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Real-world effectiveness of long acting aripiprazole: Treatment persistence and its correlates in the Italian clinical practice

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ABSTRACT

Objectives: To identify the variables that are associated with persistence to Aripiprazole-Long Acting (A-LAI), in adult patients with schizophrenia.
Methods: Observational, retrospective, non-interventional study involving 261 patients with schizophrenia.
Results: Eighty-six percent of study subjects were persistent for at least 6 months. All subjects with baseline CGI-S of 1 or 2, 95% of subjects with CGI-S of 3, 86% with CGI-S of 4, 82% of subjects with CGI-S of 5, 73% of subjects with CGI of 6 and 90% of subjects with CGI of 7 were persistent. A-LAI treatment continuation rate was higher in patients with: 1) baseline CGI score ≤ 4; 2) schizophrenia dimension (LDPS) mania score ≤ 5; 3) psychotic spectrum schizoid score ≤ 11.
Conclusions: A relatively high number of patients (n = 225, 86%) were persistent to A-LAI for at least 6 months. Not surprisingly, very severe patients were more unlikely to be persistent. However, it is noteworthy that a large number of subjects with high CGI score at the time when A-LAI was started (82% of subjects with CGI-S of 5, 73% of subjects with CGI of 6 and 90% of subjects with CGI of 7) were persistent. Larger, controlled, prospective and longer studies are warranted.

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1. Introduction

Although the efficacy of antipsychotic medications in reducing psychotic symptoms has been largely proven, poor treatment persistence is more the rule than the exception among many individuals with schizophrenia. For instance, the Clinical Antipsychotic Trials of Intervention Effectiveness trial, demonstrated that as many as 74% (1061 of the 1432 patients who received at least one antipsychotic dose) of the participating subjects discontinued medication treatment before 18 months of treatment (Lieberman et al., 2005).

Causes of non-persistence include lack (or loss) of efficacy, side effects, and poor adherence. Use of long-acting injectable antipsychotics (LAI) is one of the main strategies to improve adherence in patients with schizophrenia and several studies have shown their ability to improve rates of discontinuation, relapse, and hospitalization (Kaplan et al., 2013). Mirror-image studies have shown clinically relevant superiority of Long Acting (LAIs) compared to oral antipsychotics (Kishimoto et al., 2013). However, a recent meta-analysis of randomized clinical trials, showed no superiority of LAIs (Kishimoto et al., 2014). This difference may be accounted for by the fact that mirror-image studies are more likely to represent the population receiving LAIs in real world clinical practice. Yet, mirror-image studies may be biased by issues such as natural illness course, time effect, and expectation bias. Hence, a cautious interpretation is necessary.

Antipsychotics have different characteristics in terms of pharmacokinetic and pharmacodynamic profiles, as well as tolerability and adverse events. Indeed, it is paramount that antipsychotic treatment be tailored to the individual patient and results of randomized clinical trials are only one of the informants for treatment choice. Indeed, the choice of which specific agent or formulation should be suggested for an individual patient should be also informed by the evaluation of which specific symptoms contribute the clinical picture, what the disease course has been, what the medical and psychiatric histories are, which side effects the patient is willing to risk and ultimately, which the antipsychotic is that is more likely to be continued, based on efficacy, tolerability and patient's satisfaction with the prescribed medication.

In this study, we evaluate treatment persistence in a group of patients treated with long acting aripiprazole (A-LAI). All study participants were recruited in the setting of the Italian National Public Health System, where aripiprazole is prescribed relatively frequently (Ostuzzi et al., 2018).

We considered A-LAI persistence as an indirect measure of A-LAI real-world effectiveness, assuming that efficacy, tolerability and adherence were among the major drivers of persistence. To maximize the selection of patients that mirrored the real-world clinical practice, we chose a retrospective cohort, observational study design. We recruited consecutive patients presenting for a psychiatric visit, who were started on A-LAI at least 6 months before the inclusion visit.

Our main goal was to evaluate the clinical characteristics of a group of patients who were treated with A-LAI in a variety of clinical environments, that mirror the real-world settings in which Italian people with schizophrenia are usually treated, and to look at the differences between individuals who continued the medication for at least 6 months and individuals who discontinued the medication earlier. Specifically, we wanted to evaluate the correlations between demographic or clinical characteristics that were present at the time when A-LAI was started, or anytime in the individual lifetime (SCI-PSY, LDPS), and the likelihood to continue treatment for at least 6 months. Our analysis was based on the hypothesis that the identification of characteristics associated with persistence with A-LAI treatment may support patients' treatment choice and orientate A-LAI use in subjects with higher likelihood to benefit from, and hence continue, the medication. Also, we wanted to identify those subjects with higher likelihood of early discontinuation, for whom alternative medications, or adjunctive psychosocial interventions aimed at improving persistence, would be indicated.

2. Methods

This was an observational, retrospective, non-interventional study aimed at evaluating the influence of baseline demographic and clinical characteristics as well as the influence of lifetime rated schizophrenia symptom dimensions, on the likelihood to continue A-LAI treatment for at least 6 months. We included patients diagnosed with schizophrenia who were initiated with A-LAI (index date, baseline time-point) as per normal clinical practice at least 6 months before study entry, data collection and follow-up visit (inclusion visit). The study was approved by the Ethical Committee / Institutional Review Board at each recruitment site. Written informed consent was obtained from all participants or their legal guardians. The study was conducted between June 1st 2015 and July, 11th 2017 at 20 clinical sites in Italy (9 university medical departments, 11 community mental care departments).

Eligible patients were at least 18 years of age and were diagnosed with schizophrenia, as determined on the basis of a clinical interview conducted to verify the presence of the DSM 5 criteria. Patients were excluded if they had a primary psychiatric disorder other than schizophrenia or had participated in a clinical trial during the retrospective follow-up period. All patients presenting for a visit or a psychiatric evaluation, who met the criteria mentioned above, who had started A-LAI (at least 1 injection) at least 6 months before the inclusion visit, and who were willing to participate in the study were continuously recruited. Data from each patient was collected after informed consent was signed. Retrospective information from the start of A-LAI treatment (index date, baseline time-point) until the follow-up visit (inclusion visit) was retrospectively collected from all available source documents pertaining to the visits conducted as per clinical practice (usually once monthly) from A-LAI start to the follow-up visit (inclusion visit).

Persistence was measured by time to all-cause medication discontinuation and was assumed to reflect A-LAI's efficacy, tolerability and safety, from both patient and treating clinician's perspectives. Non-persistence was declared if the patient missed 2 consecutive or 3 non-consecutive injections of A-LAI during the retrospective follow-up period. A missed dose of A-LAI was defined as a lapse of > 45 days from the previous A-LAI injection, at all time points. Clinical records were reviewed and treating clinicians were interviewed as per the date of A-LAI interruption or discontinuation and reasons (if applicable).

Fig. 1 reports the study flow chart

2.1. Study assessments

Study assessments included a standardized evaluation of demographic and clinical characteristics at the index date, Clinical Global Impression – Severity scale (CGI-S) at index date and CGI-S up to the inclusion visit, evaluation of schizophrenia dimensions (symptoms and clusters of symptoms) as assessed by the LDPS questionnaire (Levinson et al., 2002), evaluation of psychotic spectrum as assessed via the SCI-PSY questionnaire (Sbrana et al., 2005).

The CGI-S is a 7-point scale where the clinician rates the severity of the patient's illness at the time of assessment. Considering total clinical experience, a patient is assessed on severity of mental illness at the time of rating and rated with: 1, normal, not at all ill; 2, borderline mentally ill; 3, mildly ill; 4, moderately ill; 5, markedly ill; 6, severely ill; or 7, extremely ill. CGI was demonstrated a reliable measure of illness severity in Schizophrenia (Pinna et al., 2015)

The LDPS (Levinson et al., 2002) evaluates the lifetime duration and severity of positive, bizarre positive, negative, disorganized, and mood symptoms of psychotic disorders. It is completed by the physician after extensive review of all available information for each patient. It contains 20 "clinical" items plus one item rating of quality of information. The 20 items are: Any delusions, Paranoia, Any hallucinations, Control delusions, Other bizarre delusions, Conversing/ commenting/ continuous hallucinations, Abnormal perception of thought, Psychosis without prominent mood symptoms, Blunted affect, Poverty of speech,

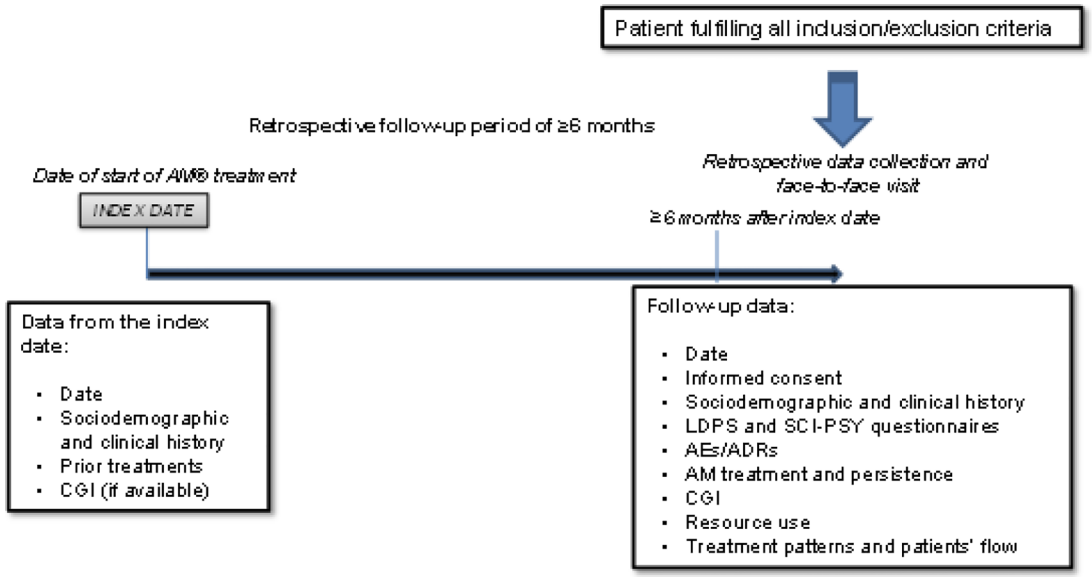


Fig. 1. Study flow chart.

Formal thought disorder, Bizarre behaviour, Depression, Maximum number of depressive features, Mania, Maximum number of manic features, Concurrent depressed mood + delusions or hallucinations, Concurrent grandiose / manic mood + delusions or hallucinations, Deterioration and Complicating factors. For each item (except for Maximum number of depressive features and Maximum number of manic features), both duration (0, absent; 1, < 2 weeks (≥ h); 2, ≥ 2 weeks; 3, ≥ 2 months or ≥ 2 episodes of ≥ 2 weeks; 4, ≥ 2 years) and severity (0, absent; 1, minimal, very mild severity or only suspected; 2, moderate, definite, clinically significant severity; 3, severe, clearly interferes with function or preoccupies; 4, very severe, gross or nearly constant effect on function) are assessed. Eighteen of the 20 items are grouped into in 8 symptom domains or dimensions (2 items rate the course of illness and atypical or comorbid features): Psychosis, Schizophrenia syndrome, Non-affective psychosis, Negative symptoms, Disorganization, Depression, Mania, and Mood psychosis. The score for each domain is the sum of severity + duration for all items within that domain. The total score ranges from 0 (minimum severity) to 160 (maximum severity).

The SCI-PSY (Sbrana et al., 2005) questionnaire is based on a spectrum model that emphasizes soft signs, low-grade symptoms, subthreshold syndromes, as well as temperamental and personality traits. The psychotic spectrum considers a psychopathological continuum, ranging from psychotic soft signs, personality disorders to full-blown major psychoses. The instrument consists of an "Structured Clinical Interview", completed by the physician during an interview with the patient, that includes 164 items, exploring lifetime symptoms and behaviors organized into five domains: "interpersonal sensitivity", "paranoid", "schizoid", "misperceptions", and "typical psychotic symptoms". Within each domain more specific subdomains are identified, including, within the "paranoid" domain, hypertrophic self-esteem, strict thinking, superstition, fanaticism, relations with others, self-reference, interpretive attitude, suspiciousness, anger/over-reactivity and hypervigilance; within the "schizoid" domain, schizoidism/autism and unusual and odd thoughts; within the "misperceptions" domain, illusions and depersonalization/derealisation; within "typical psychotic symptoms" domain, delusions, hallucinations and catatonia. Item responses are coded in a dichotomous way (yes (1) / no (0)) and domain scores are obtained by counting the number of positive answers. Total score (sum of domains scores) ranges from 0 (no psychotic symptoms) to 164 (maximum psychotic symptoms).

2.2. Statistical methods

Descriptive statistics were reported in terms of mean, standard deviation, median, minimum and maximum for continuous variables. Normality of variable distribution was tested using the Kolmogorov-Smirnov test.

The originally planned statistical approach (Cox proportional-hazards regression model) to evaluate the relationship between persistence on A-LAI and demographic and clinical characteristics assumed a frequency of events (planned rate of A-LAI discontinuation = 34.2%) that was not reflected in the study outcome (observed rate of discontinuation = 13.8%). Due to this reason (lower than expected number of events), the Cox proportional-hazards regression model output was unstable and produced unreliable results. Therefore, a stepwise binary logistic regression was performed, which is a practical alternative to Cox models in cohort studies, especially when the event incidence is low. Cox regression (estimates the hazard ratio) differs from logistic regression (estimates the odds ratio) by assessing a rate instead of a proportion.

The forward LR method started with an empty model and added the most significant term variable for each step. The method stopped when all variables not in the model had p-values that were greater than the specified alpha-to-enter value. All statistical tests were two-sided and a p-value less than 0.05 was considered as statistically significant.

A correction for multiple comparisons method was not applied because specific planned comparisons were decided *before* the study started. These "planned comparisons" were not decided after inspecting the data. Rather, the comparisons were designed into the analysis plan, approved before database lock. The statistical package "SPSS version 21.0″ (IBM Statistical Software) was used for all the analyses.

3. Results

3.1. Characteristics of patients

A total of 287 patients were deemed eligible to participate and 267 were enrolled in the study at 20 Academic and non-academic-community based sites from Italy. Six subjects were excluded due to missing data and the final sample included 261 individuals. Study participation was offered to the first patients (up to 30 per site, with competitive enrolment) that presented to the clinics and fulfilled the study entry

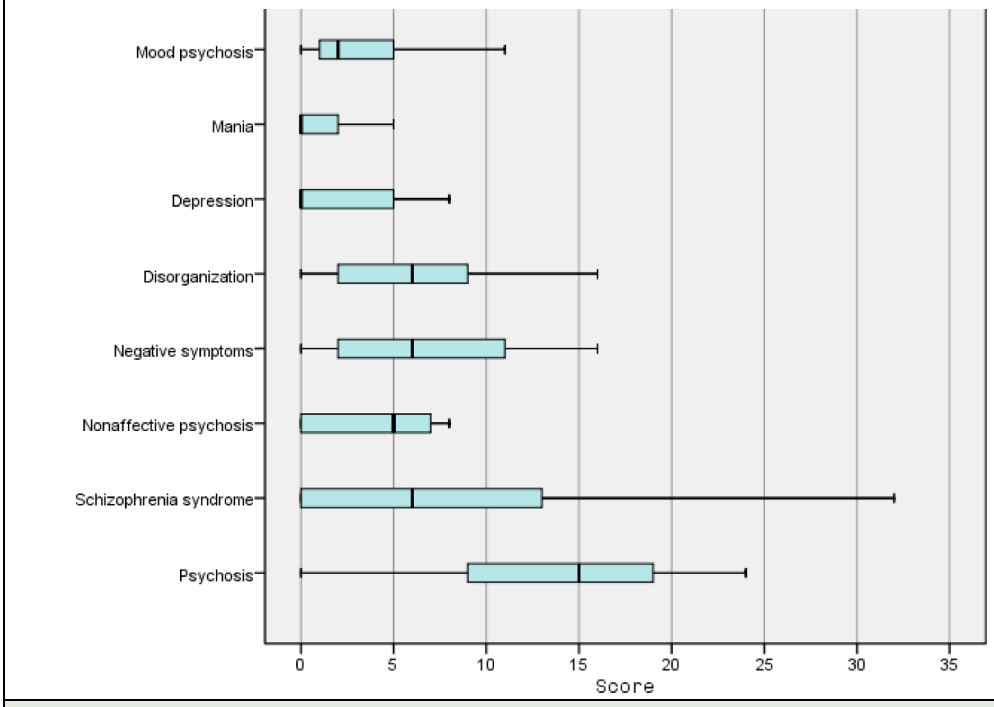
Table 1
Baseline Clinical (CGI, LDPS and SCI-PSY score) characteristics (n = 261).

CGI - AM Initiation (n = 261)

	N	Mean	SD	Median	Min	Max
Score	261	3.8	2.20	5	0	7

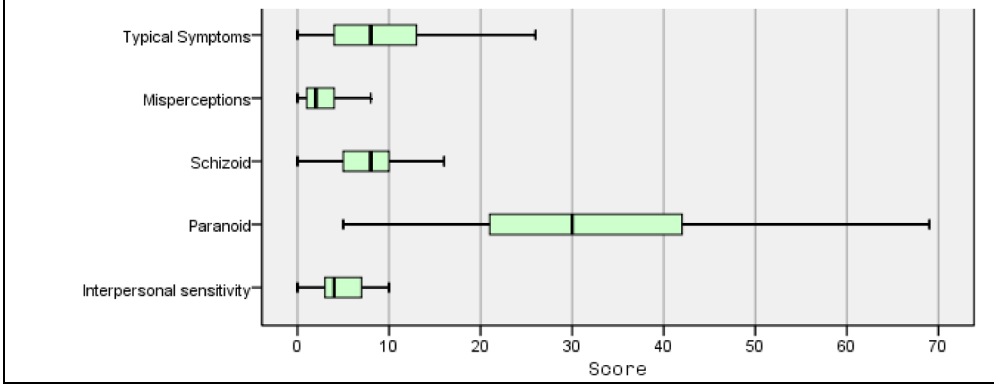
LDPS (n = 261)

	N	Mean	SD	Median	Min	Max
Total score	261	45.4	18.65	45	3	100



SCI-PSY (n = 261)

	N	Mean	SD	Median	Min	Max
Total score	261	55.9	25.83	54	7	135



criteria. Baseline demographic and clinical characteristics of the patients who were treated with A-LAI in the Italian clinical practice, as assessed via CGI, LDPS and SCI-PSY scores (n = 261) are reported in Table 1.

3.2. Persistence on A-LAI for at least 6 months

Fig. 2 shows the persistence on A-LAI for at least 6 months; 225 patients (86%) were persistent to A-LAI for at least 6 months, whereas 36 individuals (14%) interrupted the treatment before the 6-month time-point (Fig. 2).

The mean time on A-LAI for persistent subjects was 14.6 months (SD = 5.8). All persistent subjects were still on A-LAI at the time of inclusion visit. The mean time on A-LAI for non- persistent subjects was 2.7 months (SD = 1.5).

Of the 261 participating subjects, 110 (42.1%) started A-LAI on top of oral Aripiprazole: 94 of 225 persistent patients (41.8%) and 16 of 36 (44.4%) non-persistent patients. The difference was not statistically

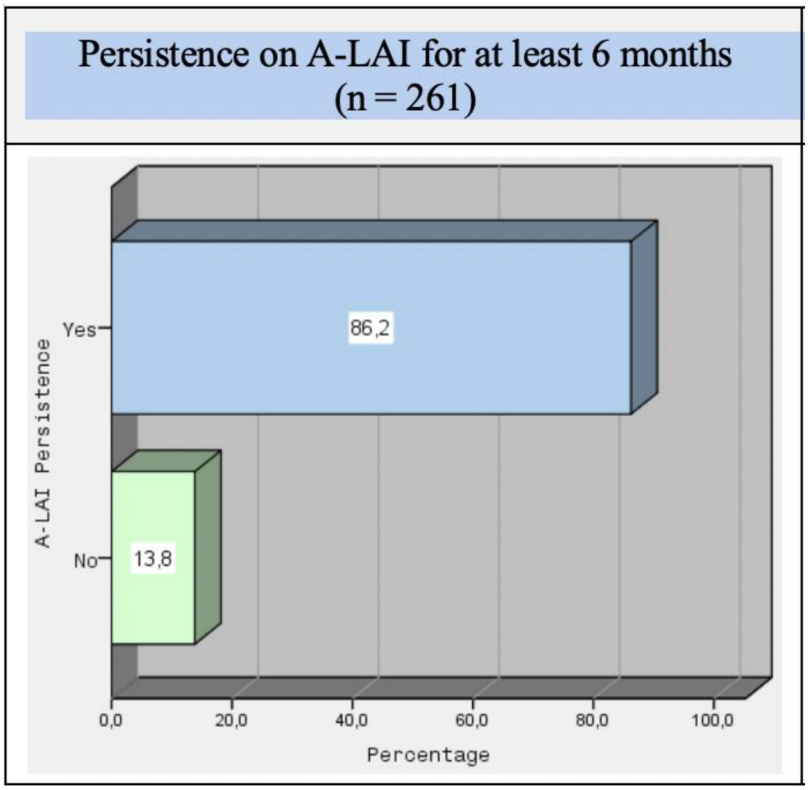


Fig. 2. Persistence on A-LAI for at least 6 months (n = 261).

significant.

Of the 261 participating subjects, 51 (19.5%) started A-LAI on top of another oral antipsychotic: 40 of 225 persistent patients (17.8%) and 11 of 36 (30.6%) non-persistent patients. The difference was not statistically significant (Chi Square test, p-value = 0.073).

The combination of A-LAI and one or more oral antipsychotic was continued for a mean of 255.1 days (SD = 202.04, median = 198, min = 4, max = 719). Specifically, the mean time in persistent patients (n = 225) was = 288.0 days (SD = 210.25, median = 216, min = 4, max = 719) and the mean time in not-persistent patients (n = 36) was 75.9 days (SD = 47.08, median = 69, min = 8, max = 159).

Table 2 reports the univariate analyses about the relationship between persistence with A-LAI for at least 6 months and baseline demographic and clinical characteristics. A statistically significant difference was observed between patients who persisted on treatment and patients who did not persist for: education, occupation, CGI-S at the time when A-LAI was started, lifetime LDPS disorganization score, and lifetime psychotic spectrum paranoid and schizoid score.

Univariate analyses (Fisher's exact test for categorical variables, Student's t-tests for continuous variables, and Mann-Whitney tests for ordinal variables) were performed to test the association between demographic and clinical characteristics of patients and persistence with AM treatment at 6 months. There were significant differences between persistent and non-persistent patients in the following parameters: Education (P = 0.019), Occupation (P = 0.009; categorized as No occupation versus any type of occupation), Health setting at AM initiation (P = 0.012), CGI at the index date (P = 0.002; categorized as Low severity [scores 1–4] and Severe [scores 5–7]), LDPS: Disorganization score (P = 0.008), SCI-PSY: Paranoid (P = 0.016) and SCI-PSY: Schizoid (P = 0.005). Regarding the educational level, only two patients (0.8%) in the non-persistent population received no compulsory education, instead a 41.8% of overall patients were educated in secondary school (42.7% persistent; 36.1% non-persistent). The majority of patients (67.8%) had no occupation at AM initiation, these rates were increased in the non-persistent population (83.3%), which presented a lower percentage of paid employees compared with the persistent population (65.3%).

Persistent patients presented higher percentages of subjects treated in an outpatient setting (P = 0.011 for the 'Health setting' at AM initiation), with lower percentages treated in inpatient care (SPDC, 28.0% persistent versus 50.0% non-persistent).

Regarding the schizophrenia specific measures, in the persistent population the following scores were found to be lower compared with the non-persistent patients: CGI score at the index date, LDPS Disorganization score, SCI-PSY Paranoid and Schizoid score. According to these results, persistent patients were less severe compared with non-persistent patients.

Table 3 reports the distribution of patients based of CGI at the time of A-LAI initiation and the percentage of persistency by CGI score

The Stepwise Binary Logistic Regression model showed that A-LAI treatment continuation rate increased in patients with CGI score ≤ 4, compared to patients with CGI ≥ 5 (A-LAI treatment continuation odds increased by 2.8 times).

The A-LAI treatment continuation rate increased in patients with lifetime schizophrenia dimension (LDPS) mania score ≤ 5, compared to patients with schizophrenia dimension mania score ≥ 6 (A-LAI treatment continuation odds increased by 3.5 times). The A-LAI treatment continuation rate increased in patients with lifetime psychotic spectrum (SCIPSY) schizoid score ≤ 11, compared to patients with psychotic spectrum (SCI-PSY) schizoid score ≥ 12 (A-LAI treatment continuation odds increased by 3.5 times).

A-LAI treatment continuation rate increased in patients with CGI score ≤ 4 and schizophrenia dimension (LDPS) mania score ≤ 5 AND psychotic spectrum (SCI-PSY) schizoid score ≤ 11, compared to patients with CGI ≥ 5 and (LDPS) mania ≥ 6 and (SCI-PSY) schizoid ≥ 12 (A-LAI treatment continuation odds increased by 4.9 times). Fig. 3 reports the percentage of patients who were persistent to A-LAI for at least 6 months and the clinical profile of patients who are more likely to persist on A-LAI. Figure 4 reports the cut off predicted values for CGI, LDPS mania score and psychotic spectrum (SCI-PSY) schizoid score.

Table 2
Relationship between demographic/clinical characteristics and persistence with A-LAI for at least 6 months (univariate analysis).

Demographic and clinical characteristics	Persistent (n = 225)	Not Persistent (n = 36)	p-value
Gender (males - females, %)	60.4–39.6	52.8–47.2	0.465 [1]
Age (median, years)	39.0	44.5	0.129 [2]
Marital status (single, %)	72.4	55.6	0.320 [1]
Education (Secondary School - University Degree, %)	42.7–10.7	36.1–2.8	0.019 [1]
Occupation (No occupation, %)	65.3	83.3	0.009 [1]
Living situation and family support (Live alone, %)	19.6	27.8	0.267 [1]
Number of previous schizophrenia relapses within the 2 years prior to the index date (mean ± SD)	1.3 ± 1.18	1.3 ± 0.88	0.893 [3]
Number of previous mental-health related hospitalizations within the 2 years prior to the index date (mean ± SD)	0.9 ± 1.25	1.1 ± 0.91	0.461 [3]
Number of previous AP within the 2 years prior to the index date((mean ± SD)	1.9 ± 1.15	1.9 ± 0.86	0.998 [3]
Last AP prior to AM (Aripiprazole, %)	61.3	63.9	0.854 [1]
History of non-compliance in the 3 months prior to the index date (Yes, %)	37.3	50.0	0.197 [1]
Alcohol and drug abuse or dependence at the index date(Yes, %)	15.6	19.4	0.621 [1]
Time since schizophrenia diagnosis (median, years)	8.0	13.2	0.100 [3]
Health setting at AM initiation (Inpatient care, %)	28.0	50.0	0.012 [1]
Reason to initiate AM treatment (Efficacy, %)	14.7	11.1	0.272 [1]
Concomitant schizophrenia medications at date of AM initiation (Yes, %)	60.0	72.2	0.350 [1]
Concomitant non-schizophrenia medications at date of AM initiation (Yes, %)	52.0	44.4	0.280 [1]
Psychiatric comorbidity: Depressive episode (Yes, %)	18.2	11.1	0.348 [1]
Psychiatric comorbidity: Schizophrenia/psychosis (Yes, %)	84.0	80.6	0.472 [1]
Psychiatric comorbidity: Bipolar disorder (Yes, %)	6.2	5.6	1.000 [1]
Psychiatric comorbidity: Anxiety disorder (Yes, %)	12.4	13.9	0.793 [1]
Psychiatric comorbidity: Eating disorder (Yes, %)	3.6	0.0	0.605 [1]
Psychiatric comorbidity: Sleep disorder (Yes, %)	14.2	25.0	0.131 [1]
Psychiatric comorbidity: Other addiction disorder (Yes, %)	15.1	19.4	0.621 [1]
CGI-S at the index date (scores ranging from 5 to 7, %)	46.2	75.0	0.002 [1]
Schizophrenia dimensions (LDPS): Psychosis score (mean ± SD)	14.0 ± 6.27	15.2 ± 4.27	0.261 [3]
Schizophrenia dimensions (LDPS): Schizophrenia syndrome score (mean ± SD)	7.6 ± 7.55	9.5 ± 7.81	0.172 [3]
Schizophrenia dimensions (LDPS): Nonaffective psychosis score (mean ± SD)	4.1 ± 3.12	4.0 ± 3.14	0.899 [3]
Schizophrenia dimensions (LDPS): Negative symptoms score (mean ± SD)	6.5 ± 4.92	6.3 ± 5.15	0.777 [3]
Schizophrenia dimensions (LDPS): Disorganization score (mean ± SD)	5.8 ± 4.38	7.9 ± 4.76	0.008 [3]
Schizophrenia dimensions (LDPS): Depression score (mean ± SD)	2.3 ± 2.69	1.9 ± 2.50	0.370 [3]
Schizophrenia dimensions (LDPS): Mania score (mean ± SD)	1.2 ± 2.18	1.8 ± 2.62	0.138 [3]
Schizophrenia dimensions (LDPS): Mood psychosis score (mean ± SD)	3.1 ± 3.15	3.7 ± 3.72	0.280 [3]
Psychotic spectrum (SCI-PSY):Interpersonal sensitivity (mean ± SD)	4.7 ± 2.71	4.5 ± 2.55	0.708 [3]
Psychotic spectrum (SCI-PSY): Paranoid (mean ± SD)	31.1 ± 15.53	37.7 ± 13.62	0.016 [3]
Psychotic spectrum (SCI-PSY): Schizoid (mean ± SD)	7.6 ± 3.78	9.6 ± 3.89	0.005 [3]
Psychotic spectrum (SCI-PSY): Misperceptions (mean ± SD)	2.6 ± 2.38	3.2 ± 2.44	0.168 [3]
Psychotic spectrum (SCI-PSY): Typical symptoms (mean ± SD)	8.5 ± 6.63	10.0 ± 6.37	0.205 [3]
Starting AM dose (mg, mean ± SD)	389.1 ± 31.04	400.0 ± 0.00	0.037 [3]

[1] Fisher`s Exact test
[2] Mann-Whitney U test
[3] Student`s t-test

Table 3
CGI-S at A-LAI Initiation and number (%) of subjects who were persistent (FAS, N = 261).

CGI at A-LAI initiation	Number of patients with CGI value	Number of persistent patients	% Persistent
0	53	52	98%
1	4	4	100%
2	2	2	100%
3	21	20	95%
4	50	43	86%
5	72	59	82%
6	49	36	73%
7	10	9	90%
Total	261	225	

4. Discussion

Personalized medicine separates patients into different groups based on biological and clinical characteristics that are unique for each person or group of persons, with the goal of tailoring interventions to the individual patient based on the predicted response and the aim of targeting treatments able to result in the best outcomes for each patient or groups of patients. In medical fields like oncology or infectious diseases, personalized medicine is the standard of practice. Mental health treatment is gradually moving in the same direction (Manchia & Carpiniello, 2018). However, most research is still conducted grouping together individuals that are very different from each other, even if they share the same diagnosis. Indeed, clinical trials are conducted based on a comparison between one medication (e.g. an antipsychotic, in schizophrenia) and another medication, or placebo, with the goal to establish which option is better. Yet, many studies do not consider that schizophrenia is a heterogeneous condition and that different patients respond differently to the same medication. For instance, a clinical trial comparing two different drugs, each resulting in 50% of response, would likely conclude that the two medications are equivalent. However, clinical practice shows that the 5 out of 10 patients who respond to the first medications are not necessarily the same 5 out of 10 patients who respond to the second drug. We believe that, although the importance of the trials like those mentioned above should not be discounted, our field would benefit from additional studies, able to go above and beyond the comparison of two drugs (or a drug and placebo) for the percentage of responders or mean change in the score of an outcome measure. For instance, it would be important to know what the demographic, clinical, biological characteristics are of the patients who tolerate and respond to one medication, compared to those who do not. To this end, we attempted to evaluate treatment persistence with A-LAI in this relatively large, retrospective, naturalistic, non-randomized study of real-world patients with schizophrenia. Of course, this design carries several limitations, which we hereby acknowledge. However, we believe that the characteristics above may also be

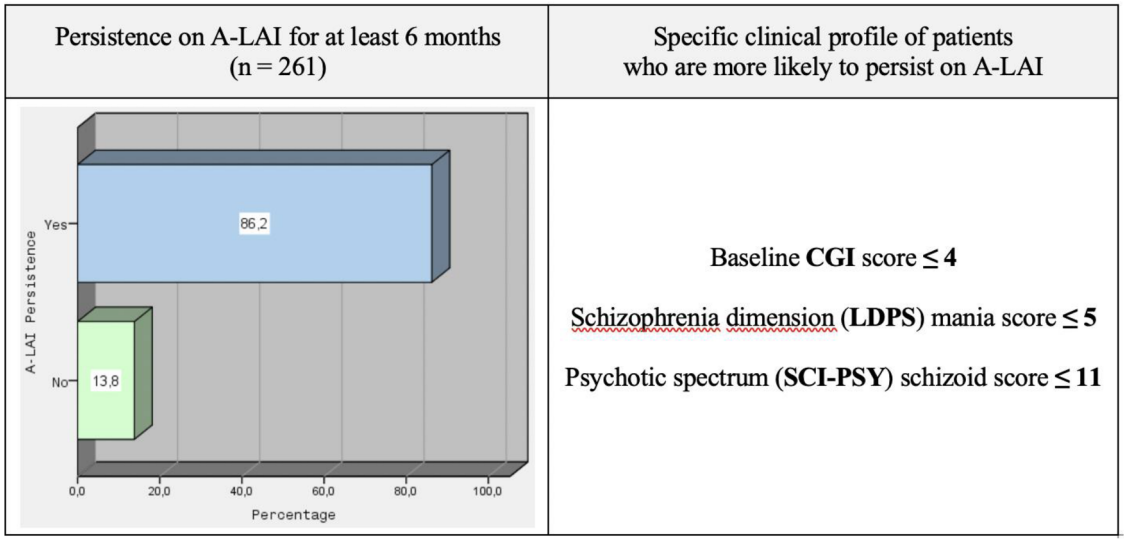


Fig. 3. Clinical profile of patients who are more likely to persist on A-LAI.

considered as a strength, in that a retrospective and non-randomized study permits to evaluate real life patients who would unlikely participate in a prospective, randomized clinical trial. Also, the retrospective design permits to evaluate the clinical course and decisions that were taken during the treatment, free of any risk of direct or indirect bias, due to the participation in a study. Indeed, even retrospective studies were included in a very recent meta-analysis on comparative effectiveness of LAI versus oral antpsychotics (Kishimoto et al., 2018).

We found a high rate of adherence and persistence, with only 14% of A-LAI patients that did not continue the medication for at least 6 months, despite the fact that the study was designed to completely reflect clinical practice and to avoid the structured setting of a clinical trial, which usually improves adherence and persistence. In fact, individuals who agree to participate in a clinical trial are usually more likely to be adherent to the prescribed medication, compared with patients who are treated in the real world standard clinical practice (Shirley and Perry, 2014). Also, the structured setting of a clinical trial, which includes regular monitoring and assessments, may reduce rates of non-adherence- non-response. Moreover, clinical trials usually have very tight inclusion and exclusion criteria, which was not the case of the present study, which included patients who were relatively severe and who started A-LAI relatively early, most likely immediately after the acute symptoms had been stabilized, as opposed to starting it several days/weeks after a complete stabilization of acute symptoms. In fact, the mean CGI at A-LAI start was 3.8, which signals either a stable yet severe schizophrenia or a syndrome that has not been completely stabilized yet, at least for some of the patients. We found that A-LAI treatment continuation odds were significantly higher in patients with CGI score ≤ 4, which suggests a relatively high persistence with A-LAI in patients with currently (at the time of A-LAI initiation) mild and moderate symptoms of schizophrenia at the time of A-LAI initiation. Of note, A-LAI is approved in Italy with an indication for adult patients who have been stabilized on oral aripiprazole. However, the label does not specify which level of stabilization is recommended, and we find it interesting that patients that were started on A-LAI at a time when they were still experiencing moderately severe symptoms of schizophrenia (CGI = 4) were still likely to benefit from the medication. It is not surprising that the very severe patients were less likely to be persistent. However, it is noteworthy that 82% of subjects with baseline CGI of 5, 73% of subjects with baseline CGI of 6 and 90% of subjects with baseline CGI of 7 were persistent.

Several limitations should be acknowledged. First, most patients were not on monotherapy. Second, the instruments exploring lifetime psychotic spectrum that were administered at the time of study entry, the SCI-PSY and LDPS, are able to catch all symptoms and signs that were present at the time when AM was started (at least 6 months before study entry). However, a study subject could have developed new (i.e., never experienced before) psychotic symptoms between the time when AM was started and the time when the individual entered the study and received the assessments. We believe that it is unlikely that this has influenced the study results but we nonetheless acknowledge this limitation.

Third Italian Mental Health system is quite different than other health care systems, and the results of our paper may not be completely applicable to other settings. For instance, the persistence on A-LAI was very high in this study, and this may be influenced by the relatively high degree of schizophrenia focused community-based psychiatric services in Italy (Piccinelli et al., 2002). Fourth, there is a possibility of a selection bias. Although the number (n = 20) of patients who declined to participate in the study is relatively small compared to the full study sample, this group might be sicker, more paranoid, more likely to be non-adherent with their medications, which might at least partially bias the results of our study. Moreover, patients who were taking A-LAI at the time of study entry may have been less likely to be missed by error from recruitment. However, during the investigator meetings, we strongly and repeatedly emphasized the need to recruit all consecutive A-LAI patients, warning the study centers to be careful to not miss those patients who were no longer taking A-LAI at study entry. Finally, we did not measure functionality and quality of life and hence are unable to completely establish treatment effectiveness. However, treatment persistence is not just a proxy of adherence. In fact, we believe that very few clinicians would continue prescribing the medication to patients that are still willing to take it but are experiencing poor functioning and quality of life.

5. Conclusions

Our results identify a specific clinical profile of patients who are clearly more likely to respond, tolerate and benefit from A-LAI. These individuals include patients with mild, moderate or relatively severe forms of schizophrenia at the time of A-LAI initiation, i.e. patients with a CGI less than 5 when the medication is started, with a lifetime SCI-PSY schizoid score up to 12 and with a lifetime LPDS mania score up to 6. That people who meet the criteria above correspond to the majority of treated patients with schizophrenia and may strongly benefit from A-LAI, consistently with our clinical observations.

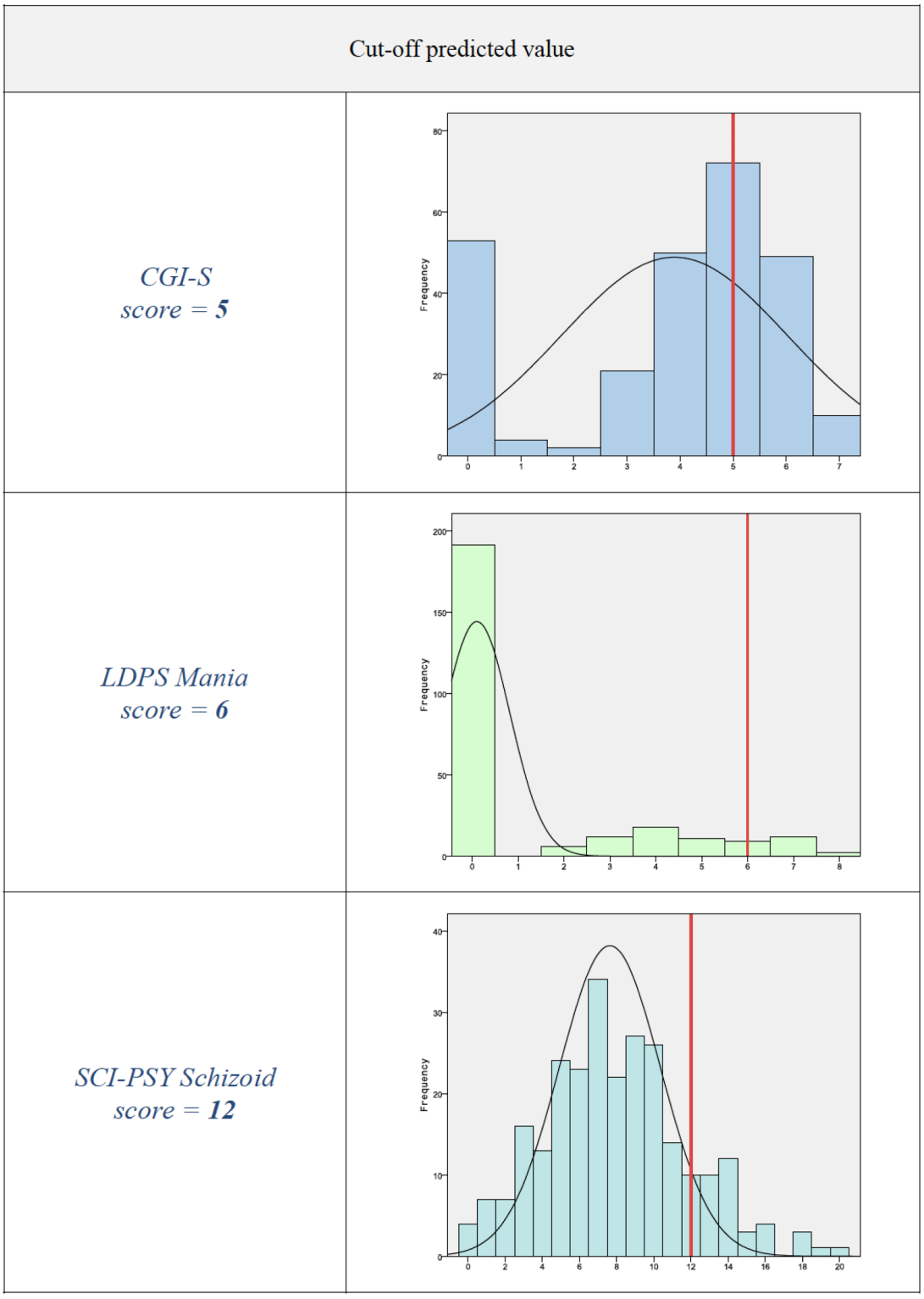


Fig. 4. Cut off predicted values.

Similarly, it is consistent with our clinical observations that extremely severe individuals are more unlikely to persist and benefit from A-LAI, unless this medication is coupled with intense adjunctive interventions (e.g., targeted psychosocial interventions, such as cognitive remediation, which was not offered at any of our recruiting sites) or, for the most severe cases, unless it is used in combination with medications such as clozapine, when monotherapy with these agents is not effective enough. However, we find it interesting that 82% of subjects with CGI of 5, 73% of subjects with baseline CGI of 6 and 90% of subjects with baseline CGI of 7 were persistent. Larger, prospective and longer (i.e. with an observation time greater than 6 months) studies are warranted.

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Contributions

Andrea Fagiolini was the signatory investigator on the study and contributed to the concept and design of the study. All authors contibuted to the interpretation of the data, revised and approved the final content of the manuscript.

Conflicts of interest

Andrea Fagiolini is /has been a consultant and/or a speaker and/or has received research grants from Allergan, Angelini, Apsen, Boheringer Ingelheim, Doc Generici, FB-Health, Italfarmaco, Janssen, Lundbeck, Mylan, Otsuka, Pfizer, Recordati, Sonofi Aventis, Sunovion, Vifor; Bernardo Carpiniello has received research grants and/or has been a consultant for, and/or has been a speaker for: ACRAF Angelini, Janssen Cilag Italia, Lundbeck Italia, Otsuka Italia; Sergio de Filippis has received research grants and/or has been a consultant for, and/or has been a speaker for: Angelini, Lundbeck, Janssen, Otsuka, Mylan; Serafino De Giorgi has received research grants and/or has been a consultant for, and/or has been a speaker for: Angelini, Eli Lilly, Generici DOC, Lundbeck, Janssen, Otsuka, Pfizer; Maria Grazia Giustra and Luisa Vernacotola are employees of Otsuka Pharmaceuticals Italy; Claudio Mencacci has received research grants and/or has been a consultant for, and/or has been a speaker for Lundbeck, Janssen, Italfarmaco; Gino Montagnani is an employee of Lundbeck Italy; Giorgio Pigato has received research grants and/or has been a consultant for, and/or has been a speaker for: Angelini, Lundbeck, Janssen, Otsuka, Pfizer, Roche, Eisai; Antonio Vita has received research grants and/or has been a consultant for, and/or has been a speaker for Angelini, Boheringer Ingelheim, Eli Lilly; Fidia, Forum Pharmaceutical; Janssen- Cilag, Lundbeck; Otsuka; Recordati; Roche.

All other Authors declare no conflict of Interest

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References

Kaplan, H, Casoy, J, Zummo, J, 2013. Impact of long-acting injectable antipsychotics on medication adherence and clinical, functional, and economic outcomes of schizophrenia. Patient Prefer Adherence 7, 1171–1180.

Kishimoto, T, Hagi, K, Nitta, M, Leucht, S, Olfson, M, Kane, JM, Correll, CU, 2018. Effectiveness of Long-Acting Injectable vs Oral Antipsychotics in Patients With Schizophrenia: a meta-analysis of prospective and retrospective cohort studies. Schizophr Bull. 44 (3), 603–619 6.

Kishimoto, T, Nitta, M, Borenstein, M, Kane, JM, Correll, CU, 2013. Long-acting injectable versus oral antipsychotics in schizophrenia: a systematic review and meta-analysis of mirror-image studies. J. Clin. Psychiatry 74 (10), 957–965.

Kishimoto, T, Robenzadeh, A, Leucht, C, Leucht, S, Watanabe, K, Mimura, M, Borenstein, M, Kane, JM, Correll, CU, 2014 Jan Jan. Long-acting injectable vs oral antipsychotics for relapse prevention in schizophrenia: a meta-analysis of randomized trials. Schizophr Bull 40 (1), 192–213.

Levinson, DF, Mowry, BJ, Escamilla, MA, Faraone, SV, 2002. The Lifetime Dimensions of Psychosis Scale (LDPS): description and interrater reliability. Schizophr Bull 28 (4), 683–695.

Lieberman, JA, Stroup, TS, McEvoy, JP, et al., 2005. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N. Engl. J. Med. 353, 1209–1223.

Manchia, M, Carpiniello, B, 2018, 16. Personalized psychiatry: promises and pitfalls. Neurosci. Lett. 669, 1–2.

Ostuzzi, G, Mazzi, MA, Terlizzi, S, Bertolini, F, Aguglia, A, Bartoli, F, Bortolaso, P, Callegari, C, Caroleo, M, Carrà, G, Corbo, M, D'Agostino, A, Gastaldon, C, Lucii, C, Magliocco, F, Martinotti, G, Nosé, M, Ostinelli, EG, Papola, D, Piccinelli, MP, Piccoli, A, Purgato, M, Tabacchi, T, Turrini, G, Ruggeri, M, Barbui, C, 2018. STAR Network Investigators- Factors associated with first - versus second-generation long-acting antipsychotics prescribed under ordinary clinical practice in Italy. PLoS One 13 (8), e0201371.

Piccinelli, M, Politi, P, Barale, F, 2002. Focus on psychiatry in Italy. Br. J. Psychiatry 181 (6), 538–544.

Pinna, F, Deriu, L, Diana, E, Perra, V, Randaccio, RP, Sanna, L, Tusconi, M, Carpiniello, B, Cagliari Recovery Study Group, 2015. Clinical Global Impression-severity score as a reliable measure for routine evaluation of remission in schizophrenia and schizoaffective disorders. Ann. Gen. Psychiatry 14, 6 13.

Sbrana, A, Dell'Osso, L, Benvenuti, A, Rucci, P, Cassano, P, Banti, S, et al., 2005. The psychotic spectrum: validity and reliability of the structured clinical interview for the psychotic spectrum. Schizophr Res. 75 (2-3), 375–387 15.

Shirley, M, Perry, CM, 2014. Aripiprazole: a review of its use as maintenance treatment for adult patients with schizophrenia. Drugs 74, 1097–1110.