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Analysis of prescribing patterns in patients treated with long-acting antipsychotics in a Department of Mental Health: VIRAL project

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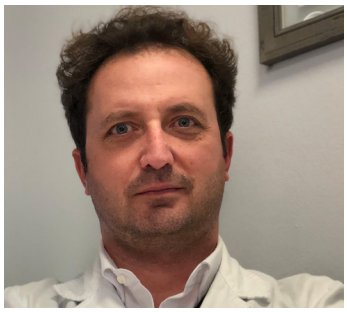

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Summary

Objectives. Despite poor adherence to antipsychotic medication leading to multiple relapse in patients with schizophrenia, LAI formulations of antipsychotic drugs remain an underutilized options. The purpose of this study is to analyze the prescription pattern of antipsychotic long acting in a department of mental health of Italy to allow clinicians to identify specificifiers for the different drugs use.

Methods. We used the electronic data from Mental Health Information System of the Puglia Region, Italy, and health care utilization from the Health Information System of the Puglia Region, Italy, to analyze 995 subjects with age ≥ 18 years and who received at least one administration of one of AP-LAI. The study was approved by the Ethics Committee of the Local Agency of Health of Lecce (VIRAL). We divided the total sample (995 subjects) in two groups: Second Generation Antipsychotics Long acting, (SGAs-L, n = 447) and First Generation Antipsychotics Long acting (FGAs-L, n = 548). We evaluated different clinical and demographic variables such as sex, age, main diagnosis, disease duration, presence of medical comorbidities, substance and/or alcohol problems.

Results. Our results showed an use of SGAs-L in younger people (age, 45.19 ± 11.69) with lower duration on illness (52.58 ± 12.25 ys) and with higher prevalence of substance and/or alcohol problems (15.2%). FGAs-L remained a more utilized option in the older patients (age, 52.58 ± 12.25 ys) in particular with schizophrenia (75.9%) or psychotic disorder otherwise specified (7,5%). The prescription pattern showed a specific indication for some SGAs-L: Aripiprazole for young (age, 40.29 ± 10.69), different diagnosis than schizophrenia (52.7%) women (57.0%), Paliperidone for young (age, 46.55 ± 11.83) schizophrenic (69.2%) man (67.6%) with high relative prevalence of medical comorbidity (15.9%), Olanzapine for patients with relative higher substance and/or alcohol problems (19.7%).

Conclusions. Age, sex, diagnosis and other clinical conditions can guide clinicians to use AP-LAI in different patients.

Key words: LAI antipsychotics, schizophrenia and related psychotic disorders, second generation antipsychotics, first generation antipsychotics, drug utilization

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Conflict of interest
The Authors declare no conflict of interest.

Introduction

Long acting injectable antipsychotics (AP-LAI) have always been one of the main therapeutic strategies in patients suffering from psychotic disorders with poor compliance with treatments. Adherence in subjects with schizophrenia is extremely low, with discontinuation rates of 74% in the first 18 months from the start of treatment [1,2] and, in subjects with the first episode, 42% at one year regardless of the treatment used, second or first generation antipsychotics [3]. The consequences of this condition are devastating with relapse rates in patients with the first episode, exceed 70% in the first 5 years [4].

The benefits of continued antipsychotic treatment for relapse prevention are well-known, such as reduction of risk of structural brain damage, treatment resistance and maintenance of social functioning [5,6]. The achievement of symptomatic remission for a period of at least 3 months in the first 2-5 years of the disease, defined as the critical period [6,7], is predictive for good personal and social functioning in the medium and long term [8].

Despite these evidence, long-acting antipsychotics continue to be an under-used option [8] with percentages of use varying on average between 10% and 25% [9,10]. The low percentage of use could lie in several factors including: a) the presence of non-univocal results deriving from the comparative studies with the relative oral formulations b) the absence of specific criteria that can guide the clinician in the choice of an LAI treatment [8-10]. The data from naturalistic studies show a significant advantage in favor of LAI antipsychotics over oral formulations in terms of reduction of the risk of relapses [11], on the other hand the data from randomized clinical trials (RCTs) do not always support this evidence [12].

The differences in these results could be linked with characteristics of the studies themselves. In controlled trials, the exclusion of subjects with usually considered associated with a high rate of non-adherence for the presence of medical comorbidities or substance abuse, would lead to not bringing out a clear difference between the different formulations. On the contrary, the inclusion of these subjects in naturalistic studies would bring an evident advantage in favor of LAI antipsychotics [13,14].

The absence of specific criteria could be barrier prevent their widespread adoption and the clinicians see this formulation reserved for patients with a long history of disease or relapses [8,15]. For the same reasons many clinicians believe that AP-LAIs should not be used until patients experience multiple relapses, are chronically ill, and/or overtly demonstrate nonadherence [16-19].

The objective of our study was to detect specific characteristics of use relative to the different long-acting antipsychotics of both first and second generation by analyzing the prescriptions of these drugs in a real-world setting.

Materials and methods

Study design

We conducted an observational, retrospective study in which all patients from the Mental Health Centers of the Mental Health Department of Lecce (13 centers for a general population of about 800,000 inhabitants on an area of 2,759 km^2) treated with AP-LAI from January, 1, 2016 to December, 31, 2017 (2 years), were enrolled.

The inclusion criteria were: a) age ≥ 18 years; b) at least one administration of one AP-LAI. The AP-LAI evaluated in this study were: fluphenazine decanoate (FLU), haloperidol decanoate (HAL), zuclopenthixol decanoate (ZUC), risperidone RP (RIS), olanzapine pamoate (OLZ), one month paliperidone palmitate (PP1), three month paliperidone palmitate (PP3), aripiprazole monohydrate (ARI). The observation nature of the study in a real-world setting did not provide for specific exclusion criteria (Fig. 1).

Prescription data were then linked, using civil registration numbers, to information on psychiatric diagnoses from the main data source of Mental Health Information System of the Puglia Region, Italy [20] and to information on health care utilization from the Health Information System of the Puglia Region, Italy [21].

The study, Valutation of Impact and Representation of Antipsychotics Long acting (VIRAL), program no. 108, was approved by the Ethics Committee of the Local Agency of Health of Lecce (Act 27, December, 13, 2018). All subjects included in the analysis signed regular informed consent for the use of their data in aggregate form for research purposes. This is an observational, retrospective study, it did not entail any additional risk to patients nor did it affect new prescriptions of any medication.

Sample and variables

The total sample (995 subjects) was divided in two groups according the class of AP-LAI: Second Generation Antipsychotics, (SGAs-L, n = 447), First Generation Antipsychotics (FGAs-L, n = 548) (Fig. 1). The main clinical-demographic characteristics were assessed: sex, age, main diagnosis, disease duration, presence of medical comorbidities, substance and/or alcohol problems. The medical comorbidities (n = 140, 14.17%) were: diabetes mellitus (n = 23), hypertension (n = 34), neurological disease (n = 15), thyroid dysfunction (n = 13), obesity (n = 11), metabolic syndrome (n = 17), hepatitis (n = 15), HIV (n = 2), Cancer (n = 3), kidney disease (n = 2), lung disease (n = 5).

The diagnoses were made according to the criteria of the ICD-9 CM: schizophrenia (ICD-9-CM codes 295.0-295.9), bipolar disorder and related disorders (ICD-9-CM codes 296.4-296.9), depressive disorders (ICD-9-CM code 296.3), personality disorders (ICD-9-CM codes 301.0-301.9) and psychotic disorder otherwise specified,

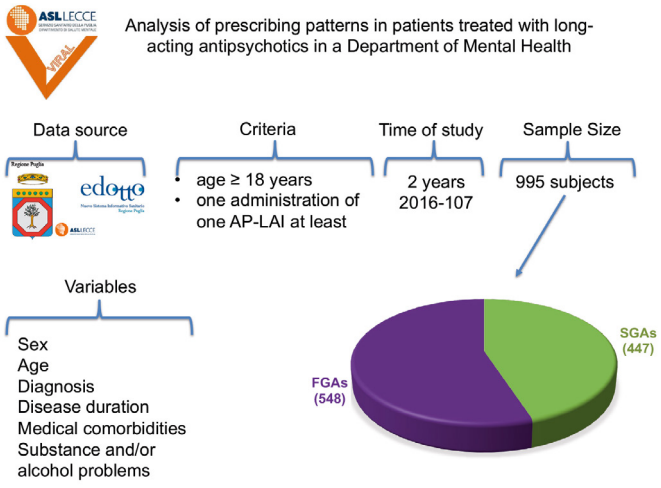


Figure 1.
Study design and sample size.

including dementia and other chronic psychotic conditions, (ICD-9-CM codes 294.0-294.9).

Statistical analysis

Sociodemographic and clinical characteristics of patients, were described by means of descriptive analysis, using means and standard deviations (SD) for continuous variables and percentages for categorical variables.
We analyzed the differences in the two groups about clinical and demographic variables examinate in the study. Then we evaluated the difference between the single drugs to define a prescribing pattern.
We used Pearson Chi-square (χ^2) test we analyzed the difference between the two groups or drugs on gender, diagnosis, presence of medical comorbidity and substance or alcol related problems.
Furthermore, the comparison between relevant estimates was carried out by means of Student's t-test for unpaired data or by means of binomial and one-way Anova tests. All tests were performed at a significance level of 0.05 (two-tailed). Statistical analysis will be carried out using statistical software (SPSS version 23).

Results

SGAs-L vs FGAs-L

We enrolled a sample of 995 subjects with an average age of 49.27 years [12,55] and with a higher prevalence of subjects of male sex (M/F = 61.51/38.49%). When we analyzed the differences between the two groups (SGAs-L *vs* FGAs-L), the difference between male and female subjects was greater in the FGAs-L group (M/F = 63.1/36.9%) than in SGAs-L group (59.5/40.5%) although not statistically significant (NS, p > 0.05) (Tab. I).
The mean age (SGAs-L *vs* FGAs-L; 45.19 ys *vs* 52.58 ys) as well as the duration of disease (SGAs-L *vs* FGAs-L; 10.85 *vs* 17.96) were statistically (p < 0.0001) lower in the SGAs-L group than in FGAs-L group (Tab. I). The difference between the two groups for both parameters was on average about 7 years.
The diagnosis of schizophrenia (FGAs-L *vs* SGAs, 75.9 *vs* 64.4%) and psychotic disorder otherwise specified (FGAs-L *vs* SGAs-L, 7.5 *vs* 3.4%) were statistically (p = 0.0001) more frequent in the FGAs-L group (Tab. I). On the contrary, in the group treated with SGAs-L, the diagnosis of bipolar disorder (SGAs-L vs FGAs-L, 28,2% vs 10,6%) was more frequent than in FGAs-L group (Tab. I). There were no differences (NS, p > 0.05) between the two groups for the other diagnoses (depressive disorder and personality disorder).
The presence of medical comorbidities was not different (p > 0.05) in the two groups (SGAs-L *vs* FGAs-L, 14.32 *vs* 13.87%) (Tab. I).
The present of substances and/or alcohol problems was more frequent in the SGAs-L group, in a statistically

Table I. Sociodemographic and clinical characteristics of patients between the two groups (SGAs-L vs FGAs-L).

Variables		SGAs-L (447)	FGAs-L (548)	p
M/F, n (%)		266/181 (59.5%/40.5%)	346/202 (63.1%/36.9)	0.242*
Age, mean ± SD (years)		45.19 ± 11.69	52.58 ± 12.25	0.0001**
Duration of disease, mean ± SD (years)		10.85 ± 8.66[a]	17.96 ± 10.28[b]	0.0001**
Diagnosis, n (%)	Schizophrenia	288 (64.4%)	416 (75.9%)	0.0001**
	Bipolar disorder	126 (28.2%)	58 (10.6%)	0.0001**
	Depressive disorder	5 (1.1%)	13 (2.4%)	NS*
	Personality disorder	13 (2.9%)	20 (3.6%)	NS*
	Unspecified psychotic manifestations	15 (3.4%)	41 (7.5%)	0.0001**
Medical comorbidity, n (%)		64 (14.32%)	76 (13.87%)	NS*
Substance and/or alchol problems, n (%)		68 (15.2%)	53 (9.7)	0.008*

*a: 12 subjects missing data; b: 7 subjects missing data; *Pearson χ^2 test; ** Student's t-test; NS = p >0.05.*

Table II. Prescribing pattern of single APs-LAI.

	M, n (%)	F, n (%)	SCZ, n (%)	Other diagnosis, n (%)	Medical comorbidity, n (%)	Substance or alchol problems, n (%)
HAL (371)	228 (61.5)	143 (38.5)	295 (79.5)	76 (20.5)	55 (14.8)	32 (8.6)
FLU (154)	106 (68.8)	48 (31.2)	110 (71.4)	44 (28.6)	16 (10.4)	20 (13.0)
ZUC (23)	12 (52.2)	11 (47.8)	11 (47.8)	12 (52.2)	5 (21.7)	1 (4.3)
ARI (93)	40 (43.0)	53 (57.0)	44 (47.3)	49 (52.7)	10 (11.8)	15 (16.1)
OLZ (71)	38 (53.5)	33 (46.5)	57 (80.3)	14 (19.7)	5 (7.0)	14 (19.7)
RP (95)	61 (64.2)	34 (35.8)	56 (58.9)	39 (41.1)	19 (20.6)	13 (13.7)
PP1 (185)	125 (67.6)	60 (32.4)	128 (69.2)	57 (30.8)	29 (15.9)	26 (14.1)
PP3 (3)	2 (66.7)	1 (33.3)	3 (100)	0 (0)	1 (33.3)	0 (0)

significant manner (p = 0.008), than in the FGAs-L group (SGAs *vs* FGAs, 15.2 *vs* 9.7%) (Tab. I).

Prescribing patterns

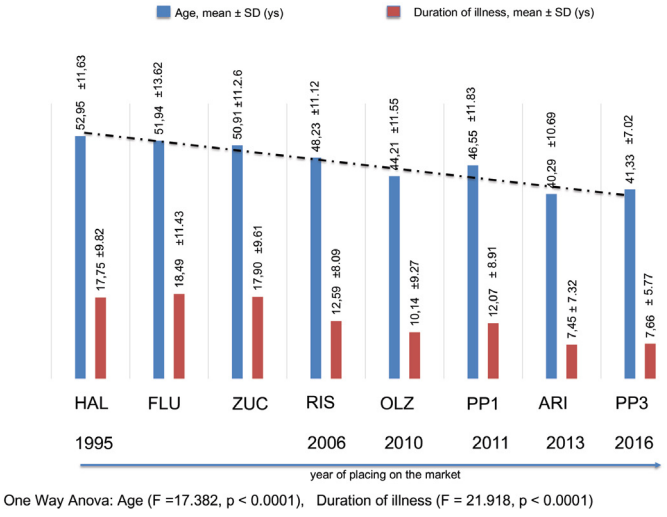
Treatment with Haloperidol decanoate (n = 371) was the main treatment prescribed among the FGAs-L group (67.7%), followed by fluphenazine decanoate (n = 154, 28.1%) and zuclopentixol decanoate (n = 23, 4.2%) (Tab. II). Within the SGAs-L group, the main treatment prescribed was Paliperidone palmitate 1 month (n = 185, 41.4%) followed by Risperidone RP (n = 95, 21.3%), Aripiprazole monohydrate (n = 93, 20.8%) and Olanzapine pamoate (n = 71, 15.9%) (Tab. II). Treatment with Paliperidone palmitate 3 month resulted in only 3 subjects (0.6%), probably conditioned by the recent marketing with respect to the observation period of the study (2016-2017).

The analysis of the clinical-demographic characteristics would seem to highlight a certain attitude of the clinicians to use specific drugs, the statistical significance found for variables such as sex, diagnosis (schizophrenia vs all other diagnosis), the presence of medical comorbidities and substance or alcohol problem, as well as age and disease duration could configure specific prescribing patterns (Tab. II, Figs. 2, 3).

Haloperidol decanoate was more prescribed in absolute terms (n = 317), in subjects affected by schizophrenia (79,5%), male sex (61.5%) and with higher age (52.95 ± 11.63) and duration of illness (17.75 ± 9.82), with more frequent medical problems (14.8%).

Fluphenazine decanoate was widely used in subjects suffering from schizophrenia (71.4%), of male sex (68.8%) and with relative higher age (51.94 ± 13.62) and duration of illness (18.49 ± 11.43) than SGAs-L group. The medical problems was less frequent in this group of patients (10.4%).

Zuclopentixol decanoate didn't present a particular use in terms of diagnosis and sex, although, as with other drugs of the same class, the subjects have a higher age (50.91 ± 11.26) and duration of disease (17.90 ± 9.61) than



One Way Anova: Age (F =17.382, p < 0.0001), Duration of illness (F = 21.918, p < 0.0001)

Figure 2.
Age and duration of illness analysis for the single AP-LAI.

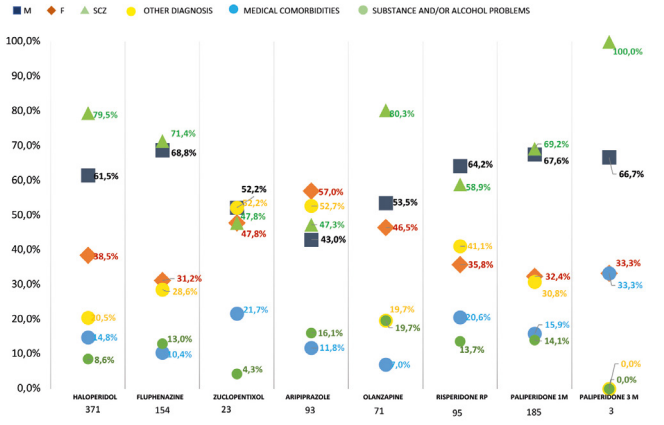


Figure 3.
Prescribing patterns of APs-LAI.

SGAs-L group. The presence of medical comorbidities would seem particularly high (21.7%).
Aripiprazole monohydrate had slightly higher prescription in female subjects (57.0%), unique than the other AP-LAI, without particular differences based on the diagnosis (SCZ *vs* Other D., 47.3 *vs* 52.7%) and with a relatively lower age (40.29 ± 10.69) and duration of illness (7.45 ± 7.32) than other AP-LAI. The present of medical comorbidities was comparable to the other AP-LAI (11.8%).
Olanzapine pamoate was more prescribed in subjects with schizophrenia (80.3%) without differences about gender (M/F, 53.5/46.5%) with a lower age (42.21 ± 11.55) and duration of illness (10.14 ± 9.27) than the FGAs-L and with statistically significant lower medical comorbidity than other AP-LAI (7.0%). On the contrary, the presence of substances and/or alcohol problems were more frequent than other AP-LAI (19.7%).
Risperidone RP was prescribed more frequent in subjects with schizophrenia (58.9%), male sex (64.2%), as FGAs-L. The age (48.23 ± 11.12) and duration of illness (12.59 ± 8.09) were lower than FGAs-L but higher than other SGAs-L with the exception of Paliperidone one month. The medical comorbidities (20.6%) and the substances and/or alcohol problems (13.7%) were present with a high frequency.
Paliperidone one month had a greater use in subjects suffering from schizophrenia (69.2%), male sex (67.6%), like the FGAs-L drugs. The age (46.55 ± 11.83) and duration of the disease (12.07 ± 8.91) were lower than the FGAs-L group but higher than the other SGAs-L. The medical comorbidities (15.9%) and substances and/or alcohol problems (14.1%) were more frequent than in other APs-LAI.
The small number of subjects treated with Paliperidone 3 month (n = 3) didn't allow an analysis of its use.

Discussion and Conclusions

Long-term pharmacological therapy can play an important role in enhancing adherence, preventing relapse, and in encouraging successful rehabilitation and re-entry into society in patients with schizophrenia [22]. The possibility to assuring continuity of treatment represent a clinical priority within the treatment plan. The development and introduction of long-acting antipsychotic treatments has been a turning point in the treatment of schizophrenia where poor adherence to antipsychotic medication leading to a need for multiple rehospitalizations and a substantial direct and indirect cost burden [23].
For several years the only present of first generation antipsychotic in long acting formulation, due to the burden of high risk of extrapyramidal side effects, has limited clinicians to be reserved this formulation only in the most extreme cases both in terms of severity and chronicity of the disease. In the last 15 years, despite the introduction of second-generation antipsychotics in long-acting formulation, reducing the likelihood of disabling side effects, the attitude of clinician would not seem to have changed [15]. Some recent evidence supports the benefits of early intervention with APs-LAI [24] but LAI antipsychotics remain an underutilized treatment option. The lack of specific indications probably represents a limit to their wider use in clinical practice.
The data of our study confirm this latter evidence by finding a shorter age and duration of illness in subjects treated with SGAs-L than in subjects treated with FGAs-L. The use of APs-LAI for indications different from schizophrenia could reflect the attitude of clinicians about the use of their oral formulations. In particular SGAs-L would seem more used for bipolar disorder while FGAs-L for psychotic disorder other specified, including dementia and other chronic psychotic conditions.
The most prescribed drugs were Haloperidol in the FGAs-L group and Paliperidone in the SGAs-L group. This finding could derive from the greater ductility of these two drugs given by the presence of a wider range in the dosage of the long acting formulations as well as by the characteristics of the sample itself constituted in the majority by subjects suffering from schizophrenia.
In general, our data confirm the use of SGAs-L in younger subjects and with a lower duration of disease, in particular for the certain drugs with a most favorable side effects' profile. Aripiprazole was more used in female subjects. Both data (age and sex) could be explained by the lower tendency of Aripiprazole to induce alterations in prolactin levels and in general sexual functioning. These side effects, particularly important for young subjects in terms of non-adherence to treatments, would seem to induce the clinician to make greater use of this molecule in this subgroup of subjects.
The SGAs-L, compared to the FGAs drugs, present a greater use in bipolar disorder; this could recall the indications present in the technical data sheet of the related oral formulations. In confirmation of this, among the various drugs belonging to the SGAs class, there was a greater use of Aripiprazole in bipolar disorder, and a greater use in schizophrenia for Paliperidone and Risperidone.
With regard to the use of substances and or alcohol, if the data reveal on the one hand a class effect with a greater use of SGAs drugs, on the other hand a specific effect for single molecule is not detected.
On the contrary, with regard to medical comorbidities, mostly cardio-metabolic, where there is no class effect (SGAs *vs* FGAs), among the second generation drugs a greater use of Risperidone and Paliperidone was found compared to Olanzapine, burdened by its greater metabolic side effect.
The naturalistic design of this analysis certainly represents a limit in the possibility of interpreting the results obtained in a more specific way. At the same time the absence of specific exclusion criteria describes the use of APs-LAI in a real-world setting.
In conclusion, our study highlights how the differences

profile in terms of indications and safety of the different APs-LAI, obviously also affect the clinician's choice of the type of long-acting antipsychotics used with increased use of SGAs-L in general in younger patients, in particular Aripiprazole for young female with different diagnosis than schizophrenia (bipolar disorder), Paliperidone for male schizophrenic patient with medical comorbidity and Olanzapine for patients with relative higher substance and/or alcohol problems.

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