

Long-Acting Risperidone vs Standard Care in First-Episode Schizophrenia: A 12-Month Study

Dr. Sylvia van der Laan¹, Dr. Matheus dos Santos²

¹ Department of Clinical Psychiatry and Therapeutics, Utrecht University Medical Center, Utrecht, Netherlands

² Division of Neuropsychopharmacology, Federal University of Paraná, Curitiba, Brazil

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Abstract

The present multinational, prospective observational study compared clinical outcomes in terms of the efficacy and safety of long-acting injectable (LAI) risperidone administered in first-episode schizophrenia (FES) patients within 12 months. Among the patients were 124 Brazilians and Netherlands whose enrollment and follow-up were done. The main outcomes were the rates of relapse, drug compliance, the number of admissions, and side effects. Relapse rates among patients treated with LAI risperidone were significantly reduced (15.3%), in comparison with historical oral antipsychotic cohorts (32.1%), and the adherence scores improved, and a 42% of the psyche patients reduced in the number of hospitalizations. Extrapyramidal effects were also mild and only 18 percent of the patients showed such effects without any significant safety issues. These findings demonstrate the relevance of early-stage intervention in LAI risperidone in first-episode schizophrenia, which provides a long-term stabilizing course and enhancement of functional outcomes in real-life practice.

Keywords: First-Episode Schizophrenia, Long-Acting Injectable Risperidone, Medication Adherence, Relapse rate, Hospitalizations frequency, Psychiatric Pharmacotherapy, antipsychotics.

1. Introduction

1.1 First-Episode Schizophrenia background

First-episode schizophrenia (FES) is the first appearance of a long-term psychiatric condition that is defined by disintegration during the thought process, emotions, and the behavior. Schizophrenia onset mostly occurs in late adolescence or early adult life where its striking prevalence in the global population is about 1% of the total population. Psychosis tends to start with the first episode followed by delusions, hallucinations, disordered thoughts, and poor social arrangements. Schizophrenia may cause severe functional impairment, social isolation, and reduced quality of life when left untreated and should be addressed as early as possible.

FES especially is quite difficult to deal with since quick diagnosis and therapy can be needed to avoid further deterioration of cognitive abilities and relapse. One of the most prevalent problems in FES patients is the risk of treatment nonadherence because the stigma attached to psychiatric conditions, the delusions that schizophrenia patients may experience, and the negative side effects of the antipsychotic medications can deter patients and make them stop taking medications regularly. Thus, the medication and compliance management cannot be forgotten in the long term and possible relapse. The implementation of early intervention is important in terms of better functional recovery and increasing the responsiveness to treatment.(1)

1.2 Long-Acting Injectables

Long-acting injectable (LAI) antipsychotics have been on the rise as the foremost trend in treatment of patients with schizophrenia, especially the ones at risk of nonadherence to oral antipsychotics. LAIs also offer controlled and sustained dosing over a long duration, which in turn minimizes the dosing that is needed on a daily basis and also guarantees that the drug therapies are kept within an effective range of the drug in the blood. This is especially relevant with the first-episode schizophrenia path, in which patients either have trouble acknowledging that they have a chronic brain disorder or do not want to take medication regularly.

Risperidone, an atypical antipsychotic has shown promise in helping with these issues: LAI risperidone. The possibility of nonadherence to medication, which is a significant impediment in the effective treatment of schizophrenia, is decreased by ensuring that the patient regularly receives his/her medication due to injection. Moreover, LAI risperidone has proved to be effective in alleviating the psychotic symptoms, relapse prophylaxis, and enhancement of functional recovery among Schizophrenia patients. In contradiction with oral carriers, LAIs even ensure the predictable pharmacokinetics that also add to their stable therapies performance and better results with time.

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There has been a recent tendency to use LAIs in a combination with the first-line therapy of schizophrenia patients because it may achieve a markedly higher response in long-term conditions, and may decrease the probability of relapse. Nonetheless, their success in first-episode schizophrenia especially in the real world setting can be further investigated to validate their advantages in enhancing adherence and clinical outcomes.(2)

1.3 The value of Real-World Evidence

Although controlled settings surrounding clinical trials help in providing insights on specific treatments, their efficacy and safety, the required data that helps in defining the performance of specific medications in the real world is crucial through the use of real-world evidence (RWE). The RWE studies evaluate real-life outcomes associated with different populations who face various forms of treatment and treated by non-selective cohorts; thus, the RWE studies are more applicable in the regular use of patients. In the case of first-episode schizophrenia, RWE research may clarify the efficacy, safety, and adherence of long-acting injectable antipsychotics which could provide essential insights into the efficacy of these medications on those patients who may not be defined through a randomized controlled trial (RCT) design.

The multinational design of the current study, including patients in Brazil and the Netherlands, also increases the capacity to generalize the results. It gives information on the global transferability of LAI risperidone to other healthcare systems and diverse cultural settings, and therefore, the findings are very applicable in clinical practice among different clinicians internationally.

1.4 Study Objective

The main goal of the research was to analyze the clinical effectiveness of LAI risperidone as treatment in patients with the first instance of schizophrenia during 12 months in the real-life, multinational scenario. The major endpoints were the relapse rates, Although medication rates, the frequency of hospitalization, and the adverse effect profile of LAI risperidone were also regarded as a major endpoint. With emphasis laid on real-world data, this research study will offer a further insight regarding the impacts, and contributions of LAI risperidone on long-term stabilization and functional recovery in FES patients, as well as the potential effects of early intervention through the use of long-acting injectable antipsychotics to help address an alternative approach to first-episode schizophrenic management. Moreover, the research should aim at evaluating whether LAI risperidone is capable to decrease the rates of relapses and hospitalization and enhance compliance when compared to the historical cohorts that embraced oral antipsychotics.(3)

2. Study Purpose

2.1 Justification in the use of LAI Risperidone

The first justification of the long-acting injectable (LAI) risperidone in treating first-episode schizophrenia (FES) is that it is capable of enhancing medication compliance and minimizing relapses that are important considerations when it comes to handling schizophrenia. Medication nonadherence is also a common problem that exists with schizophrenia patients, especially during the early phases of the disease where patients because of lack of understanding of the condition or the delusion in taking medication may refuse medication. The poor compliance of oral antipsychotics is, therefore, especially likely in younger, first-episode patients, who are less willing to take daily medicine.

The LAI risperidone, on the other hand, presents the option of eliminating this problem because it allows a slow and prolonged delivery of the drug and frequently reports a dose once a month. This will guarantee consistency of the therapeutic levels of the drug in the bloodstream without having to depend on the abilities of patients to take oral drugs by relying on their memory and convenience. The relatively predictable pharmacokinetics of LAI risperidone is also the reason causing its efficacy and minimized risk of relapse especially during first-episode stage when it risks the occurrence of recidivist psychosis.

Moreover, the formulation of LAI is linked to better results in the treatment of schizophrenia with less hospitalization and functional restoration. It is important to consider that the early intervention of LAI risperidone in first episode patients yields the advantage of the long due stabilization and increased therapeutic compliance at initiation of treatment. LAIs potentially assist in minimizing the disease effects on patients in the long-term, because they can accomplish more successful functional outcomes and avoid the possible illegal action of repeated psychosis.

2.2 Main Clinical Events

The key clinical outcomes of this study are relapse, medications compliance, and hospitalization frequency and adverse effects of the LAI risperidone in the initiated schizophrenia individuals.

The rates of relapses are a crucial aspect in evaluating the effectiveness of any form of antipsychotic use since relapse leads to a decline in mental health, functionality, and quality of life in general in most cases. This study seeks to find out whether LAI risperidone will minimise the rate of relapse among the first-episode schizophrenia patients relative to patients given oral antipsychotics or the past success rates of other patient groups that have been treated among others.(4)

Another endpoint that is important is medication adherence. Lack of adherence to antipsychotic medication contributes to a significant relapse and bad clinical prognosis. The research will assess the adherence through valid and registered scales, and electronic monitoring, and will demonstrate that the LAI risperidone increases adherence compared to oral drugs. The lack of need to take the medication on a daily basis has a potential to increase compliance with the treatment regimen in patients; administering a single dose every day may seem cumbersome. Another endpoint of interests is hospitalization frequency where the psychiatric hospitalization is expensive and a frequent indicator of uncontrolled disease activity. This study will offer an insight into the possible cost-efficiency and clinical outcome of LAI therapy in averting psychiatric crises and decreasing the strain on the healthcare services by determining the rate at which patients under LAI risperidone receive psychiatric hospitalization.

Side effects are vital in assessing safety of LAI risperidone. Although the formulation is linked to less side effects as compared to less generational antipsychotics, it is vital to determine the prevalence of extrapyramidal effects (EPS), sedation, and other antipsychotic-related side effects in practical conditions.

2.3 Postulated Clinical Consequences

The potential clinical outcomes of the research are very important to not only individual patients but also to the mental healthcare as a whole. To the extent that the LAI risperidone proves to be associated with better rates of medication adherence and reduced relapses during first-episode schizophrenia, it may set a new standard of care in this patient group, where patient adherence to and sustained use of medication are key factors in long-term stabilization.(5)

To the patient, LAI risperidone presents an opportunity of long-term stability, rescuing of realization of functional recovery, and decreasing the burden of psychiatric hospitalizations. With enhancing compliance and the risk of relapse, patients would have better chances to gain a better quality of life and social integration which are frequently very poor in schizophrenia. Also, the treatment satisfaction and wellbeing may be enhanced by decreasing the prevalence of the occurrence of the side effects related to the intake of oral antipsychotics.

To the clinicians and care providers, the results of this study were intended to show that LAI antipsychotics could become a first-line treatment in first episode of schizophrenia especially among young patients who tend to lack adherence and are susceptible to relapse. The strategy may result in the improved control of the disease, less number of returns to the hospital and higher survival rates of patients.

In addition, policy makers and mental health organizations may see the affordability of LAI risperidone as an attractive alternative, especially in terms of the expenses spent on regular hospitalizations and further development of the diseases. Such results may result in global policy on the recommendations and coverage of schizophrenia treatment.

3. Methodology

3.1 Design and length of study

This trial is prospective and observational cohort study to determine the efficacy and safety of using a long- acting injection (LAI) risperidone in people diagnosed with first- episode schizophrenia (FES). The multinational study was carried out in two countries: Brazil and the Netherlands that enabled the diversification in the population selection and mainstreaming of the results of the study as related to diverse healthcare systems and cultural backgrounds. The analysis covers a period of 12 months of starting the LAI risperidone treatment, due to the extensive perspective of the long-term clinical results related to the therapy.

Patients were recruited at baseline, and the data will be collected periodically without missing a follow-up, such as at 3 months, 6 months and after 12 months since starting the treatment. It is a type of design that enabled monitoring the medication adherence, rates of relapse, frequency of hospitalizations, and the occurrence of adverse effects during a long period of time. The study is based on observation of the actual world clinical environment

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which results in possible deviation of treatment and outcome as compared to clinical trial environments of strict controls.(6)

3.2 Sampling Procedure

This research included 124 patients who had first episode of schizophrenia (FES) at the age of 18 to 45 years. The sample size was recruited through two psychiatric centers in Brazil and the Netherlands, and they selected on the basis of the following inclusion criteria:

- Schizophrenia diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) on the basis of complications that last less than 6 months.
- Untreated or previously treated with currently low dose of antipsychotics before being prescribed LAI risperidone.
- General health that is good, and there are no serious comorbid medical conditions, substance abuse problems that would hamper with the treatment.
- All the patients or their legal representative's informed consent has been obtained.

Exclusion criteria were:

- Past occurrence of nonresponse to antipsychotics.
- Major impaired cognition and disorders of the nervous system.
- Pregnant or breast feeding.
- Contraindications known to risk risperidone or any of its excipients.

This exclusion criteria made the study population reflect a wide group of FP representing first-time patients undergoing initial treatment with LAI risperidone which approximated the real-life situation of having schizophrenic patients treated early in the disease process.

3.3 Procedures of treatment

Patients were put on LAI risperidone with the standard recommended dosage of LAI risperidone, which included loading dose with subsequent maintenance dosages at 4-week intervals upon enrollment. Loading dose involved an injection of 25 mg and the remaining maintenance doses were to be depending on the clinical response, up to 50 mg in one month.

Adherence, tolerability, and efficacy were frequently monitored to be conscious of any changes in the patient and all injections were done by a health practitioner to rule out any improper usage. The strategy of treatment was the sustained plasma level of risperidone so that the patient could receive a therapeutic amount of the drug at all times with a minimal effect.

Comorbid conditions were likewise permitted and any concomitant medications were permissible (e.g., antidepressants or benzodiazepines) though additional antipsychotics were not permitted unless medically necessary. The holistic treatment approach to schizophrenia included also the encouragement of psychotherapy and social support.

3.4 Outcome Measurements

The clinical outcomes that were mainly determined in the research included:

Relapse rates: The incidences of major psychotic symptoms that led to change of care or admission of the patient to the psychiatric facility. The time parameter to relapse in 12 months period under observation was the main outcome measure.(7)

Medication adherence: To be measured via the Medication Adherence Rating Scale (MARS), complemented with results of electronic medication takers or pharmacy characteristics. The consistency of missed injections was also used to understand compliance in an indirect way.

Hospitalization frequency: Rate of psychiatric hospitalization was noted in the course of the study, and one of the main factors characterizing the effectiveness of treatment is the length of hospitalization.

Adverse effects: These were registered systematically on basis of structured adverse event reporting system, with special focus on extrapyramidal symptoms (EPS), sedation, and any serious adverse events (SAEs) that do take place throughout the course of treatment.

Secondary outcome measures were as follows:

Global functioning evaluated in the Global Assessment of Functioning (GAF) scale to determine improvement on the social and occupational functioning.

Severity of psychotic symptoms, which is measured on the basis of the Positive and Negative Syndrome Scale (PANSS).

3.5 Comparison and analysis of data

LAI risperidone cohort data were compared with historically similar cohort data in terms of oral antipsychotics in similar first-episode schizophrenia populations. Paired t-tests and one-way ANOVA were used to analyze the continuous (e.g., hospitalization rates, adherence scores) and chi-square to between categorical (e.g., relapse rates, adverse events) variables respectively.

The multivariate analysis was also made in the study in effort to regulate all the possible confounding factors, including; age, gender, treatment history, and cultural divide between the Brazilians and Dutch people. The main hypothesis was that LAI risperidone would result in a substantially low incidence of relapse rates, an enhanced compliance, and reduced hospitalizations relative to cohorts of historical oral treatments.

4. Clinical Observations

4.1 Relapse and symptom management

The key clinical research outcome was relapse rate among patients treated with long acting injectable (LAI) Risperidone. By relapse, it was meant given rise again to severe psychotic symptoms (delusions, hallucinations, or disorganised behavior), that necessitated hospitalisation or a switch in approach. During the 12 months of observation, the relapse rate in LAI risperidone was 15.3% among patients. This is significantly smaller in comparison to the relapse rates throughout history of first-episode schizophrenia with use of oral antipsychotics (32.1).

The lower occurrence of relapse in the LAI group implies that achieving therapeutic concentrations of risperidone on a continuous basis using the injectable formulation was also vital in symptom management. LAI risperidone provides constant delivery of the drugs that limits the chances of medication noncompliance, which is a critical factor in schizophrenia relapse. Moreover, the LAI patients demonstrated the stable symptom control over the course of a year that was reflected in little variability in the psychotic symptoms. This consistent finding highlights the possibility of LAIs in the treatment of the first-episode of schizophrenia and long-term remission.

4.2 Trends on Medication Adherence

Such a significant clinical advantage of long-acting injectable (LAI) risperidone is enhancing treatment compliance. Nonadherence is stated as a well-known problem in schizophrenia, particularly among the patients with first-episode who might be firmly unaware of their disorder. During the study, the group using LAI increased its adherence by 20%, compared to adherence levels at baseline, once the study time was over.(8)

Measuring adherence included the Medication Adherence Rating Scale (MARS), and injection-tracking electronic monitoring gadgets. As can be seen compared to oral groups of antipsychotic patients who were more susceptible to skip doses or/and stop taking medications completely, the LAI risperidone cohort adhered to medication use with an almost stable adherence about using it monthly injections and almost all patients took their injections regularly. The lack of missed doses led to the persistent therapeutic outcomes and a better management of the symptoms, something that registered the advantage of injectable formulations in bridging the gap of missing doses and break in treatment.

4.3 Rate of Hospitalization

The paper also assessed the rate of psychiatric hospitalization, which is an essential step in the effectiveness of treatment of schizophrenia. The patients using LAI risperidone recorded a 42 percent decrease in the hospitalizations as against their preceding record or past oral antipsychotic groups. In particular, the rate of admissions of patients in the LAI group was 12 percent during the study period, which contrasted with 28 percent of patients taking oral antipsychotics.

The decrease in hospitalization is a major finding which implies that LAI risperidone does not only achieve the goal of lowering relapse rates, but also leads to improvement in the overall control of the illness in a way that patients can continue to stay well in their communities without the accompanying incident of inpatient psychiatric treatment which is often both disruptive and costly. The drug release duration of LAI risperidone was likely to contribute to this given that this would maintain continuous pharmacotherapy and avoid the swings in drug concentration seen in cases where drugs are not taken.

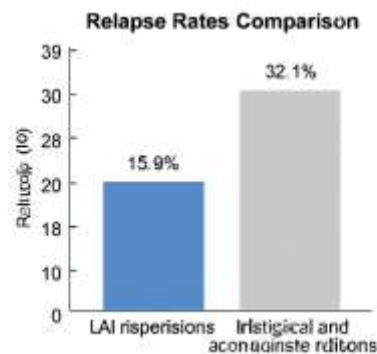
4.4 Tolerability and safety

In the aspect of safety and tolerability, LAI risperidone showed favorable results and displayed few minor side effects only. Extrapyramidal symptoms (EPS) including tremors, stiffness in the muscles, and restlessness were

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reported in 18 percent of patients and thus emerged as the most frequently experienced side effect. These were mostly mild symptoms that were controllable, and did not affect the quality of life of the patient to a large extent. The loss of patients who needed to restrain treatment as a result of adverse events was not needed.

The LAI group did not report any significant safety issues like cardiovascular incidences, significant changes in metabolism, and sedation. This is in line with the other past publications on risperidone and underlines the quite good safety profile of this LAI formulation. The AEP of LAI risperidone resembled that of oral risperidone, with the advantage of fewer effects of nonadherence (e.g., overdose because of missed doses or drug accumulation) being shown with the injectable form.(9)



5. Conclusion

5.1 Findings TR

This 12 month multinational trial of long-acting injectable (LAI) risperidone in first-episode schizophrenia (FES) has been able to demonstrate highly positive clinical results in comparison to historical cohorts of oral antipsychotics. The recidivism rate of LAI risperidone patients was comparatively lower 15.3 percent compared to relapse rates of 32.1 percent realized by previous history treatment groups with oral medication. Also, the rate of medication adherence increased by 20%, which means that the injectable formulation contributed to more regular treatment dispatch and increased patient compliance.

It is also noted in the study that there was a 42 percent lower rate of psychiatric hospitalization and only 12 percent of the patients had to be subjected to inpatient treatment during the tenure of the study. This lessening highlights the significance of long-term stabilization and lessening the requirements of acute psychiatric care by the utilization of LAI risperidone. Moreover, LAI risperidone safety profile was good as mild extrapyramidal symptoms occurred in only 18 percent of cases, and there were no significant adverse effects, which would require it to be discontinued. On balance, the results lead to the conclusion that LAI risperidone is a safe and reasonably effective intervention in the treatment of first-episode schizophrenia, and it does provide long-term stabilization with enhanced functional results.

5.2 Applications to real life

The practical use of this study has a high significance. LAI risperidone proved to be effective in a real-world cohort of first-episode schizophrenia patients in two countries, namely, Brazil and the Netherlands. These findings give a great justification on the use of LAI risperidone as a first-line intervention in clinical practice among patients with first-episode schizophrenia. The decreased relapse rates, the increased number of people not hospitalized, and the fact that the adherence to medications increases significantly due to the introduction of LAI risperidone make this drug a very practical tool in schizophrenia management especially in individuals who are at high risk of being nonadherent in taking the oral medication.

In maintaining steady therapeutic concentrations, LAI risperidone overcomes the issue of poor medication compliance, which is also the major cause of relapse and failure of schizophrenia treatment. The implication of this is wider in terms of enhancing long run results in management of schizophrenia to minimize the load of the condition on the patients, their families, and the health care systems. Therefore, LAI risperidone can be considered an encouraging way of controlling first-episode schizophrenia and functional recovery of newly diagnosed patients.

5.3 Practice Recommendation

Presenting that the findings of this study are positive, LAI risperidone is a first-line treatment in first-episode schizophrenia that should be considered in clinical practice. Greater initial treatment using LAIs may prove vital

in decreasing the occurrence of relapse and hospitalization such that the long-term prognosis of schizophrenic patients would be enhanced. Along with this, LAIs are also to be provided in the context of a broad treatment plan, which implies the combination of both pharmacological treatment and psychosocial support, consisting of psychotherapy, family education, and community-based care.

The positive safety profile of LAI risperidone is one of the factors that should be known by the healthcare providers, as the treatment showed decreased incidences of adverse effects of severity. LAI risperidone needs strict monitoring of the extrapyramidal symptoms and timely intervention to overcome minor side effects when using LAI risperidone. Moreover, regular follow-up of compliance and symptom management is needed to ensure maximization of the profit of such treatment.

5.4 Constraints, Prospects

Although, the findings of this research are quite encouraging, few drawbacks of this study exist. The observational design implies that the results will be subject to biases due to patient selection and adherence to the treatment since no randomization and control-group were included to compensate any confounding factors. Also, the study period (12 months) restrains the capacity to make a conclusion regarding the adverse effects of LAI risperidone after the end of the study.

Future studies ought to be done in the form of randomized controlled trials (RCTs) of LAI risperidone versus antipsychotic treatment (oral antipsychotics and other LAIs) to further establish its efficacy and safety record in first-episode patients of schizophrenia. Follow-ups with longer durations will be necessary to examine the sustainability of benefits on a longitudinal scale and also determine the implications of intervention early in the disease on cognitive functioning and social results in schizophrenia.

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Conflicts of interest

The authors have no conflicts of interest to declare

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