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First generation *vs* second generation long acting antipsychotic: a real-world comparison

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Summary

Objectives. Antipsychotic (AP) treatment discontinuation is not uncommon: long-acting injectable (LAI) APs are effective in contrasting discontinuation. The current study focused on the comparison between patients treated with first (FG-LAI) and second (SG-LAI) generation LAIs recruited in a real-world context.

Materials and methods. Recruitment took place at the Community Mental Health Center (CMHC) in Novara, from January 1st, 2017 to June 30th, 2018. Inclusion criteria were: age ≥ 18, diagnosis of Schizophrenia, treatment with FG-LAI or SG-LAI, stable clinical conditions. Patients were excluded if treated with clozapine or with more than one LAI, or presenting acute clinical conditions. FG-LAI and SG-LAI patients were evaluated at baseline (T0) and after an 18-months follow-up (T1). Socio-demographic and T0/T1 clinical data were retrieved from medical records, databases and structured clinical interviews; assessment included the Clinical Global Impression (CGI) and Personal and Social Performance Scale (PSP).

Results. Ninety patients (n = 90) were recruited, 45 in each of the two groups (FG-LAI and SG-LAI). Compared to SG-LAI patients, FG-LAI ones were older, with lower academic titles and more often unemployed at T1; they were more often antipsychotics-naïve and changed therapy during follow-up in a lower percentage of cases. The average CGI test score decreased in both groups at follow-up; PSP global score and PSP-D (aggressiveness) decreased in FG-LAI patients, while in SG-LAI patients other PSP subscales decreased as well.

Conclusions. Real world data can play an important role in understanding treatment patterns, compliance and outcomes. Treatment with APs is necessary to change patients' outcome, and choice of medication should be tailored on patient's specific and unique features.

Key words: schizophrenia, long acting antipsychotic, real-world

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Conflict of interest
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Introduction

Schizophrenia is a chronic mental illness with a prevalence of 0.3%-0.7% [1], and is considered by the World Health Organization (WHO) the fourteenth cause of disability worldwide [2]. Treatment with antipsychotic (AP) medication is essential for schizophrenia in both the acute and stabilization phase, as well as in relapse prevention. Regrettably, AP discontinuation is not uncommon: it is more frequent in the first five years after diagnosis, with no significant differences between first (FGA) or second (SGA) generation APs, with

an estimated rate between 40 and 70% [3]. Treatment discontinuation is often due to lack of insight and poor adherence and leads to an increased risk of relapses [4]. This is estimated to span from 77% in the first year, up to 90% in the following two years in patients who stop taking AP medications, while in those with a good treatment compliance the recurrence rate stands at 3% [5]. Long-acting injectable (LAI) formulations are currently available for both FGAs and SGAs and are effective in contrasting treatment discontinuation and the consequent increased risk of relapse. Besides the possible improvement of therapeutic adherence [6], one further advantage of LAI formulations is the limited variability of the blood concentration of the medication, compared to oral formulations. While once chronic patients, with frequent relapses, poor awareness of disease and poor adherence to treatments were considered the best candidates for LAI treatments, in the last decade various factors contributed to change this assumption [7-11]. The enormous impact of therapeutic non-adherence on the course of the disease has become more evident and the need to address this problem since the early stages has arisen [12,13]. Actually, recent evidence suggests that LAIs are effective for treating first-episode psychosis and for the early treatment of schizophrenia [14,15]. Furthermore, studies exploring patients' subjective experience suggest that LAIs may facilitate the daily routine of pharmacological intake, improving attitudes towards medications in general [16-20]. Despite many studies are available about the use of FGAs and SGAs LAIs in schizophrenia, just a few have focused on real world practices, measuring clinical and socio-demographic features (including symptom profiles, adherence and attitude towards treatments). Most studies are randomized controlled trials, where the population included is highly selected (typical exclusion criteria are: refusal, comorbid substance abuse, suicidal or antisocial behavior, or other psychiatric or physical comorbidity) [21]. With the purpose of filling this gap in the literature, the cross-sectional phase of the STAR Network "Depot" Study aimed at evaluating how claimed cultural changes in LAIs prescription may have affected real-world practices. An unselected population of patients starting a LAI medication was assessed to explore possible predictors of the LAI class prescribed [22]. This study underscored the difficulty to compare the highly selected population from previous studies to those reflecting real-world practice as closely as possible.

With the aim of adding to the existing literature about the real-world use of LAIs, the current study focused on LAIs prescription, in particular on the comparison of socio-demographic and clinical features between patients treated with FG-LAI or SG-LAI generation antipsychotics recruited at a Community Mental Health Center (CMHC).

Materials and methods

Recruitment took place at the local CMHC in Novara, from January 1st, 2017 to June 30th, 2018. Inclusion criteria were the following: age ≥ 18 years, diagnosis of schizophrenia (according to the Diagnostic and Statistical Manual - 5 DSM-5 criteria), treatment with either FG-LAI or SG-LAI, stable clinical conditions (no changes in LAI dosage in the three months before the enrollment). Patients were excluded if matching the following criteria: being on clozapine therapy, being treated with more than one LAI, acute clinical condition and/or admission to the Psychiatry Ward within the three months before enrollment. Patients were divided into two groups on the basis of the LAI treatment, FG-LAI group and SG-LAI group, and evaluated at baseline (T0) and after an 18-months follow-up (T1).

Data about each patient were retrieved from medical records, computer databases and structured clinical interviews, and included: socio-demographic information (gender, age, education, employment at baseline and follow-up, marital status); baseline clinical data (somatic comorbidities, alcohol or drug abuse, duration of treatment at the CMHC more than 5 years, previous treatment with oral AP or LAI, concurrent therapy with oral antipsychotics); follow-up clinical data (switches - LAI type at T1, concurrent therapy with oral antipsychotics, severe adverse events, hospitalizations and suicide attempts during the follow-up period).

Patients were also assessed with the following clinician rated measures, both at baseline and follow-up: Clinical Global Impression (CGI) [23] and Personal and Social Performance Scale (PSP) [24]. The CGI is one of the most widely used brief assessment tools in psychiatry; it is a 3-item observer-rated scale that measures illness severity (CGI-S), global improvement or change (CGI-C) and therapeutic response; it has proved to be a robust measure of efficacy in many clinical drug trials, and is easy and quick to administer [25]. The PSP evaluates social and personal functioning, taking into consideration the individuals' functioning, independent of symptomatology. The PSP considers four areas of social and individual performance (socially useful activities, including work and study; personal and social relationships; self-care; disturbing and aggressive behaviors) [26]. The final score is a measure of functioning, ranging from 0 to 100%.

Statistical analyses were performed using SPSS v 19; t-tests for unpaired data and χ-square test were used to compare the two groups of FG-LAI and SG-LAI patients, with a statistical significance level of $\alpha = 0.05$.

Results

Ninety patients (n = 90) matching inclusion criteria were recruited; 45 of them were treated with FG-LAIs and 45 with SG-LAIs. With more detail, all patients in the FG-LAI group were treated with Haloperidol Decanoate (T0 average dose = 95.27 mg; T1 average dose = 82.5 mg); in the SG-LAI group, 60% (n = 27) of patients were treated with Paliperidone Palmitate (T0 average dose = 87.5 mg; T1

average dose = 79.69 mg), 27% (n = 12) with Risperidone Long Acting (T0 average dose = 45.31 mg; T1 average dose = 48.44 mg) and 13% (n = 6) with Aripiprazole Long Acting (T0 average dose = 300 mg; T1 average dose = 260 mg).

Socio-demographic features

Socio-demographic features of both subgroups FG-LAI and SG-LAI patients are reported in Table I.

Baseline data

Clinical features

In both groups most patients had neither somatic comorbidities (FG-LAI: n = 23, 51%; SG-LAI: n = 26, 58%), nor concurrent alcohol or drug abuse (FG-LAI: n = 31, 69%; SG-LAI: n = 38, 85%). In both groups, patients had a history of prior contacts with the CMHC of more than 5 years (FG-LAI: n = 40, 89%; SG-LAI: n = 38, 85%). However, none of these differences was statistically significant ($p > 0.05$).

Previous treatments

At recruitment, in the FG-LAI group 71% (n = 32) of patients were drug-naive while 12 patients (27%) were on oral therapy with antipsychotics (mainly haloperidol) and only 1 patient with Fluphenazine Decanoate.
Seventeen of the patients in the SG-LAI group (38%) had been previously treated with haloperidol decanoate, and 14 (31%) with oral antipsychotics (olanzapine, risperidone and aripiprazole); 9 (20%) were antipsychotic-naive and 5 (11%) were already treated with a SG-LAI.
In the FG-LAI group, antipsychotics-naive patients were significantly more than in the SG-LAI one ($p < 0.0001$).
At T0, 36% (n = 16) of FG-LAI patients and 42% (n = 19) of SG-LAI was also taking an oral antipsychotic drug.

Follow-up clinical data

Switches

In 96% (n = 43) of cases in the FG-LAI group there was no therapeutic switch during the observation period, while in SG-LAI in 65% (n = 29) of cases ($p = 0.0002$) therapetic switch occured.
At T1, the number of patients who had also an oral antipsychotic drug remained unchanged for FG-LAI patients (n = 16) while it was reduced from 42% to 36% (n = 16) for the SG-LAI; these differences were not statistically significant ($p > 0.05$).

Severe adverse events, hospitalizations and suicide attempts in the follow-up period

No statistically significant difference was found between the two groups of FG-LAI and SG-LAI patients in severe adverse events and in admissions to the Psychiatry Ward during the follow-up period.
With more detail, 2 patients (4%) in the FG-LAI group showed severe adverse event (stroke cerebri), while 7 (16%) in the SG-LAI group did (including: hypertensive peaks, diabetes, rigidity, hyperprolactinemia, amenorrhea, extrapyramidal effects). Regarding hospital admissions, 5 patients (11%) in the FG-LAI group and 2 (4%) in the SG-LAI group were admitted to the Psychiatry Ward.
No suicide attempt was registered in either group during the follow-up period.

CGI and PSP scores

No statistically significant difference was observed in the CGI and PSP scores of the two groups.
CGI scores showed statistically significant changes from T0 to T1 in both groups; specifically, the average CGI test score decreased from 4.09 to 3.71 ($p = 0.036$) in FG-LAI patients, and from 4.38 to 3.84 ($p = 0.0098$) in SG-LAI ones.

Table I. Socio-demographic features: comparison of the FG-LAI and SG-LAI groups.

		FG-LAI	SG-LAI	p
N		45	45	
Mean age		56.31	49.67	**0.024***
Gender	Females	23 (51%)	21 (46%)	0.67
	Males	22 (49%)	24 (54%)	
Academic title	Primary school	36 (80%)	25 (55%)	**0.013***
	High school	9 (20%)	20 (45%)	
Employment status T0	Unemployed	42 (93%)	39 (86%)	0.29
	Employed	3 (7%)	6 (14%)	
Employment status T1	Unemployed	42 (93%)	33 (73%)	**0.01***
	Employed	3 (7%)	12 (27%)	
Marital status	Single	34 (75%)	34 (75%)	1
	In a relationship	11 (25%)	11 (25%)	

** $p < 0.05$.*

Table II. Personal and Social Performance (PSP) subscales.

PSP Subscales		T0	T1	p
PSP-A professional activity	FG-LAI	3.13	2.89	> 0.05
	SG-LAI	2.80	2.44	**0.0008***
PSP-B reports social	FG-LAI	2.82	2.56	> 0.05
	SG-LAI	2.89	2.44	**< 0.0001***
PSP-C personal care	FG-LAI	2.38	2.27	> 0.05
	SG-LAI	1.87	1.67	**0.0195***
PSP-D aggressiveness	FG-LAI	0.56	0.36	**0.0313***

** $p < 0.05$.*

As far as PSP scores are concerned, a significant change from T0 to T1 was observed in FG-LAI patients for average PSP global score (T0 = 49.33; T1 = 43.11) (p = 0.005) and PSP-D subscale which significantly decreased from T0 to T1 (p = 0.0313).
In SG-LAI patients the decrease from T0 to T1 of the average PSP global score was not statistically significant (T0 = 53.78; T1 = 52.44) (p > 0.05).
PSP subscales scores at T0 and T1 in both subgroups of patients are described in Table II.

Discussion

Real-world data are defined as everything that goes beyond what is normally collected in phase III clinical trials in terms of efficacy and are also labeled as anything that is not interventional [27]. Randomized clinical trials (RCTs) are actually considered the gold standard for establishing the efficacy of a given therapy in a group of patients; they focus on evaluating the efficacy of therapies rather than on the delivery of care, hence they have internal, but not external validity. Therefore, real world data, with no strict inclusion and exclusion criteria, can play an important role generating long term efficacy and safety data, evaluation of epidemiology and burden of disease, treatment patterns, compliance, persistence, and health outcomes of different treatments [27].
In the present study, patients in the FG-LAI group were all treated with Haloperidol Decanoate and the average dose from T0 to T1 was reduced from 95.27 mg to 82.5 mg. FG-LAIs have a wide range of licensed doses; for haloperidol decanoate optimally effective doses appear to be around 50-100 mg per 4 weeks [10], as for the patients of this sample.
SGAs do not represent a homogeneous class of drugs, as emerges also in the variability of the medications used in the current sample [22]: the most used LAIs were Paliperidone Palmitate (60%) and Risperidone Long Acting (27%), and only 13% of SG-LAI patients were in treatment with Aripiprazole Long Acting; Olanzapine long acting was not used. These data are consistent with those reported in the literature; for example Pilon [28] and coworkers reported that the most commonly prescribed SGA-LAIs were paliperidone palmitate (65.6%) and Risperidone Long Acting (32.2%) [28]. All the SGA-LAIs were used in a therapeutic range, as reported in literature [29,30].

Socio-demographic features

As described in the literature [28], the average age in the SG-LAI group was significantly lower than that in the FG-LAI group, probably because older patients started therapies previously, when SG-LAI were not so commonly used. It should be underscored that SG-LAIs were largely available during the study period, but in previous times, some SG-LAIs were not yet routinely reimbursed by the Regional Health Service (e.g.: aripiprazole) [31].
In a long-term perspective of recovery, there is consensus in literature on the need of individualizing antipsychotic treatment; since the first episode the NICE guideline on the treatment and management of psychosis and schizophrenia recommends that "treatment with antipsychotic medication should be considered an explicit individual therapeutic trial" [32]. The choice of the antipsychotic medication should be tailored on patient's specific and unique features; in particular, psychiatrists may start considering the option of LAIs, especially SGAs, also with first-episode or recent-onset[10]. This can explain why in the SG-LAI group patients are younger. Treatment with SGAs is preferred in young patients because of emerging data from the comparison between SGAs and FGAs, supporting lower rates of relapse, overall treatment failure and hospitalization with the first [29,30].
In our sample, patients showed a low socio-economic status in both groups (low level of schooling, unemployment, single status). Schizophrenia is a chronic disabling illness: 80% of adults with this diagnosis had some persistent problems with social functioning [32].
Even if there is a great number of patients with low socio-economic status in the SG-LAI group, according to literature data on this topic [22], they are more often younger, with higher schooling level and more frequently employed. Moreover, it is interesting that at the end of the follow up period patients continued to be mainly unemployed in both groups, but the rate is lower for patients in the SG-LAI group. Social functioning improvement is considered as one of the most important outcomes in schizophrenia, and clinicians often base their judgments on changes in patients' engagement in socially useful activities, such as work [34]. Different studies in the literature show that SGAs are better than FGAs for overall efficacy, in particular on negative symptoms [29]: this can explain why patients in the SGA-LAI group in our study were more often employed at follow up, compared to those in the FGA-LAI group. Moreover, if there are less symptoms and relatively fewer side effects, greater adherence to therapy is expected, together with a lower risk of recurrence and a better social functioning.

Baseline data

Previous treatments

Recent studies suggest the switch to LAI as a possible optimization therapeutic strategy for schizophrenic patients who already achieved clinical stabilization with oral antipsychotics; furthermore, as already underscore, it is encouraged the early consideration of using SG-LAI also in recently diagnosed patients [35].

In our study, we found that in the FG-LAI group, antipsychotics-naive patients were significantly more than in the SG-LAI one ($p < 0.0001$). This can be related to the slow dose titration and the long time required to achieve steady state levels, which is particularly important for SGA-LAIs[10]. This disadvantage is most evident in acute patients for whom a rapid dose titration may be required; therefore, SGA-LAIs have generally been preferred for those patients who are at least partially stabilized after a period on oral treatment[10].

Follow-up data

Switches

Patients in treatment with SG-LAIs changed antipsychotic treatment during the follow-up period in a fairly higher percentage of cases (65%) than those in the FG-LAI group ($p = 0.0002$). Switching of medication over time is common in clinical practice [32]; generally, the switch from one LAI to another is motivated by the poor efficacy or tolerance of the first drug used [36], but this may also reflect the need in clinical practice to search collaboratively for the drug that offers the best balance of efficacy and tolerability for each patient [32].

Studies found no significant differences in psychopathology, hospitalizations, side effects such as dyskinesia or extrapyramidal symptoms (EPS) in patients with schizophrenia treated with different types of FG-LAIs; when patients were randomly assigned to stay on current FG-LAI or switch to SG-LAI, it was shown that patients switching to SG-LAI experienced significantly more weight gain and increases in prolactin levels [10]. These data can explain why people in our sample more often continued the treatment with FG-LAI, because it may represent the best balance between therapeutic and collateral effects for the patient. Other switching studies about SG-LAI have shown that patients with mild, residual symptomatology treated with conventional LAIs experience significant improvement in psychiatric and movement disorder symptoms after the switch and also report a better quality of life. Pursuing recovery is one of the main outcomes in patients with schizophrenia, and there is a strong agreement among psychiatrists that the most important factors in selecting a pharmacological agent are efficacy and tolerability [34].

CGI and PSP scores

CGI and PSP scores are important to evaluate patients' functioning in real life: personal resources and social context explain 53.8% of real-life functioning variance in patients with schizophrenia living in the community and treated with antipsychotics, mainly second-generation drugs [37].

The CGI scores decrease from T0 to T1 in the two groups ($p < 0.05$ in both groups) supports the improvement which can be achieved with both FG-LAIs. Early intervention and continuity of treatment are crucial for achieving long-term remission, preventing a malicious course of the disease and reducing costs and burden of disease[29]. These goals can be achieved with both FG-LAIs or SG-LAIs, and treatment should be individualized based on efficacy, side effects, and costs. Better outcomes, as evidenced by an improvement in clinical symptoms, are also related to better life-functioning and quality of life[10].

The PSP average score significantly decreased from T0 to T1 in patients in the FG-LAI group ($p = 0.005$) and also the PSP-D subscale (assessing disturbing and aggressive behaviors) ($p = 0.0313$).

The PSP scale assesses personal and social performance, and it is known that SG-LAIs may reduce both positive and negative symptoms, but they're not without side effects: in the ACLAIMS trial no significant difference in efficacy was found between those taking SG-LAIs (paliperidone palmitate) and FG-LAIs (haloperidol decanoate); however, those in the paliperidone palmitate group had higher serum prolactin levels and gained more weight, while the haloperidol decanoate group experienced more akathisia, used more antiparkinsonian medications and lost weight [6]. It is important to consider the characteristics of each molecule on an individual basis, trying to reach a reasonable balance between therapeutic and collateral effects, to reach the best overall performance. Considering aggressiveness, it is known that LAIs are chosen for patients with behavioral disorders [10]: the study by Mohr showed how LAI treatment may improve psychotic symptoms and cause overall reduction in violent behavior; all LAIs were better than oral therapy from this standpoint [38]. The literature comparing FG-LAIs and SG-LAIs about aggressiveness is scant, but it is known that FG-LAIs are more used in clinical practice than SG-LAIs in patients with behavioral disorders.

In the SG-LAI group there is a significant reduction from T0 to T1 in professional activities, social relationships and personal care. In the PSP subscales, the patient's degree of severity is rated on a six-point scale from absent to very severe difficulties in the given area, so if there's a reduction in the score, there is an improvement. Regarding SG-LAIs, it is known that they're effective in reducing positive, but in particular negative symptoms; some studies found that those on LAI risperidone have significantly lower ratings on a psychotic symptom scale (positive and negative syndrome scale, PANSS) compared with those on FG-LAI [6]. Symptoms reduction may help patients to improve their personal and social resources feeling much more satisfied with themselves.

Conclusions

Some limitations should be underscored. Firstly, the low sample size and the short period of follow-up, limit the possibility to generalize results. A second limit is the lack of scales assessing symptoms, which could be investigated in future research. Larger studies are required in order to investigate recovery over time focusing on differences between FG-LAI and SG-LAI. Further real-world studies should be performed in order to better explain how long-acting injectable LAI formulations may influence patients' outcome and adherence to therapy, helping the clinician to identify treatment on patient's specific and unique features; moreover, the choice between FG-LAIs and SG-LAIs should be tailored on patients' features, including not only symptoms, but also age, global functioning, side effects and previous psychiatric history.

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Main implications for psychiatric care

- The present work adds to the existing literature about LAIs, presenting real-world data from an Italian CMHC, about the socio-demographic and clinical features of patients treated with first or second generation LAIs. Clinical practice may be more useful than clinical trials with selected patients to understand how patients may respond to pharmacological treatment.
- From the present study we can say that LAI formulations may influence patients' outcome and adherence to therapy: the clinician should tailor treatment on patient's specific and unique features, mainly symptoms, but also age, global functioning, side effects and previous psychiatric history.

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