 6th (T6) and 12th (T12) month showed a statistically significant difference from the initial scores (T0): Anxiety, Depression, Hostility, Hallucinations, Disorientation, Conceptual disorganisation, Blunted affect, Motor retardation, Tension, Distractibility, Motor hyperactivity ($p < 0.001$, t-test). Only two items of BPRS, Elevated affect and Suspiciousness, showed a statistically significant difference at T12 but not at T6 from the initial score (T0).

The relevant adverse effects were exclusively represented by sedation (4%), weight increase (4%), orthostatic hypotension (8%) and EPS (4%), which required a supplementary therapy (benzodiazepines or promethazine or anticholinergic drugs) in 4% of cases at T6 and 8% at T12, but not the discontinuation of treatment.

The hospitalization days of patients treated with LAIR were statistically significant reduced during the 1-year long-acting injectable risperidone treatment in comparison to the previous year ones of the same patients [hospitalization days T0–T12 (20.76 ± 38.48) vs. hospitalization days −12m–T0 (3.84 ± 9.55), $t = 2.2$, $p < 0.0001$, $df = 24$, (t-test)] (Fig. 2).

FIGURE 2

HOSPITALIZATION DAYS DURING THE 1-YEAR LAIR TREATMENT (T0-T12) IN COMPARISON TO THE PREVIOUS YEAR ONES OF THE SAME PATIENTS (-12M–T0)



Hospitalization days during the 1-year LAIR treatment (T0-T12) in comparison to the previous year ones of the same patients (−12m–T0).
Hospitalization days (T0-T12) (20.76 ± 38.48) vs. hospitalization days (−12m–T0) (3.84 ± 9.55)
*$p < 0.0001$, $t = 2.2$, $df = 24$ (t-test).

DISCUSSION

The present data suggest that long-acting injectable risperidone may be safe and effective for long-term 1-year treatment of outpatients affected by Schizophrenia and other Psychotic Disorders, also in a severe and chronic ill population as suggested by our sample.

More than 50% of our patients showed an improvement just after 6 months which persisted up to 12 months of LAIR treatment, as evidenced by the statistically significant score change in the three evaluation scales.

The improvement of psychotic symptoms with LAIR treatment, shown by the statistically significant score change at T6 and at T12, concerned the following BPRS items: Hallucinations and Suspiciousness for positive symptoms, Blunted Affect for negative symptoms and Conceptual Disorganisation for disorganized symptoms, according to the three fundamental areas of DSM-IV diagnostic criteria, which have to be assessed in order to define the clinical remission in Schizophrenia, as indicated by Schizophrenia Working Group of Andreasen et al.[45] The depressive and anxious symptoms of our sample ameliorated as suggested by the statistically significant score change of the following items of BPRS at T6 and T12: Anxiety, Depression, Tension. Also Elevated Mood appeared improved at the end of the observation period (12th month), so to hypothesize that LAIR might have a sort of stabilizing effect in long-term treatment, as indicated by the pivotal studies on Bipolar Disorders.[46–47] Besides, the improvement of Hostility, Disorientation and Distractibility, both at T6 and T12, could suggest that LAIR treatment exerted a positive influence on the therapeutic compliance and cognitive functions of our patients, as observed by other studies.[33,35–36,48]

In our study, the improvement of psychotic symptoms was always associated with a concomitant better functioning as indicated by the statistically significant change in GAF scores at T6 and T12, in accordance with data of other studies which put in evidence that the quality of life of psychotic patients treated with LAIR improved due to restored functioning.[32–48]

The efficacy of LAIR treatment on all these areas could explain the low frequency of readmission observed in our outpatient sample: the days of hospitalization during the 1-year LAIR treatment were statistically significant reduced in comparison to the admission days reported by the same patients in the previous year (although the validity of statistical inference was reduced by the high value of Standard Deviation of our data). This data might indicate a positive action of LAIR on preventing relapse and cognitive impairment, as suggested by some

Authors.[19,49–51] Besides, it supported the observation about the lowering of the cost of mental health resources by means of reducing hospitalizations during LAIR treatment.[52–55]

The relevant side effects of LAIR treatment consisted of sedation, weight increase, orthostatic hypotension and EPS, according to the pharmacologic profile of risperidone, which mildly affected only few patients who completed the 1-year treatment without discontinuation.

In our sample the improvement was just obtained after 6-month LAIR treatment and persisted up to the 12th month. Other studies evidenced that symptom and functioning improvement could be observed after 6-month long-acting antipsychotic therapies,[56] as well as early discontinuation of antipsychotic depot, caused by many different reasons (drug effectiveness, injection intervals, non-adherence to treatment, staff service organization, etc.),[57] was quite common during the first six months of treatment. In our sample, all drop out cases interrupted the treatment before the 6th month of LAIR treatment, mainly due to absence of compliance. The other causes (EPS and sexual impotence) of the LAIR treatment discontinuation were similar to those reported in other studies.[58–61] Our sample drop-out rate (23%) was inferior to that one found in randomized controlled trials with LAIR (51%)[58] or typical antipsychotic depot, which ranged from 19% over 24 weeks to 50.5% at 52 weeks.[12]

Our data, limited by the small sample and the naturalistic methodology without a placebo or an active comparator drug group, does not permit to draw definitive conclusions. This small study represents the real use of new formulation drug inside a Mental Health Service: a prudent prescription (the mean dose was far from the maximum dose permitted) in the most resistant and severe cases, with long illness period and high rate of previous hospitalizations, who can be representative of the population of a psychiatric service.

In order to better identify therapeutic advantages and risks of this new formulation drug, further studies and clinical experience are necessary.

CONCLUSIONS

According to literature data,[62] our data suggest that this new formulation drug may be an appropriate therapy for 1-year treatment of outpatients affected by Schizophrenia and other psychotic disorders, since it showed:

- good efficacy on positive, negative, disorganized and affective symptoms of Schizophrenia and other Psychotic disorders

- reduced hospitalizations
- improved functioning also in severe and chronic patients
- few and mild adverse effects
- persisted effectiveness from the 6th up to the 12th month of treatment.

Nevertheless, we have to put in evidence that the effectiveness of a long-acting atypical antipsychotic drug must be evaluated for a longer period than 1 year, since many side effects, as weight gain and metabolic syndrome, and preventive effect on relapse and functioning deterioration may develop over many years of continuous treatment. ✤

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