



Review Article

# Observational Study of Long Acting Antipsychotic Prescription Patterns in Ourense Region, Spain (314,853 Inhabitants)

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**Citation:** Campos JA, Docasar L, Dominguez M, Grandio L (2022) Observational Study of Long Acting Antipsychotic Prescription Patterns in Ourense Region, Spain (314,853 Inhabitants). Ann Case Report 7: 805. DOI: 10.29011/2574-7754.100805

**Received:** 22 March 2022; **Accepted:** 26 March 2022; **Published:** 29 March 2022

## Abstract

**Introduction:** Estimate the percentage of patients on antipsychotic monotherapy with long-term injectables, and determine if, after starting with LAIs, there was a reduction in the number of visits to the emergency department, as well as hospital admissions, measured during the previous 12 months. At the beginning with LAIs, and the following 12 months to know the impact of its use on the Ourense EOXI (314,853 inhabitants).

**Material and methods:** This is an observational study with medications, in which all patients who started treatment with LAIs, from January 1, 2005, until December 31, 2015, were collected retrospectively in the Ourense health area; hospital admissions and emergency department visits were studied in the year before and after starting the injections.

**Results:** The sample is made up of 457 patients of which 285 (62.4%) are men, and 172 are women (38%). Admissions and visits to the emergency department were statistically significantly reduced after 12 months of LAI treatment ( $p < 0.001$ ). The percentage of patients on absolute monotherapy was 12.3%, while the percentage of patients on antipsychotic monotherapy was 42.2%.

**Conclusions:** Our data confirm that LAI treatment has been effective in most of the study's patients.

**Keywords:** LAIs: Long-Acting Injectables; Schizophrenia; Antipsychotics

## Introduction

Schizophrenia is a chronic and disabling disease, where the majority of patients experience multiple relapses during the course of the disease [1,2]. Relapse, characterized by an acute psychotic exacerbation, can have serious implications. For example, there is a risk that patients will harm themselves or others, jeopardize personal relationships, their educations or work situations [3], causing greater stigmatization of the disease. Also, relapse may have a biological risk. It has been argued that active psychosis

reflects a period of disease progression, since patients may not return to their previous level of functioning, and resistance to treatment may appear [4-6]. In a prospective 5-year follow-up of patients with a first psychotic episode, it was found that the most frequent risk factor for relapse was the suspension of antipsychotic medication [1], a very frequent occurrence during the early stages of the disease [7-10]. Improving medication adherence, and preventing relapse, are key in managing schizophrenia. Antipsychotics are the main treatment for schizophrenia, since they have been shown in clinical trials and routine practice to decrease symptoms in the acute phase and prevent new outbreaks in the long term. Injectable antipsychotics, currently known as

LAI (long-acting antipsychotic injectables), are medications that are released progressively in the body so that they work for days, weeks and months, and not just hours, as happens with classic oral medications. Although they existed decades ago (they first began to be used in the 1960s), the current ones have little to do with the initial drugs, which were only used to treat very serious cases that were reluctant to respond to conventional treatment. The first injectables were highly sedating drugs that, although they ended the symptoms, also reduced the intellectual and creative capacity of the person to whom they were administered. These drugs are no longer in use, and have given way to another type of drug: the new generation LAIs. LAIs were developed several decades ago as a strategy to address partial or covert non-adherence, and to simplify schedule timelines. More recently, second generation antipsychotics (SGAs) have also been made available as LAIs expanding the therapeutic options [11,12]. In clinical practice, LAIs are prescribed to a low percentage of patients, and in an even smaller proportion to patients upon their first episodes [13-17].

### Justification

Despite the fact that every day more patients are treated with LAIs, we do not understand their adherence as a treatment, their effectiveness, the most common side effects that these drugs cause in the patient, and even the rate of patients who decide to abandon the treatment and the causes of discontinuation [18]. There is sufficient evidence on the progression of schizophrenic disease after successive relapses, and a better therapeutic response after the first episode, than in subsequent ones. In 7-year follow-up studies, up to 80% of patients affected by deterioration are observed, which is correlated with a greater number of episodes [19]. When the follow-up reaches 15 years, 1 in 6 patients does not obtain remission after a new episode [20]. For authors such as Lieberman, the time to response increases after each episode [21]. Difficulties in identifying the risk of relapse [22], ineffectiveness of rescue medications when it occurs, lack of adherence, and discontinuation of treatment [23], all have potentially serious consequences, not only objectifiable in the clinic and imaging tests [24-27], but also in the functionality of the patient [28]. Of all these consequences, the loss of functionality “in the real world” and autonomy are the ones that have the greatest impact on the patient’s day-to-day life. Understanding functionality in the real world, that which allows having a “projected life” appropriate to their circumstances, sufficient autonomy not to depend on caregivers [29-31], and minimal social relationships, are often completely absent [32-34].

### Objectives

- Estimate the percentage of patients in antipsychotic monotherapy with long-term injectables (the use of benzodiazepines, and concomitant biperiden.)

- To determine if, after starting with LAIs, there was a reduction in the number of visits to the emergency department, as well as in hospital admissions, measured during the 12 months prior to starting with LAIs, and the 12 months afterward.
- Analyze the dropout rate and withdrawals from LAIs.
- Study the variables that are associated with abandonment of treatment.
- To determine the sociodemographic characteristics, and the consumption of toxics, in patients with injectables.

### Material and methods

This is an observational study with medications, in which all patients who started treatment with LAIs, from January 1, 2005, until December 31, 2015, were collected retrospectively in the Ourense health area; hospital admissions and emergency department visits were studied in the year before and after starting the injection. The characteristics of the patients were analyzed, including the diagnostic variables, concomitant treatments, the addictive profile of narcotic substances, and the number of withdrawals, and their causes, as well as the side effects. A database and a form were created, and the descriptive analysis was subsequently carried out, comparing data on admissions and visits to the emergency department, before and after treatment with LAIs.

### Inclusion criteria

Patients with a diagnosis of schizophrenia, who started treatment with LAIs after medical prescription by one of the Specialist Physicians of the Psychiatric Service of the Ourense Health Area, in the period from January 1, 2005 to December 31, 2015.

### Exclusion criteria

Individuals <18 years, pregnant patients, patients who started treatment with LAIs in another health area other than Ourense, or transferred to another health area after starting treatment, patients with LAIs diagnosed from another pathology, institutionalized patients, patients for whom there is no record of attendance in medical reviews / consultations in a primary hospital or emergency care in the 12 months prior to or after the start of treatment, patients who did not accept to enter the study after reading the informed consent, legally incapacitated patients, and whose caregivers do not accept that the patient participate in the study after reading the informed consent.

### Study variables

Variables are determined in the data collection form. This includes: sociodemographic data, type of LAI, diagnosis, substance dependence, concomitant oral treatment, emergency room visits,

psychiatric hospitalizations 12 months prior to the initiation of LAI, and 12 months after starting LAI, side effects, withdrawal of LAI and reason for ending treatment.

### Statistical analysis

Initially, we carried out a descriptive analysis, where the qualitative variables are expressed as frequency and percentage. Continuous variables are expressed as mean  $\pm$  standard deviation, median [minimum-maximum]. To know the normality of the variables, the Kolmogorov-Smirnov / Shapiro-Wilk tests are applied. Parametric / non-parametric tests were performed to determine the potential association between the study variables (Chi-Square, T-Student, Mann-Whitney U). Using tests for paired samples, the number of admissions and emergency care in the last 12 months before and after the administration of LAIs are compared. In all analyses, differences with  $p < 0.05$  are considered statistically significant. Analyses will be performed using SPSS 15.0, Epidat 4.1, and free software R (<http://www.r-project.org>) –librarysurvival, librarysmoothHR.

### Ethical aspects

The study was carried out with respect to national and European regulations regarding clinical research, and following international ethical recommendations for research, which will respect the fundamental principles established in the Declaration of Helsinki and in the Council of Europe Convention Regarding Human Rights and Biomedicine. Both the management of the data

collected, and the management of medical records will comply at all times with the requirements of the Organic Law on Data Protection.

### Results

The sample is made up of 457 patients of which 285 (62.4%) are men, and 172 are women (38%). The total results of the study are shown below, graphically presenting the distribution by type of LAI (Table 1), Admissions and visits to the emergency department 12 months before and after treatment with LAI are shown in Table 2. A significant decrease ( $p < 0.001$ ) was observed in the number of visits to the emergency department, admission to psychiatric units, and in the days of admission. There are 2 patients with long-term admission, one of 2 years and the other of 1 year. On the days of admission, the patients who are in medium and long-term psychiatric hospitalization were not taken into account, since they had already spent 365 days in hospital. The percentage of substance use is represented in Table 3. Which represents the number of patients and dependence according to the number of substances. The percentage of patients on absolute monotherapy was 12.3%, while the percentage of patients on antipsychotic monotherapy was 42.2%. The association of benzodiazepines occurred in 51.9% of patients, while the association of biperiden occurred in 24.7% of cases. 8.1% of patients had side effects from the use of LAI: 3.9% parkinsonism, 3.1% metabolic disturbances, 0.9% akathisia and 0.2% sedation. Treatment discontinuation occurred in 9.85% of patients. Table 4 details the reasons for discontinuation.

LAI	Dose	Number of patients	% from total
Paliperidone palmitate 1-monthly		299	65.43%
	50 mg	71	15.54%
	75 mg	50	10.94%
	100 mg	100	21.88%
	150 mg	78	17.07%
Aripiprazole 1-monthly		71	15.54%
	300 mg	19	4.16%
	400 mg	52	11.38%
Risperidone LAI		69	15.10%
	25 mg	11	2.41%
	37.5 mg	18	3.94%
	50 mg	40	8.75%
Olanzapine LAI	300 mg	2	0.44%
Zuclophentixol LAI	n/a	11	2.41%
fluphenazine LAI	n/a	3	0.66%
Paliperidone palmitate 3-monthly	n/a	2	0.44%

TOTAL		457	100%
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**Table 1:** Patients distribution.

	Media	SD	Median	Min	Max	p-value
Emergency room visits 12 Months Pre-LAI	0.6	1.12	0	0	8	
Emergency room visits 12 Months Post-LAI	0.29	1.18	0	0	20	<0.001
Psychiatric hospitalizations 12 Months Pre-LAI	0.51	0.88	0	0	6	
Psychiatric hospitalizations 12 Months Post-LAI	0.2	0.58	0	0	4	<0.001
Bed days 12 Months Pre-LAI	13.32	31.536	0	0	271	
Bed days 12 Months Post-LAI	3.76	16.619	0	0	209	<0.001

p- value Wilcoxon test.

**Table 2:** Emergency room visits, psychiatric hospitalizations and bed days: 12 months prior to the initiation of LAI, and 12 months after starting LAI.

Substance	Number of patients	Percentage
Cocaine	80	17.50%
Cannabis	66	14.40%
Opioids	44	9.60%
Alcohol	102	22.30%
Other substances	10	2.20%

**Table 3:** Substance abuse percentage.

	n	%
Total discontinuations	45	9.85%
Withdraw (patient decision)	25	5.47%
Adverse effects (medical reason)	7	1.53%
Lack of efficacy	2	0.44%
Other reasons	11	2.41%

**Table 4:** Treatment discontinuations.

## Discussion

This is a sufficiently representative study of the clinical care area (314,853 inhabitants), since there is no other 24-hour emergency facility or psychiatric hospitalization, in competition with the University Hospital of Ourense, at a private or public level. It includes acute, medium, long stay hospitalization units, day hospital, home hospitalization, mental health plus addictive behavioral units, and community care continuity teams. In addition, all the prescriptions for LAIS are dispensed from this location's pharmacy service. The prescription profile in the area would conform to the technical sheet, with no indications outside of psychosis being observed. And the higher rate of males is similar

to that reported by most authors [6]. The bibliography on LAIS prescription shows at least 5 large areas of consensus: 1) As a first step in the history of clinical indication, the improvement with oral atypical antipsychotics noted by comparison to conventional orals, mainly in terms of side effects and in negative symptoms [35-38]; 2) Evidence of improvement with use of LAIS oral treatments, especially in adherence, but also in other clinical aspects, when incorporating LAIS of atypical antipsychotics [39-48]. In the results of our study, we see the withdrawal of treatment does not reach percentages higher than 9.8%, - due to the patient's decision in 5.5% of cases, and only due to lack of efficacy in 0.4% cases. 3) There is later progress with the addition of monthly LAIS treatment including paliperidone palmitate and aripiprazole [48-52]; in our series, 65.43% of the patients received treatment with monthly paliperidone palmitate, 15.54%, aripiprazole, and 15.10% risperidone; with a total of more than 96% of prescriptions of LAIS for atypical neuroleptics; 4) This is the increasingly explored approach even among a patient's first episodes and young patients [53-57]; 5) And finally, as a consequence of all this, issues arise regarding the reduction of spending and increasing efficiency [58]. At present, this trend would continue with the quarterly and semi-annual LAIS treatment. In this sense, the results of our study show a significant decrease in emergency room care and psychiatric hospitalization. 35.2% of the patients made frequent visits to the emergency room in the year prior to the injection, and required hospital admission in 34.6%, and a drastic reduction was found, reducing to 15.8% and 13.6% respectively after the use of LAIS; findings superimposable to the Tiihonen study, in a retrospective of a cohort of 29,000 patients with schizophrenia [59]. It is significant that 21.9% of LAIS drugs administered from the addictive behaviors unit is in probable relation with the percentage of dual cases, which reaches as much as 60% of



patients with schizophrenia. A male, with dual pathology, would be one of the most frequent characteristics in the clinical profile of the LAI user. The consumption of narcotic substances, and concomitant medication, including eutimizers - which could fulfill other functions such as treatment for behavioral disturbances, in the case of those related to impulsivity, or craving problems - would both be predictors of greater LAI prescription in schizophrenia, among others [60]. Metabolic disturbances, together with parkinsonism, constitute the most frequent side effects, with 3.1% and 3.9% respectively. Finally, it should be noted that although so-called “mirror image studies”, such as this one, are considered methodologically appropriate to assess the comparative efficacy of antipsychotic formulations, the evidence from mirror image studies should also be interpreted with caution in view of the great methodological limitation constituted by the lack of control groups. And, in addition to the availability of these studies, more research is needed to compare the efficacy, tolerability, and safety of long-acting injectable antipsychotics to develop their risk-benefit profile. In addition, studies to confirm efficacy and safety in pediatric and geriatric patients with schizophrenia.

## Conclusions

There is growing scientific evidence on the efficiency of the use of LAIs, even in early stages of the schizophrenic spectrum, and that they coincide with the data of our study, mitigating the high individual and family cost (reduction of readmissions, visits to the emergency department and average stay), plus clinical status derived from relapses. Our data confirm that LAI treatment has been effective in most of the study patients. Only 2 treatments were withdrawn due to lack of efficacy (0.44%). A multicenter study would be beneficial, expanding the knowledge of the risk-benefits with LAIs.

## Acknowledgments

The authors would like to acknowledge the support of the Epidemiologist Department of the Instituto de Investigación Sanitaria Galicia Sur.

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