UNIVERSITÀ DEGLI STUDI DI VERONA
DEPARTMENT OF NEUROSCIENCE, BIOMEDICINE AND MOVEMENT SCIENCES

PhD School in Life and Health Sciences
PhD in Neuroscience, Psychological and Psychiatric Sciences, and Movement Sciences

Cycle XXX/2014

Long-acting antipsychotics: patient's features and prescribing attitudes in Italy. Findings from the cross-sectional phase of an observational, longitudinal, multicenter study.

S.S.D. MED/25

Coordinator: Prof. Leonardo Chelazzi

Tutor: Prof. Corrado Barbui

Candidate: Dr. Giovanni Ostuzzi

Abstract

Scientific background. Long-acting injectable antipsychotics (LAIs) are considered one of the most important tools for ensuring medication adherence in people with chronic psychosis. In recent times many authors promoted an earlier and broader use of LAIs, considering not only their efficacy in preventing non-adherence (and therefore relapses), but also their potential role in simplifying the daily medication routine, ultimately ameliorating patient's quality of life. On this background, this study aims at describing how this new perspective influenced prescribing pattern in Community Psychiatry Services, with a specific interest in comparing first- and second-generation antipsychotics.

Methods. The STAR Network "Depot" Study is an observational, longitudinal, multicenter study involving 35 Italian Community Psychiatry Services. Adult patients initiating a new LAI were recruited over a 12-months period and assessed for relevant socio-demographic and clinical features (employing also validated rating scales) at baseline, after 6 and 12 months. Descriptive statistics and a stepped multivariate logistic model accounting for the inter-center variability were employed.

Results. Only results from the recruitment (or cross-sectional) phase will be discussed here. Four-hundred-fifty-one patients, mostly males over their 30s, were recruited. Patients were heterogeneously distributed between higher and lower levels of education, social functioning, overall symptom profiles and medication adherence. Beside schizophrenia, also bipolar disorders, personality disorders and mental organic conditions were well represented. Paliperidone and aripiprazole were the most frequently prescribed medications. Analyses showed that, compared to first-generation LAIs, second-generation LAIs were more likely to be prescribed to younger, employed patients, with higher affective symptoms, a diagnosis different from schizophrenia or bipolar disorder, and fewer previous LAI prescriptions.

Discussion. LAIs are prescribed to heterogeneous populations of patients, often even off-label. The advocated paradigm shift is under way in clinical practice, although it appears to be largely limited to second-generation LAIs.

Index

Introduction

In recent years, many authors highlighted the potential advantages of a broader and earlier prescription of long-acting injectable antipsychotics (LAIs) based on several assumptions, including (a) the growing evidence of their superiority in preventing relapses, hospitalization and lack of adherence, as compared to oral antipsychotics, which is of utmost relevance in the early stages of disease; (b) the progressive overcoming of old misconceptions about the perceived coercion and stigma associated with these formulations; and (c) the growing awareness that the practicality of LAIs may contribute to considerably simplify the daily routine of patients, possibly ameliorating their overall quality of life and even their global attitude toward psychotropic medication. Also, the scenario widely changed in the last decade, considering the progressive introduction of second-generation antipsychotics (SGAs) LAIs on the market, and, in general, a growing interest in the use of SGAs not only for the treatment of schizophrenia and related chronic psychosis, but also for bipolar disorder and resistant depression.

The STAR Network "Depot" study was designed with the aim of describing a population of patients initiating a new LAI in Italian Community Psychiatric Services and to longitudinally assess their clinical status, as well as adherence and subjective perception of medications over one year of treatment. The first phase focused on describing socio-demographic and clinical features this cohort of patients at baseline, with the ultimate goal of evaluating prescribing patterns of LAIs, and to assess whether and how the new perspective on their clinical employment was actually implemented in clinical practice. Relevant features of the cohort will be described in detail, and possible associations between these features and the choice of FGA versus SGA LAIs will be explored using a stepped logistic analysis. Results will be critically discussed in the light of available scientific evidence, methodological advantages and pitfalls, current clinical guidelines, regulatory implications, as well as factors specifically related to the setting of care.

Chapter 1

Scientific Background

The problem of both hidden and overt non-adherence to medications is of major concern in mental health, and particularly in patients with psychotic disorders (Nosé et al., 2003), leading to severe consequences on the disease's course (Stevens et al., 2016; Kirschner et al., 2013; Stahl, 2014). It is estimated that up to 40% of patients will autonomously suspend the antipsychotic medication within one year from its introduction, and about four over five of these patients will experience a disease relapse within the following five years. Furthermore, the number of psychotics relapses during the first five years of disease is associated a higher risk of chronic course of disease, functional impairment, social and relational withdrawal, and irreversible brain damage. This is particularly worrisome considering that the actual level of adherence is likely to be usually underestimated by clinicians. Patients' attitudes toward psychotropic medications and their level of adherence are complex and multifaceted constructs, in which many interacting factors come into play (Nunes et al., 2009) (Figure 1).

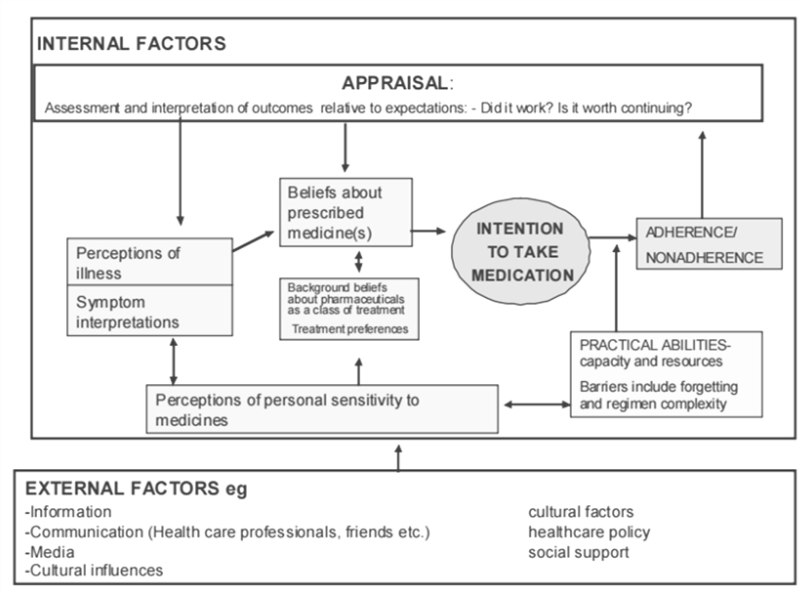


Figure 1. Internal and external factor involved in determining therapy adherence and attitudes toward psychotropic medications. From Horne, R. Concordance, Adherence and Compliance in Medicine Taking. Report for the National Co-ordinating Centre for NHS Service and Delivery Organisation R&D (NCCSDO) (2005), p. 139; reported in Nunes et al., 2009.

Intramuscular long-acting formulations of antipsychotics (LAIs) were developed with the primary aim of controlling this phenomenon (Haddad et al., 2014). Some disadvantages of these medications have frequently been highlighted, including pain on the injection site, lack of flexibility in dose adjustments, and the patient's perception of stigma and coercion (Brissos et al., 2014). However, relevant advantages emerged as well. For instance, these formulations allow the complete tracking of drug intake, lowering the risk of self-medication and harmful drug use (Narasimhan et al., 2007; Brissos et al., 2014), and have also been claimed to prevent acute adverse events and relapses due to sudden drug interruptions (Moncrieff, 2006). The main advantages and disadvantages of LAIs are reported in Table 1.

Table 1. Summary of the main advantages and disadvantages of LAIs.

Advantages	**Disadvantages**
▪ Complete adherence traceability; ▪ Lower risk of disproportionate medication intake (on voluntary or involuntary basis); ▪ Closer monitoring of the patient; ▪ Higher bioavailability: it is easier to detect and maintain the minimum effective dose; ▪ No risk of symptoms of sudden medication interruption; ▪ Practicality: less time dedicated to the therapy (including going to retrieve the prescription, going the pharmacy, remember to take the oral medication one or more times every day); ▪ Possible reduction conflicts with parents and other family members, who are frequently required (implicitly or explicitly) to supervise the correct intake of medications.	▪ Pain and lesions in the site of injection (particularly for oily preparations); ▪ Slow titration; ▪ Slow resolution of possible adverse events after suspending the medication; ▪ Less flexibility in personalizing the overall dose; ▪ Post-injection dysphoria; ▪ *Post-injection delirium/sedation syndrome* (olanzapine); ▪ Perception of a coercive or even punitive intent by administering of the medication; ▪ Perception of LAI as stigmatizing medications.

When comparing the risk of relapse between LAI and oral antipsychotics, observational studies (including prospective, retrospective and mirror-image studies)

generally showed a clear advantage of the former (Tiihonen et al. 2006; Tiihonen et al., 2011; Brnabic et al. 2011; Bitter et al., 2013), also when combined in meta-analyses (Kirson et al., 2013; Kishimoto et al., 2013). On the contrary, randomized controlled trials (RCTs) produced controversial evidence. A meta-analysis by Leucht and colleagues (Leucht et al., 2011) showed that outpatients taking LAIs had a lower risk of relapse, as compared to the oral group (10 RCTs of at least one year of follow-up; 1672 patients; relapse rate: RR 0.70, 95% CI 0.57 to 0.87), while another meta-analysis (Kishimoto et al., 2014), which included also studies with shorter follow-up periods and recruiting inpatients, did not show significant differences between the two antipsychotic formulations (21 RCTs; 4950 patients; relapse rate: RR 0.93, 95% CI 0.80 to 1.08). Such conflicting data may be at least partially explained by relevant methodological limitations of RCTs in these particular patients (Ostuzzi and Barbui, 2016; Fagiolini et al., 2017). As a matter of fact, these studies are particularly prone to selection bias, considering that recruited patients must adhere to rigid therapeutic schedules (for example, double-dummy procedures) and should therefore have relatively high levels of adherence. This bias might be responsible for a high degree of indirectness of RCTs, hampering their generalizability to real-world clinical practice. On the other hand, observational studies may have some advantages in terms or external validity, as a large number of patients from real-world settings can be recruited and can undergo longer follow-up periods (Kane et al., 2013).

Qualitative studies exploring the subjective experience of patients prescribed with LAIs contributed to rethink the possible role of perceived stigmatization associated with these formulations. In many cases, patients emphasized the enhanced practicality of LAIs, a reduced perception of being controlled by parents or other family members, and an overall better overall attitude toward medications (Patel et al., 2009; Das et al., 2014; Walburn et al., 2001; Iyer et al., 2013; Pietrini et al., 2016).

As a result of this growing body of knowledge, the most influential clinical guidelines agree in recognizing LAIs as (a) a valid tool for preventing disease relapses and optimizing adherence; (b) a choice which is justified from the early phases of disease; (c) a practical approach to simplify the routine of patients, which should be therefore

always discussed and presented as an alternative option to oral antipsychotics. Excerpts from some of the most recent guidelines are reported in Table 2.

Table 2. Synthesis of the most recent guidelines on LAI prescription

Source	Year	Excerpts from the recommendation
BAP (British Association of Psychopharmacology) (Barnes et al., 2011)	2011	▪ A depot/long-acting injection formulation should be considered when this is preferred by the patient, previous non-adherence has led to frequent relapse or the avoidance of non-adherence is a clinical priority. ▪ The place of antipsychotic depot/long-acting injections for first-episode schizophrenia [and for the treatment of aggressive behavior] remains uncertain
SIGN (Scottish Intercollegiate Guidelines Network) (SIGN, 2013)	2013	▪ Individuals with schizophrenia who request depot and those with medication adherence difficulties should be offered maintenance treatment with depot antipsychotic medication. ▪ Service users should be given the option of oral or depot medication, in line with their preference.
NICE (National Institute for health and Clinical Excellence) (NICE, 2014)	2014	▪ Consider offering depot/long-acting injectable antipsychotic medication to people with psychosis or schizophrenia: (a) who would prefer such treatment after an acute episode; (b) where avoiding covert non-adherence (either intentional or unintentional) to antipsychotic medication is a clinical priority within the treatment plan. ▪ When initiating LAI [...] take into account the same criteria recommended for the use of oral antipsychotic medication [...].
RANZCP (Royal Australian and New Zealand College of Psychiatrists) (Galletly et al., 2016)	2016	▪ Long-acting injectable antipsychotic agents should be offered to patients early in the clinical course of schizophrenia. ▪ Consider the use of long-acting injectable antipsychotic medicines if: - the individual prefers a long-acting injectable medicine, - adherence has been poor or uncertain, - there has been a poor response to oral medication. ▪ Long-acting injectable antipsychotic agents, particularly SGAs, provide an important treatment option in all phases of the disease for people whose adherence to oral treatment is poor.

Very few available evidence focuses on the pharmacological and clinical characteristics of single LAIs, the choice of which can be influenced by several

considerations. First, because of pharmacokinetic features, LAIs may not be simply comparable to oral counterparts in terms of efficacy and tolerability (Ereshefsky & Mascarenas, 2003), although this hypothesis failed to be confirmed by data from clinical studies (Ostuzzi et al., 2017a). Second, beside the known differences between antipsychotics (Leucht et al., 2013), the tolerability of LAIs may be influenced by other pharmacological features (Whyte and Parker, 2016), including the type of preparation of the injection (oily preparations of FGA LAIs are more likely to have a locally irritant effect), the volume of injected medication, the time required for reaching the steady state, the absorption rate (and therefore the interval between administrations), and also some mandatory clinical precautions (e.g. the necessity of a three-hour clinical monitoring for patients administered with olanzapine pamoate) (see Table 3).

Table 3. Main pharmacological characteristics of LAIs (adapted from Whyte and Parker, 2016).

Medication	**Preparation for the injection**	**Frequency of administration**	**Time to reach the steady state (approximate)**	**Notes**
Haloperidol decanoate	Sesame oil preparation	4 weeks	12-16 weeks	-
Fluphenazine decanoate	Sesame oil preparation	2-5 weeks	12 weeks	-
Zuclopenthixol decanoate	Vegetal oil preparation	2-4 weeks	8 weeks	-
Risperidone long-acting	Watery preparation	2 weeks	8 weeks	-
Paliperidone palmitate	Watery preparation	4 weeks	20 weeks	-
Olanzapine pamoate	Watery preparation	2-4 weeks	12 weeks	Mandatory 3-hour clinical monitoring
Aripiprazole long-acting	Watery preparation	4 weeks	20 weeks	-

In order to pragmatically inform this choice, randomized clinical trials comparing two or more LAIs head-to-head would be of relevance. Currently only few studies

have been conducted, and they did not show relevant differences between LAIs, with the possible exception of aripiprazole long-acting, which was superior in terms of quality of life, efficacy and tolerability when compared with paliperidone palmitate (Naber et al., 2015) (Table 4). Of notice, only this study included quality of life as the primary outcome. Considering this lack of evidence, NICE guidelines (NICE, 2014) explicitly recommend to take into account the same criteria applied for the choice of oral antipsychotic medication when beginning a LAI.

Table 4. Synthesis of randomized controlled trials comparing LAIs head-to-head

First author, year	Comparison	Main study characteristics	Synthesis of results
Li et al., 2011	PALI vs. RIS	OL; n=452; dia=SCZ; FU=13	No efficacy and tolerability differences.
Pandina et al, 2011	PALI vs. RIS	DB; n=259; dia=SCZ; FU=13	No efficacy and tolerability differences.
McEvoy et al., 2014	PALI vs. ALO	DB; n=311; dia=SCZ/SCZ-AFF at high relapse risk; FU=24	No efficacy differences. Different tolerability profiles emerged.
Naber et al., 2015	PALI vs. ARI	OL; n=295; dia=SCZ; FU=28	ARI was superior in terms of quality of life, efficacy and tolerability.

Legend: PALI=paliperidone; RIS=risperidone; ALO=haloperidol; ARI=aripiprazole; n=number of included patients; dia=diagnosis; SCZ=schizophrenia; SCZ-AFF=schizo-affective syndrome; FU=weeks of follow-up; OL=open-label design; DB=double-blind design.

Evidence from the first decade of 2000 showed that LAIs were generally prescribed to severely ill patients, with long-lasting disease, frequent relapses, low insight of

disease and poor adherence to treatments, or to patients with behavioral issues, impulsivity, aggressiveness (including not only patients with psychosis, but also mental organic conditions, such as mental retardation, dementia and substance abuse) (Svedberg et al., 2003; Shi et al., 2007; Waddell and Taylor, 2009). Since then, many factors contributed to change the scenario. First, most second-generation LAIs (SGA-LAIs) were introduced on the market only in the last decade (with the only exception of risperidone, available in Europe from 2003) (Citrome, 2013; Ostuzzi et al., 2017b). Second, growing evidence supported the role of antipsychotics (and SGAs in particular) not only for schizophrenia or other chronic psychoses, but also for affective disorders (Cipriani et al., 2011; Gigante et al., 2012; Kishi et al., 2016). Third, many authors claimed the need for a renewed view on the potential benefits of LAIs. According to this perspective, LAIs are generally underused, but may in fact provide benefits to a broader number of patients, including in particular younger patients, at early stages of disease, and not only patients with a longstanding chronic disease, frequent relapses, low adherence and poor insight (Patel et al., 2005; Altamura et al., 2012; Maia-de-Oliveira et al., 2013; Stahl, 2014; Heres, 2014; Carpenter and Buchanan, 2015; Stevens et al., 2016). This "paradigm change" is claimed on the basis of new insights on:

a. the long-term impact of the early interruption of antipsychotic treatments (Stevens et al., 2016; Stahl, 2014; Kirschner et al., 2013);
b. the practicality of LAIs and therefore their impact on quality of life as perceived by patients (Walburn et al., 2001; Iyer et al., 2013; Montemagni et al., 2016), in contrast with a rooted idea of LAIs as coercive and stigmatizing medications (James et al., 2012; Patel et al., 2010; Stevens et al., 2016);
c. a possibly enhance tolerability of LAIs over their oral counterparts due to favorable pharmacokinetic features (Ereshefsky and Mascarenas, 2003; Mannaert et al., 2005; Fleischhacker et al., 1994; Moncrieff, 2006). This hypothesis still need to be fully verified, although it is not supported by data from available RCTs (Ostuzzi et al., 2017a).

Although in the last fifteen years we witnessed a growing interest for LAI medications in scientific literature, only few original studies on prescribing patterns have been conducted in recent years (Rossi et al., 2012; Morrato et al., 2015; Singh et al, 2016; Lee et al., 2017; Decuypere et al., 2017; Pilon et al., 2017; McCreath et al.,

2017). Furthermore, the generalizability of these studies is limited by heterogeneous methodology and inclusion criteria, as well as a limited number of patients recruited. Therefore, it is not clear whether and how the advocated paradigm shift was implemented in real-world clinical practice.

In conclusion, current scientific evidence on LAIs efficacy produced conflicting data, raising clinical and methodological issues. This scientific knowledge is particularly complex to interpret and to translate into straightforward guidelines for clinicians. Alongside with efficacy data from clinical trials and meta-analysis, observational and descriptive studies, possibly including qualitative outcomes on subjective perception and attitude toward medication, may be of great value for helping the clinician in identifying who may really benefit from a LAI under ordinary clinical practice.

Chapter 2

Materials and methods

Research Aims

The STAR Network "Depot" is composed by a cross-sectional phase and a subsequent longitudinal phase. The cross-sectional phase (already concluded) aimed at assessing how the change of scenario around the clinical role of LAIs was received and implemented into real-world Psychiatry Services in Italy. The longitudinal phase (still ongoing) aims at evaluating the impact of LAIs on a number of outcomes pertaining symptom profiles and subjective perception of treatments.

In particular, the following aims were pursued:

1. Describing the socio-demographic characteristics and the main clinical features (including symptom profiles, adherence and attitude towards treatments) of a population of patients beginning a new treatment with a LAI;
2. Evaluating whether these characteristics differ according to the type of LAI;
3. Describing the characteristics of prescribers and to examine which reasoning and evaluation underpinned the choice of a LAI;
4. Evaluating, after 6 and 12 months of follow-up, the impact of LAIs using the following outcomes: (a) symptom profiles; (b) treatment adherence; (c) hospitalizations frequency; (d) rate of patients prematurely withdrawing the treatment. On a descriptive and explorative purpose, possible associations between these outcomes and the main socio-demographic and clinical characteristics of patients will be assessed.

The STAR Network

Participating centers are part of the STAR Network (*Servizi Territoriali Associati per la Ricerca*), which is a consortium of clinicians and researchers from Community Psychiatric Services all over Italy. The main aim of this group it to perform pragmatic studies on clinically relevant topics, by gathering data from real-world practice. The activities of the STAR Network are coordinated by the Unit of Clinical

Psychopharmacology, Section of Psychiatry, University of Verona (Prof. Corrado Barbui). In recent years this group contributed to provide new insights on relevant aspects related to the field of psychopharmacology, including the use of lithium for patients at risk of suicide, the combination of antipsychotics for treatment-resistant patients, and the risk of QTc prolongation of psychotropic medications (Barbui et al., 2011; Girlanda et al., 2014; Nosé et al., 2016). All of the STAR Network studies were conducted independently, without industry funding or support.

Study design

This is an observational, longitudinal and multicenter study. Patients referring to the participating Community Psychiatry Services and beginning a LAI were consecutively enrolled over a period of 12 months (cross-sectional phase). The follow-up phase (currently ongoing) includes two follow-up evaluations at 6 and 12 months.
The present thesis is focused on results from the cross-sectional phase of the study, which corresponds to the aims 1 and 2, while the follow-up phase of the study is currently ongoing.

Treatments

Eight LAIs are currently marked in Italy, with the following therapeutic indications:

1. haloperidol decanoate (Haldol Decanoate), indicated for the maintenance treatment of psychosis;
2. zuclopenthixol decanoate (Clopixol Depot), indicated for acute and chronic dissociative syndromes, as well as other paranoid and hallucinatory syndromes, particularly when the clinical picture is characterized by anxiety, restlessness, psychomotor hyperexcitability and affective reactions;
3. fluphenazine decanoate (Moditen Depot), indicated for schizophrenia and manic syndromes, and in the long-term treatment of chronic psychosis;
4. olanzapine pamoate (Zypadhera), indicated for the maintenance treatment of adult patients with schizophrenia sufficiently stabilized during acute treatment with oral olanzapine;

5. risperidone long-acting (Risperdal Consta), indicated for the maintenance treatment of schizophrenia in patients currently stabilized with oral antipsychotics;
6. paliperidone palmitate 1-month (Xeplion): indicated for maintenance treatment of schizophrenia in adult patients stabilized with paliperidone or risperidone;
7. paliperidone palmitate 3-months (Trevicta): indicated for the maintenance treatment of schizophrenia in adult patients who are clinically stable on 1-monthly paliperidone palmitate injectable product;
8. aripiprazole long-acting (Abilify Maintena): indicated for maintenance treatment of schizophrenia in adult patients stabilized with oral aripiprazole.

Perphenazine Enantate (Trilafon Enantate) is no longer available on the market in Italy. It is relevant to highlight that LAIs have usually different (and more limited) indications as compared to their oral counterparts. Table 5 synthetically shows therapeutic indications of LAIs and oral antipsychotics.

Table 5. Therapeutic indications of LAIs

Drug	Form	SCZ	BIP	Acute Mania	DEM	Mental Retardation	Notes
OLA	oral	X	X	X			-
	LAI	X					Patients already stabilized with oral OLA.
RIS	oral	X		X	X	X	Includes aggressiveness in dementia and mental retardation.
	LAI	X					Patients already stabilized with oral RIS.
ARI	oral	X	X	X			Includes mania starting from 13 years old.
	LAI	X					Patients already stabilized with oral ARI.
PALI	oral	X					-
	LAI	X					Patients already stabilized with oral RIS or PALI.
HAL	oral	X	X	X	X	X	Includes psychomotor agitation.
	LAI	X	X*	X*			Indication: "Psychosis".
ZUC	oral	X	X*	X	X*	X	-
	LAI	X*	X*	X*	X*	X*	-
FLU	oral	-	-	-	-	-	Not available in Italy.
	LAI	X	X*	X			Includes "long-term treatment of outpatients with chronic psychosis".

Legend: OLA=olanzapine; RIS=risperidone; ARI=aripiprazole; PALI=paliperidone; HAL=haloperidol; ZUC=zuclopenthixol; FLU=fluphenazine; SCZ=schizophrenia; BIP=bipolar disorder; DEM=dementia; *=unclear because regulatory indications use generic terms and does not explicitly refer to diagnosis (e.g. psychomotor hyperexcitability, paranoid syndromes, etc.)

Inclusion criteria

We included patients of 18 years of age or above, willing to sign an informed consent, and beginning a LAI therapy (a) for the first time ever, or (b) after having assumed a LAI in the past and having interrupted this medication for at least 3 months. The simultaneous intake of psychotropic medications (including antipsychotics) did not represent an exclusion criterion. Patients were enrolled with no restrictions in terms of settings within the Community Psychiatric Service, including Hospital Psychiatric wards, daytime community facilities and residential facilities.

Tools

In order to collect socio-demographic and clinical data, the following tools were administered at the baseline evaluation:

- Enrolment form, which includes socio-demographic information (age, sex, marital status, living conditions, schooling, employment situation), clinical and pharmacological information (year of the first contact with psychiatric professionals, psychiatric diagnosis, medical co-morbidities, alcohol or psychoactive substance use/dependence, hospital admission in the last 12 months, characteristics of the LAI prescribed and of other medications taken), and characteristics of the clinician who prescribed the LAI (sex, age, years of clinical experience);
- Brief Psychiatry Rating Scale (BPRS) (Overall and Gorham, 1962), compiled by the clinician, which assesses overall symptom profiles by measuring 18 psychiatric symptoms. Each symptom is rated from 1 (lowest intensity) to 7 (highest intensity). This rating scale has been validated in Italian (Roncone et al. 1999; Roncone et al. 2003). The overall level of symptomatology should be considered mild, moderate and severe for scores ranging from 31 to 40, 41

to 52 and higher than 52, respectively. Beside the total score, we also calculated the score of five subscales according to Shafer (2005), namely:

- affect (anxiety, guilt, depression, somatic);
- positive symptoms (thought content, conceptual disorganization, hallucinatory behavior, grandiosity);
- negative symptoms (blunted affect, emotional withdrawal, motor retardation);
- resistance (hostility, uncooperativeness, suspiciousness);
- activation (excitement, tension, mannerisms–posturing).

- Drug Attitude Inventory 10 items (DAI-10) (Hogan et al., 1983), self-administered, which measures attitudes toward medications. The score ranges between -10 and 10, with higher scores indicating a better drug attitude. Positive scores indicate an overall positive attitude toward medications. This rating scale has been validated in Italian (Rossi et al. 2001);
- Kemp's 7-point scale (Kemp et al. 1996; Kemp et al. 1998) compiled by the clinician, which assesses overall adherence to treatments. The score ranges from one to seven, with higher scores indicating higher levels of adherence. Scores of five and above indicate an overall good acceptance of medications.

Each enrolled patient will subsequently be assessed at 6 and 12 months with a Follow-up form, aimed at gathering information on possible diagnostic and therapeutic changes, hospital admissions, LAI interruption or switch, premature withdrawal from the study. BPRS, DAI-10 and Kemp's 7-point scale will be administer at each time point. Treatment withdrawal is defined as not assuming the LAI for at least 2 consecutive times, whichever the reasons are. Also patients withdrawing the treatment during the follow-up will undergo the same evaluation. Switching from a LAI to another will not be considered as a withdrawal.

Data management

After having enrolled the patient, completed forms were sent to the coordinating center at the Unit of Clinical Psychopharmacology, Section of Psychiatry, University of Verona. Data were archived both as hard copy and electronic form. All study data

were entered in a computerised database and stored by the Unit of Clinical Psychopharmacology of the University of Verona. The correctness and consistency of data was ensured by the double-entry technique and by a set of electronic and manual edit checks. The consistency of data between the recruitment and follow-up forms and the computerised database will be verified.

Data collected in the study corresponding to a patient were recorded anonymously. Patients were identified by a unique number both in the recruitment and follow-up forms, and in the database. Total confidentiality of data was and will be guaranteed throughout the entire course of the study, in accordance with the Declaration of Helsinki.

Data analysis

All statistical analyses were performed with STATA 13.0 (STATA Corp, College Station, Tex). Descriptive statistic was employed for describing the main epidemiological characteristics of the recruited population. Continuous variables were expressed as means and standard deviations, while categorical variables were expressed as percentages. In order to describe possible associations between clinical and socio-demographic characteristics and the class of LAI prescribed, both bivariate and multivariate logistic regression analyses were performed. A bivariate analysis employing the class of LAI (0=first-generation LAIs; 1=second-generation LAIs) as the dependent variable, was applied to a number of variables of clinical relevance. Selected continuous and categorical variables were transformed into dichotomous or simpler categorical data, in order to directly compare two or more categories of clinical relevance. All the following variables were analyzed: mean age, nationality (Italians versus non-Italians), living conditions (poor autonomy level versus good autonomy level), level of education (diploma/University degree versus other), working conditions (employed versus unemployed), diagnosis (schizophrenia spectrum versus bipolar disorder versus other diagnosis), mean BPRS score, mean BPRS subscales scores (including affective symptoms, positive symptoms, negative symptoms, resistance, activation), mean DAI-10 score, mean Kemp's 7-point scale score, mean number of hospitalizations in the last year, mean length of hospitalizations, history of compulsory hospitalization, alcohol abuse, substance

abuse, presence of medical comorbidity, number of previous depots, number of psychotropic drugs in the last year, mean cumulative dose of psychotropic drugs taken in the last year expressed as the ratio between the prescribed daily dose (PDD) and the defined daily dose (DDD) (Nosé et al., 2008), type of center (academic versus non-academic centers), place of recruitment (north versus south-center Italy), prescriber's mean age. As a subsequent step, all variables for which a statistically significant association emerged after the bivariate analysis were included as independent variables in a first, intermediate multivariate model. A final simpler multivariate model included only variables for which a statistically significant association emerged from the intermediate model. Regression analyses were based on robust estimator of variance (cluster option of STATA vce command) to account for the multicenter observational design (Williams, 2000).

Chapter 3

Results of the study

Participating centers

Thirty-five Italian Community Psychiatric Centers took part to the study (Figure 2). Each center received a formal approval from the local Ethics Committee (EC) and began patients recruitment. The first patient was recruited in December 2015 and the last in May 2017. Participating centers contributed to the recruitment to a different extent, with a mean of 12.9 patients for each center (standard deviation (sd) 13.42; median 10; range 2-70). The majority of centers (25) recruited in a community, non-academic, setting. However, the number of patients recruited from academic and non-academic centers was equally distributed (54.5% vs. 45.4%, respectively). The majority of centers (25) were located in Northern Italy, however the number of patients recruited in these centers was only slightly superior to the number recruited in Central and Southern Italy (59.4% vs. 40.6%, respectively).

Figure 2. Location of recruiting centers

Socio-demographic characteristics

A total of 451 patients were recruited and included in the analysis (Table 6). In this cohort, 177 patients were females (39.2%) and the mean age was 41.8 (standard deviation (sd) 13.42). The large majority of patients were Italian citizens (88.2%). The most represented foreign countries were Romania (7 patients), Morocco (5 patients) and Bangladesh (4 patients). A slight majority of patients showed a low degree of autonomy, considering that 50.8% lived with their parents or other relatives, and 6% lived in a residential home. A possibly higher degree of autonomy was observed for those living with the spouse/husband and/or children (21.1%) and for those living alone (22.2%). The education level was relatively high, considering that 40% of patients had a diploma and 9.9% had a university degree, while the remaining half of the cohort had no more than lower secondary education. At the time of recruitment 22.2% of patients were employed. A large majority of the cohort (85%) was not conjugated at the time of enrolment in the study.

Table 6. Socio-demographic features

Variables	All LAIs, n=451
Age, mean (sd)	41.8 (13.42)
Age categories, n (%)	
18-30	111 (24.6)
31-45	161 (35.7)
46-60	144 (31.9)
>61	35 (7.8)
Female, n (%)	177 (39.2)
Italian, n (%)	390 (88.2)
Housing conditions, n (%)	
Alone	100 (22.2)
With partner and/or children	95 (21.1)
With other relatives	229 (50.8)
Any residential home	27 (6)
Marital status, n (%)	
Non-conjugated	383 (85.1)
Conjugated	67 (14.9)
Educational level, n (%)	
Illiterate/no title	7 (1.6)
Primary school	27 (6.1)
Secondary school	189 (42.5)
Diploma	178 (40)
University degree	44 (9.9)
Work, n (%)	
Employed	100 (22.2)
Unemployed	221 (49)
Student	15 (3.3)
Retired	68 (15.1)
Housewife/other	47 (10.4)

N=number of patients; LAIs=long-acting antipsychotics; PDD/DDD=prescribed daily dose/defined daily dose; BPRS=Brief Psychiaty Rating Scales; DAI-10=; sd=standard deviation

Clinical features

In terms of diagnosis, 55.9% of patients suffered from schizophrenia, 16.5% from schizoaffective disorder, 18% from bipolar disorder, 6% from personality disorders, and the remaining 3.5% from various conditions, including obsessive-compulsive disorder and conditions with a medical/organic base (mental retardation, mental organic disorders, dementia) (Table 7). At the time of enrollment, patients were under the care of a Psychiatry Service from a mean period of 11.9 years (sd 10.04). Of those, 13.8% had had a disease duration lower than one year, 22.3% between 2 and 5 years, 16.5% between 6 and 10 years, and 47.4% of 11 years or more. Sixty-five patients (14.4%) had alcohol abuse issues at the time of enrollment, and 90 (20%) abused of psychotropic substances, mostly cannabis (76.7%). Overall, 120 patients (about 27% of the whole cohort) used alcohol or substances or both. Slightly more than one over four patients (28.2%) suffered from at least one physical comorbidity. Among those, 37.8% suffered from endocrine, metabolic or nutritional disorders and 18.1% suffered from cardiovascular disorders. In terms of symptom profiles, the mean BPRS score was 48.99 (sd 14.73), with relatively low mean scores at the subscales measuring negative symptoms (mean 7.79, sd 3.68), affective symptoms (mean 10.53, sd 4.33), resistance (mean 9.40, sd 4.47), and activation (mean 7.62, sd 3.34), while higher scores emerged in terms of positive symptoms (mean 12.09, sd 5.41). The mean DAI-10 score was 1.98 (sd 5.35) and the mean Kemp's 7-point scale score was 4.80 (sd 1.44). Three over five patients (59.9%) had at least one hospital admission in the last 12 months, and the overall mean number of days of hospitalization was 22.7 (sd 19.48). About 20% of patients had at least one hospitalization on a compulsory basis.

Table 7. Clinical features and symptom profiles

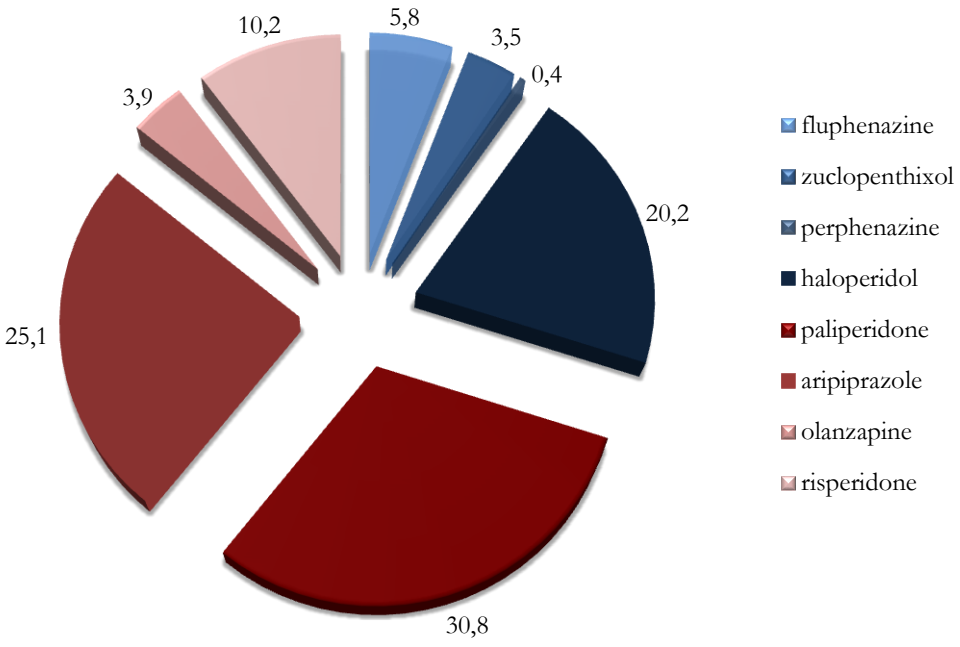
Variables	All LAIs, n=451
Diagnosis, n (%)	
Schizophrenia	251 (55.9)
Schizoaffective disorder	74 (16.5)
Substance-related psychosis	2 (0.4)
Bipolar disorder	81 (18)
Obsessive-compulsive disorder	4 (0.9)
Personality disorder	27 (6)
Mental retardation	4 (0.9)
Mental organic disorder	4 (0.9)
Dementia	2 (0.4)
Time from disease onset, mean years (sd)	11.89 (10.04)
Alcohol abuse, n (%)	65 (14.4)
Substance abuse, n (%)	90 (20)
Substances, n (%)	
Cannabis	69 (76.7)
Cocaine	13 (14.4)
Other	8 (8.9)
At least one medical comorbidity, n (%)	127 (28.2)
Medical comorbidity, n (%)	
Infective disease	8 (6.3)
Endocrine/metabolic disease	48 (37.8)
Cardiovascular disease	23 (18.1)
Neurologic disease	10 (7.9)
Gastrointestinal disease	11 (8.7)
Other	27 (21.2)
BPRS, mean (sd)	48.99 (14.73)
BPRS positive symptoms, mean (sd)	12.09 (5.41)
BPRS negative symptoms, mean (sd)	7.79 (3.68)
BPRS affective symptoms, mean (sd)	10.53 (4.33)
BPRS resistance, mean (sd)	9.40 (4.47)
BPRS activation, mean (sd)	7.62 (3.34)
DAI-10, mean (sd)	1.98 (5.35)
Kemp's 7-point scale, mean (sd)	4.80 (1.44)
At least one hospitalization in the last year, n (%)	270 (59.9)
At least one compulsory hospitalization, n (%)	89 (19.7)
Length of hospitalizations, mean days (sd)	22.75 (19.48)
Last year's cumulative dose of psychotropic drugs: PDD/DDD, mean (sd)	1.80 (2.03)
LAIs PDD/DDD, mean (sd)	1.34 (1.17)
Number of previous depots, n (%)	
0	316 (70.1)
1	103 (22.8)
2+	32 (8.1)

n=number of patients; LAIs=long-acting antipsychotics; PDD/DDD=prescribed daily dose/defined daily dose; BPRS=Brief Psychiaty Rating Scales; DAI-10=; sd=standard deviation

Pharmacologic features

At the time of recruitment, most patients were prescribed with paliperidone long-acting (30.8%), aripiprazole (25.1%), haloperidol decanoate (20.2%) and risperidone long-acting (10.2%). A smaller proportion of patients were prescribed with fluphenazine (5.8%), olanzapine (3.9%), zuclophentixol (3.5%) and perphenazine (0.4%) (Figure 3). For 70.1% of patients this was the first prescription of a LAI. The vast majority of patients (91.6%) was taking at least another psychotropic drug orally before introducing the LAI. About one over three patients (32.1%) experienced at least one adverse event of the antipsychotic medication in the last year, in most cases extrapyramidal symptoms (44.1%) and psychic symptoms (23.4%) (sedation, difficulty in concentrating, tiredness, etc.). The ratio between the prescribed daily dose (PDD) and the defined daily dose (DDD) of psychotropic drugs (including antipsychotics, antidepressants, mood stabilizers, benzodiazepines and anticholinergic drug) taken in the last year was 1.80 (sd 2.03), meaning that their cumulative dose was almost doubled with respect to the dose usually required. Also the cumulative dose of LAIs prescribed was higher than the defined daily dose (PDD/DDD 1.34, sd 1.17). For the majority of recruited patients (70.1%) this was the first LAI ever prescribed. The 22.8% was prescribed with another LAI in the past, and the 8.1% with two or more (Table 7).

Figure 3. LAIs prescribed



Comparison between classes of antipsychotic

Table 8 reports the comparison between FGA and SGA LAIs. Raw data for each group, the results of the bivariate analysis and the two multivariate models employed are reported for a number of clinically relevant variables. The bivariate analysis showed that being prescribed with a SGA LAI was significantly more likely in:

- patients of younger age (OR 0.97, 95% CI 0.95 to 0.98);
- patients employed (OR 1.81, 95% CI 1.06 to 3.07);
- patients with a higher score on the subscale of the BPRS measuring affective symptoms (OR 1.08, 95% CI 1.03 to 1.14);
- patients with a higher score on the DAI-10 scale (which indicates an overall better attitude towards medications from the point of view of the patient) (OR 1.05, 95% CI 1.01 to 1.09);
- patients with a higher score on the Kemp's 7-point scale (which indicates an overall better adherence to medications from the point of view of the clinician) (OR 1.05, 95% CI 1.01 to 1.09).

On the contrary, being prescribed with a SGA LAI was significantly less likely in:

- patients living alone or with their partner and/or children; in patients with a diagnosis of the group "other" (which includes personality disorders, obsessive-compulsive disorder, substance-related psychosis, mental retardation, mental organic disorders and dementia), as compared with the group of patients with schizophrenia/schizoaffective disorder (OR 0.38, 95% 0.20 to 0.72);
- patients with a higher score on the subscale of the BPRS measuring resistance (OR 0.95, 95% CI 0.91 to 0.99);
- patients with a higher number of hospitalizations in the last year (OR 0.82, 95% CI 0.69 to 0.99);
- patients with at least one medical comorbidity (OR 0.61, 95% CI 0.39 to 0.94);
- patients with a higher number of LAIs prescribed in the past (OR 0.67, 95% CI 0.50 to 0.90).

The intermediate multivariate model, which included all previously reported significant variables as possible confounders, confirmed a statistically significant association only for five of those reported above:

- younger age (OR 0.97, 95% CI 0.95 to 0.99);

- being employed (OR 1.99, 95% CI 1.02 to 3.90);
- having a diagnosis of the category "other" (OR 0.30, 95% CI 0.14 to 0.67);
- having a higher score on the BPRS subscale measuring affective symptoms (OR 1.10, 95% CI 1.05 to 1.15);
- a higher number of LAIs prescribed in the past (OR 0.73, 95% CI 0.55 to 0.96).

The final multivariate model, which included only these five variables as possible confounders, confirmed for all of them a statistically significant association with the dependent variable:

- younger age (OR 0.97, 95% CI 0.95 to 0.98);
- being employed (OR 2.01, 95% CI 1.14 to 3.56);
- having a diagnosis of the category "other" (OR 0.28, 95% CI 0.13 to 0.60);
- having a higher score on the BPRS subscale measuring affective symptoms (OR 1.09, 95% CI 1.04 to 1.14);
- a higher number of LAIs prescribed in the past (OR 0.69, 95% CI 0.52 to 0.93).

In synthesis, the two subsequent logistic regression models allowed to detect a robust association between the prescription of SGA LAIs and younger age; being employed; having a diagnosis different from schizophrenia, schizoaffective or bipolar disorder; having a higher score on the BPRS affective subscale; having a higher number of LAIs prescribed in the past.

Table 8. Bivariate and multivariate comparison between FGAs and SGAs

Variables	SGAs LAIs, n=316	FGAs LAIs, n=135	SGAs vs. FGAs		
			unadjusted OR [95% CI]	adjusted OR* [95% CI]	adjusted OR** [95% CI]
Age, mean (sd)	40.08 (13.16)	45.89 (13.18)	**0.97 [0.95 to 0.98]**	**0.97 [0.95 to 0.99]**	**0.97 [0.95 to 0.98]**
Female, n (%)	117 (37.03)	60 (44.44)	0.73 [0.49 to 1.11]	-	-
Italian, n (%)	268 (87.01)	122 (91.04)	1.52 [0.77 to 2.99]	-	-
Lives alone or with partner/children, n (%)	126 (39.87)	69 (51.11)	**0.63 [0.42 to 0.95]**	0.85 [0.49 to 1.46]	-
Diploma or University degree, n (%)	164 (52.40)	58 (43.94)	1.40 [0.93 to 2.11]	-	-
Employed, n (%)	79 (25)	21 (15.56)	**1.81 [1.06 to 3.07]**	**1.99 [1.02 to 3.90]**	**2.01 [1.14 to 3.56]**
Diagnosis, n (%) Schizophrenia spectrum Bipolar disorder Other	 233 (74.20) 60 (19.11) 21 (6.69)	 92 (68.15) 21 (15.56) 22 (16.30)	 ref. 1.13 [0.65 to 1.96] **0.38 [0.20 to 0.72]**	 ref. 1.11 [0.53 to 2.30] **0.30 [0.14 to 0.67]**	 ref. 1.09 [0.52 to 2.31] **0.28 [0.13 to 0.60]**
BPRS, mean (sd)	49.27 (15.38)	48.35 (13.11)	1.00 [0.99 to 1.02]	-	-
BPRS affective symptoms, mean (sd)	10.95 (4.44)	9.55 (3.92)	**1.08 [1.03 to 1.14]**	**1.10 [1.05 to 1.15]**	**1.09 [1.04 to 1.14]**
BPRS positive symptoms, mean (sd)	12.16 (5.64)	11.92 (4.85)	1.01 [0.97 to 1.05]	-	-
BPRS negative symptoms, mean (sd)	7.93 (3.75)	7.45 (3.49)	1.04 [0.98 to 1.10]	-	-
BPRS resistance, mean (sd)	9.08 (4.48)	10.13 (4.37)	**0.95 [0.91 to 0.99]**	0.96 [0.90 to 1.03]	-
BPRS activation, mean (sd)	7.61 (3.46)	7.65 (3.07)	1.00 [0.94 to 1.06]	-	-
DAI-10, mean (sd)	2.38 (5.25)	1.07 (5.47)	**1.05 [1.01 to 1.09]**	1.02 [0.96 to 1.07]	-
Kemp's 7-point scale, mean (sd)	4.93 (1.40)	4.48 (1.50)	**1.24 [1.08 to 1.44]**	1.02 [0.78 to 1.35]	-
N. of hospitalizations in the last year, mean (sd)	0.79 (1.07)	1.04 (1.11)	**0.82 [0.69 to 0.99]**	0.86 [0.66 to 1.11]	-
Length of hospitalizations (days), mean (sd)	13.38 (19.33)	14.33 (17.32)	1.00 [0.99 to 1.01]	-	-
At least one compulsory hospitalization, n (%)	56 (31.82)	33 (35.11)	0.86 [0.51 to 1.46]	-	-
Alcohol abuse, n (%)	44 (13.92)	21 (15.56)	0.88 [0.50 to 1.54]	-	-
Substance abuse, n (%)	63 (19.94)	27 (20.00)	1.00 [0.60 to 1.65]	-	-
At least one medical comorbidity, n (%)	79 (25.08)	48 (35.56)	**0.61 [0.39 to 0.94]**	0.82 [0.54 to 1.26]	-
Number of previous LAIs, mean (sd)	0.33 (0.65)	0.52 (0.70)	**0.67 [0.50 to 0.90]**	**0.73 [0.55 to 0.96]**	**0.69 [0.52 to 0.93]**
Number of psychotropic drugs in the last year, mean (sd)	1.35 (0.97)	1.48 (1.12)	0.88 [0.73 to 1.08]	-	-
Last year's cumulative dose of psychotropic drugs: PDD/DDD, mean (sd)	1.88 (2.19)	1.60 (1.59)	1.08 [0.96 to 1.22]	-	-
University center, n (%)	169 (53.48)	77 (57.04)	0.86 [0.58 to 1.30]	-	-
South-center Italy, n (%)	132 (41.77)	51 (37.78)	1.18 [0.78 to 1.79]	-	-
Prescriber's age, mean (sd)	45.63 (10.36)	46.69 (12.26)	0.99 [0.97 to 1.01]	-	-

* the intermediate multivariate model including variables for which a statistically significant association emerged in the bivariate analysis
** the final multivariate model including variables for which a statistically significant association emerged from the intermediate model
Bold characters indicate a p-value < 0.05.
The % reported in parenthesis refers to the ratio calculated respectively on all LAIs (first column), FGA LAIs (second column); SGA LAIs (third column)
n=number of patients; sd=standard deviation; OR=odds ration; CI=confidence interval; BPRS=brief psychiatry rating scale; DAI=drug attitude inventory; PDD=prescribed daily dose; DDD=defined daily dose

Chapter 4

Critical appraisal of results

The recruited population included a wide range of socio-demographic and clinical characteristics. A relevant part of the cohort met the features typically described in older studies (before the broad availability of most SGA LAIs), as patients were mostly males in their middle adulthood, with low educational level, no employment, a long-standing diagnosis of schizophrenia, and moderate-to-severe level of psychopathology (Shi et al., 2007; Barnes et al., 2009; Citrome et al., 2010; Crivera et al., 2011; Haddad et al., 2016). At the same time, relatively high functioning levels emerged in a surprisingly large part of the population, considering that about 43% of patients lived alone or with the partner and/or children, more than one out of five patients were employed, and half of the patients had a diploma or a University degree. Similar considerations apply to clinical features, considering that, beside a large number of patients with chronic conditions and severe symptom profiles, also patients with mild-to-moderate levels of symptom profiles were well represented. Further, data showed a relatively short course of disease (lower than 5 years) in about 36% of patients, and an overall good attitude towards medications in 61% of patients as perceived by the clinician, and in 59% of patients as perceived by the patients themselves. Interestingly, a variety of diagnosis emerged. Almost one out of five patients had a bipolar disorder, as expected considering the recently broadened use of antipsychotics for affective disorders (Cipriani et al., 2011; Zhou et al., 2015). In about 6% of patients the LAI was probably prescribed to manage severe behavioral symptoms arising from personality disorders or underlying somatic conditions (such as mental retardation or dementia), although the use of antipsychotics in these cases is at least controversial, particularly in the long-term (Lieb et al., 2010; Maust et al., 2015).

In general, these data seem to confirm the expectation that a broader spectrum of individuals is currently prescribed with LAIs as compared to the past. As discussed above, highly selected populations from previous studies can be hardly compared with the present study, which employed a pragmatic, naturalistic approach, aimed at

minimizing patients' selection and reflect real-world practice as closely as possible. However, mean age and gender were generally in line with data from previous studies with a catchment timespan including most recently released SGA LAIs (Marcus et al., 2015; McCreath et al., 2017; Pilon et al., 2017; Gaviria et al., 2017; Decuypere et al., 2017; Singh et al., 2016; Greene et al., 2017), while other socio-demographic details were not available.

The use of LAIs on a broader number of clinical conditions may raise regulatory issues, considering that licensed indications of SGA LAIs are limited only to patients with schizophrenia in a maintenance phase with oral antipsychotics. Therefore, SGA LAIs were prescribed off-label to all patients without a diagnosis of schizophrenia (almost one out of five patients). On the contrary, indications of FGA LAIs are much less narrow, often referring to symptom domains rather than specific diagnosis, and may therefore be prescribed to patients with several different diagnosis. The common off-label prescription of LAIs confirms the already well-known trend of oral antipsychotics (Driessen et al., 2016).

Some clinical characteristics of the cohort appeared to be consistent with what expected in the general population of patients with chronic psychosis, in particular the high prevalence of patients with comorbid physical conditions (about one out of four patients had at least one comorbidity, mostly endocrine/metabolic or cardiovascular) and with a "dual diagnosis", considering that one out of four used alcohol or substances (Regier et al., 1990; Mitchell et al., 2013).

In most cases LAIs were prescribed after a period of severe disease relapse, considering the high number of patients hospitalized in the previous year, the high rate of compulsory admissions, and the long mean length of stay. This may suggest that, despite the recommendation of offering LAIs from the early phases of disease (NICE, 2014; Galletly et al., 2016), in many cases these formulations are still chosen after failed attempts with other treatments.

More than two out of three patients were prescribed with SGA LAIs. The most commonly prescribed medications were paliperidone palmitate (30.8%), aripiprazole LAI (25.1%) and haloperidol decanoate (20.2%). These results are in line with data from some of the previous studies (Pilon et al., 2017; Greene et al., 2017; Lee et al.,

2017), although in some other studies rates appeared to be extremely heterogeneous (Marcus et al., 2015; McCreath et al., 2017; Dimitropoulos et al., 2017), which is likely to be related to a number of factors influencing local prescribing patterns, as well as different recruitment timespan of studies (and therefore different availability of SGA LAIs). The use of aripiprazole LAI was surprisingly high compared to other recent studies (Marcus et al., 2015; McCreath et al., 2017; Pilon et al., 2017; Greene et al., 2017). The advantages of this medication compared to other antipsychotics have been repeatedly stressed: it is relatively safe in terms of motor, metabolic and endocrine adversities (in particular it does not alter prolactin levels), and it proved to be comparable to other SGAs in terms of efficacy for the treatment of schizophrenia (Leucht et al., 2013; Khanna et al., 2014). Further, robust results from a recent meta-analysis showed a better overall acceptability of aripiprazole LAI as compared to the oral counterpart, although the interpretation of this data is still unclear (Ostuzzi et al., 2017a). On the other hand, paliperidone substantially equals olanzapine and risperidone in terms of metabolic effects and prolactin raise (Leucht et al., 2013). Its choice over these two medications is likely to be related to an enhanced practicality of paliperidone palmitate, considering that risperidone LAI needs a biweekly administration, and olanzapine pamoate is burdened by complex regulatory requirements. Haloperidol decanoate, besides its possible disadvantages (e.g. motor symptoms, QTc prolongation, locally irritant preparations), remains a widely used medication in clinical practice, possibly because of its relatively safe metabolic profile (Leucht et al., 2013), and the flexibility of the LAI in terms of doses and frequency, as compared to other LAIs (including SGAs).

The logistic multivariate model comparing FGA LAIs and SGA LAIs showed that the latter were prescribed significantly more often to younger, employed individuals, with a diagnosis schizophrenia or bipolar disorder, with higher levels of affective symptoms, and without a previous history of LAI prescription. This profile resembles closely the one pictured by those claiming a cultural change in the clinical use of LAIs. This trend is similar to what emerged from previous studies, although in many cases only FGA LAIs and risperidone LAI were compared (Singh et al., 2016; Lammers et al., 2013; Nielsen et al., 2015), the adjustment for confounders was not performed (Marcus et al., 2015; Pilon et al., 2017; Nielsen et al., 2015), and social and clinical variables possibly associated with the class of LAI were not analyzed.

Notably, no significant differences emerged between patients prescribed with FGA LAIs and SGA LAIs in terms of overall symptom profiles, adherence and attitudes towards medications, both as perceived by psychiatrists (Kemp's 7-point score) and by patients (DAI-10 score). To our knowledge, the study by Singh and colleagues (Singh et al., 2016) is currently the only available study employing the DAI (in this case, the version with 30 items), and it reached similar conclusions, although in this case only FGA LAIs and LAI risperidone were compared.

As expected according to current trends in literature (Kapur & Remington, 2001; Müller-Spahn, 2002; Masan, 2004), SGAs were preferred when targeting affective symptoms. This may also reflect the common idea of FGAs as medications associated with apathy, lack of initiative, anhedonia, indifference, blunted affect (the so-called neuroleptic-induced deficit syndrome) (Schooler, 1994; Kirkpatrick, 2014).

This study has limitations. First, the cross-sectional design cannot detect a causal association between variables, therefore all statistical associations discussed should be regarded as merely exploratory. Second, we employed simple and easily administrable scales in order to minimize any interference with routine real-world practice, although this might have affected the precision in measuring some variables of interest, in particular symptom profiles and patients' attitudes toward medications. Third, characteristics of recruiting centers were heterogeneous in terms of recruitment settings (community centers, hospital wards, rehabilitation facilities, etc.), and they contributed to the recruitment to a different extent. Also, various local factors may have strongly influenced prescribing attitudes of each center (e.g. hospital internal guidelines, availability of medications, and long-standing local habits). This, along with the wide inclusion criteria applied, led to extremely heterogeneous features of the population recruited. This reflects the complexity of real-world clinical settings, but may at the same time affect the internal validity of results (Carlson & Morrison, 2009). In order to address this limitation, we employed statistical techniques accounting for inter-center variability. Still, the representativeness of the sample, and therefore the epidemiological validity of data, remains a relevant element of discussion.

Some authors found that SGA LAIs are preferred over FGA LAIs mostly by younger psychiatrists (Stip, 2017), who may be more prone to promptly translate new

scientific insights into clinical practice as compared to older colleagues (Choudhry et al., 2005). However, this data was not confirmed by our analysis. Further elements on prescribers' features and reasoning underpinning the choice of a LAI were collected during the enrolment phase of the STAR Network "Depot" Study. Relevant insights can emerged from the analysis of this data, which were however beyond the overall scope of this thesis.

Conclusions

In the last 10-15 years international experts advocated for a paradigm shift in the use of LAIs (Patel and David, 2005; Altamura et al., 2012; Stahl 2014; Stevens et al., 2016; Maia-De-Oliveira et al., 2013). This alternative interpretation of LAIs took place and gradually shaped in parallel with the production and marketing of SGA LAIs, and with a progressively widened clinical application of SGAs in general.

This study showed a notable change in LAIs prescribing habits, as compared with previous epidemiological surveys. The advocated cultural change in the use of LAIs is currently under way in Italian Community Psychiatric Services, as showed by more flexible and heterogeneous prescribing patterns, directed at a wider range of clinical conditions and functioning levels. This change appears to be mostly restricted to SGA LAIs, while prescribing patterns of FGA LAIs are practically unchanged as compared to the past, as they are mostly reserved to older patients, with lower functioning levels, previous failed attempts with other antipsychotics, and, commonly, behavioral issues.

Results from this study may arguably suggest that this change in prescribing attitudes is underpinned by at least three pre-conditions. First, the increased diffusion of SGA LAIs and the progressive characterization of some of them as versatile (use not only for schizophrenia, but also in affective disorders), safe (water preparations), and tolerable options (low metabolic, endocrine and sedative impact of aripiprazole and, to a lesser extent, paliperidone) (Fagiolini et al., 2016; Leucht et al., 2013), compatible with higher functioning levels in everyday life. Second, the progressive overcoming of old misconceptions (primarily from the prescriber's side) on stigma and coercion of LAIs, which may, on the contrary, ease the burden of stigma associated with oral medications (e.g. by avoiding daily monitoring of a correct medication intake by parents). Third, the gradual recognition that the practicality of LAIs is a critical added value, which may contribute to relieve patients from the daily routine of oral medications and its pitfalls, also decentralizing the issue of medications from the patient-clinician relationship.

In conclusion, a new prescribing approach to LAIs is a matter of growing interest not only for academics, but also for psychiatrists working in real-world community settings. Although LAIs are broadly accepted as a valuable tool for managing poor adherence, their use alone cannot represent an exhaustive response to such a multifaceted issue, as confirmed by recent findings (Lee et al., 2017). The extent to which these formulations and, more importantly, single LAI medication, can contribute to adherence, attitude toward medications, and overall subjective well being, still need to be accurately assessed. The follow-up phase of the STAR Network "Depot" Study will explore the overall adherence over one year of follow-up in patients prescribed with LAIs, and how this is influenced by various socio-demographic, clinical and pharmacological factors, including the antipsychotic prescribed.

References

Altamura AC; Aguglia E; Bassi M; Bogetto F; Cappellari L; De Giorgi S; Fagiolini A; Ferrannini L; Girardi P (2012): Rethinking the role of long-acting atypical antipsychotics in the community setting. Int Clin Psychopharmacol 27(6), 336-49.

Barbui C; Accordini S; Nosè M; Stroup S; Purgato M; Girlanda F; Esposito E; Veronese A; Tansella M; Cipriani A; CHAT (Clozapine Haloperidol Aripiprazole Trial) Study Group (2011): Aripiprazole versus haloperidol in combination with clozapine for treatment-resistant schizophrenia in routine clinical care: a randomized, controlled trial. J Clin Psychopharmacol 31(3), 266-73.

Barnes T; Shingleton-Smith A; Paton C (2009): Antipsychotic long-acting injections: prescribing practice in the UK. The The British Journal of Psychiatry 195 (52), S37-S42.

Barnes TR; Schizophrenia Consensus Group of British Association for Psychopharmacology (2011): Evidence-based guidelines for the pharmacological treatment of schizophrenia: recommendations from the British Association for Psychopharmacology. J Psychopharmacol 25(5), 567-620.

Barnes TR; Shingleton-Smith A; Paton C (2009): Antipsychotic long-acting injections: prescribing practice in the UK. The British journal of psychiatry. Supplement 52, S37-42.

Brissos S; Veguilla MR; Taylor D; Balanzá-Martinez V (2014): The role of long-acting injectable antipsychotics in schizophrenia: a critical appraisal. Ther Adv Psychopharmacol 4 (5), 198–219.

Brnabic AJM; Kelin K; Ascher-Svanum H; Montgomery W; Kadziola Z; Karagianis J (2011): Medication discontinuation with depot and oral antipsychotics in outpatients with schizophrenia: comparison of matched cohorts from a 12-month observational study. Int J Clin Pract 65 (9), 945–953.

Carlson MDA; Morrison RS (2009): Study design, precision, and validity in observational studies. Journal of palliative medicine 12 (1), 77–82.

Carpenter WT Jr; Buchanan RW (2015): Expanding Therapy With Long-Acting Antipsychotic Medication in Patients With Schizophrenia. JAMA Psychiatry 72(8), 745-6.

Choudhry NK; Fletcher RH; Soumerai SB (2005): Systematic review: the relationship between clinical experience and quality of health care. Ann Intern Med 142(4), 260-73.

Cipriani A; Barbui C; Salanti G; Rendell J; Brown R; Stockton S; Purgato M; Spineli LM; Goodwin GM; Geddes JR (2011): Comparative efficacy and acceptability of antimanic drugs in acute mania: a multiple-treatments meta-analysis. Lancet 378(9799),1306-15.

Citrome L (2013): New second-generation long-acting injectable antipsychotics for the treatment of schizophrenia. Expert Rev Neurother 13(7), 767-83.

Citrome L; Jaffe A; Levine J (2010): Treatment of schizophrenia with depot preparations of fluphenazine, haloperidol, and risperidone among inpatients at state-operated psychiatric facilities. Schizophrenia research 119 (1-3),153–159.

Covell NH; McEvoy JP; Schooler NR; Stroup TS; Jackson CT; Rojas IA; Essock SM (2012): Effectiveness of switching from long-acting injectable fluphenazine or haloperidol decanoate to long-acting injectable risperidone microspheres: an open-label, randomized controlled trial. The Journal of clinical psychiatry 73 (5), 669–675.

Crivera C; DeSouza C; Kozma CM; Dirani RD; Mao L; Macfadden W (2011): Resource utilization in patients with schizophrenia who initiated risperidone long-acting therapy: results from the Schizophrenia Outcomes Utilization Relapse and Clinical Evaluation (SOURCE). BMC psychiatry 11, 168.

Das AK; Malik A; Haddad PM (2014): A qualitative study of the attitudes of patients in an early intervention service towards antipsychotic long-acting injections. Ther Adv Psychopharmacol 4 (5), 179–185.

De Risio A; Lang AP (2014): History and therapeutic rationale of long acting antipsychotics. In Curr Clin Pharmacol 9 (1), 39–52.

Decuypere F; Sermon J; Geerts P; Denee TR; De Vos C; Malfait B; Lamotte M; Mulder CL (2017): Treatment continuation of four long-acting antipsychotic

medications in the Netherlands and Belgium: A retrospective database study. PLoS One 12(6), e0179049.

Dimitropoulos E; Drogemuller L; Wong K (2017): Evaluation of Concurrent Oral and Long-Acting Injectable Antipsychotic Prescribing at the Minneapolis Veterans Affairs Health Care System. Journal of clinical psychopharmacology 37 (5),605–608.

Driessen J; Baik SH; Zhang Y (2016): Trends in Off-Label Use of Second-Generation Antipsychotics in the Medicare Population From 2006 to 2012. Psychiatr Serv 67(8), 898-903.

Ereshefsky L; Mascarenas CA (2003): Comparison of the effects of different routes of antipsychotic administration on pharmacokinetics and pharmacodynamics. J Clin Psychiatry 64 (Suppl. 16), 18–23.

Fagiolini A; Alfonsi E; Amodeo G; Cenci M; Di Lella M; Farinella F; Ferraiuolo F; Fraguas D; Loparco N; Gutierrez-Rojas L; Mignone ML; Pataracchia G; Pillai G; Russo F; Sanchez-Gistau V; Spinogatti F; Toscano M; Villari V; De Filippis S (2016): Switching long acting antipsychotic medications to aripiprazole long acting once-a-month: expert consensus by a panel of Italian and Spanish psychiatrists. Expert Opin Drug Saf 15(4), 449-55.

Fagiolini A; Rocca P; De Giorgi S; Spina E; Amodeo G; Amore M (2017): Clinical trial methodology to assess the efficacy/effectiveness of long-acting antipsychotics: Randomized controlled trials vs naturalistic studies. Psychiatry Res 247, 257-264.

Fleischhacker WW; Meise U; Günther V; Kurz M (1994): Compliance with antipsychotic drug treatment: influence of side effects. Acta Psychiatr Scand Suppl 382, 11–15.

Galletly C; Castle D; Dark F; Humberstone V; Jablensky A; Killackey E; Kulkarni J; McGorry P; Nielssen O; Tran N (2016): Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the management of schizophrenia and related disorders. Aust N Z J Psychiatry 50(5), 410-72.

Gaviria AM; Franco J; Rico G; Muntané G; Sáez C; Sánchez-Gistau V; de Pablo J; Vilella E (2017): Noninterventional, Naturalistic, Retrospective Study to Describe Prescription Patterns of Long-Acting Injectable Antipsychotics and the Impact of

Introducing a New Atypical Antipsychotic in the Spanish Province of Tarragona Catchment Area. The primary care companion for CNS disorders 19 (2).

Gentile S (2013): Adverse effects associated with second-generation antipsychotic long-acting injection treatment: a comprehensive systematic review. Pharmacotherapy 33 (10), 1087–1106.

Gigante AD, Beny Lafer B, Yatham L (2012): Long-acting injectable antipsychotics for the maintenance treatment of bipolar disorder. CNS Drugs 26, 403-20.

Girlanda F; Cipriani A; Agrimi E; Appino MG; Barichello A; Beneduce R; Bighelli I; Bisoffi G; Bisogno A; Bortolaso P; Boso M; Calandra C; Cascone L; Castellazzi M; Corbascio C; Parise VF; Gardellin F; Gennaro D; Hanife B; Lintas C; Lorusso M; Luca A; Luca M; Luchetta C; Lucii C; Maio F; Marsilio A; Mattei C; Moretti D; Nosè M; Occhionero G; Papanti D; Pecile D; Percudani M; Prestia D; Purgato M; Restaino F; Romeo S; Sciarma T; Strizzolo S; Tamborini S; Todarello O; Tozzi F; Ziero S; Zotos S; Barbui C (2014): Effectiveness of lithium in subjects with treatment-resistant depression and suicide risk: results and lessons of an underpowered randomised clinical trial. BMC Res Notes 7, 731.

Greene M; Yan T; Chang E; Hartry A; Touya M; Broder MS (2017): Medication adherence and discontinuation of long-acting injectable versus oral antipsychotics in patients with schizophrenia or bipolar disorder. Journal of medical economics, 1–8.

Haddad PM; Brain C; Scott J (2014): Nonadherence with antipsychotic medication in schizophrenia: challenges and management strategies. Patient Relat Outcome Meas 5, 43–62.

Haddad PM; Taylor M; Niaz OS (2009): First-generation antipsychotic long-acting injections v. oral antipsychotics in schizophrenia: systematic review of randomised controlled trials and observational studies. Br J Psychiatry Suppl 52, S20-8.

Haddad PM; Lambert T; Lauriello J (2016): Antipsychotic Long-acting Injections: Oxford University Press.

Heres S (2014): Long-acting injectable antipsychotics: an underutilized treatment option. J Clin Psychiatry 75(11), 1263-5.

Hogan TP; Awad AG; Eastwood R (1983): A self-report scale predictive of drug compliance in schizophrenics: reliability and discriminative validity. Psychological medicine 13, 177–83.

Iyer S; Banks N; Roy M-A; Tibbo P; Williams R; Manchanda R; Chue P; Malla A (2013): A qualitative study of experiences with and perceptions regarding long-acting injectable antipsychotics: Part I-patient perspectives. Can J Psychiatry 58 (5 Suppl 1), 14S-22S.

James BO; Omoaregba JO; Okonoda KM; Otefe EU; Patel MX (2012): The knowledge and attitudes of psychiatrists towards antipsychotic long-acting injections in Nigeria. Ther Adv Psychopharmacol 2(5), 169-77.

Kane JM; Kishimoto T; Correll CU (2013): Assessing the comparative effectiveness of long-acting injectable vs. oral antipsychotic medications in the prevention of relapse provides a case study in comparative effectiveness research in psychiatry. J Clin Epidemiol 66 (8 Suppl), S37-41.

Kapur S; Remington G (2001): Atypical antipsychotics: new directions and new challenges in the treatment of schizophrenia. Annual review of medicine 52, 503–517.

Kemp R; Hayward P; Applewhaite G; Everitt B; David A (1996): Compliance therapy in psychotic patients: randomised controlled trial. BMJ 312 (7027), 345–349.

Kemp R; Kirov G; Everitt B; Hayward P; David A (1998): Randomised controlled trial of compliance therapy. 18-month follow-up. Br J Psychiatry 172, 413–419.

Khanna P; Suo T; Komossa K; Ma H; Rummel-Kluge C; El-Sayeh HG; Leucht S; Xia J (2014): Aripiprazole versus other atypical antipsychotics for schizophrenia. The Cochrane database of systematic reviews (1), CD006569.

Kirkpatrick B (2014): Developing concepts in negative symptoms: primary vs secondary and apathy vs expression. J Clin Psychiatry; 75 Suppl 1, 3-7.

Kirschner M; Theodoridou A; Fusar-Poli P; Kaiser S; Jäger M (2013): Patients' and clinicians' attitude towards long-acting depot antipsychotics in subjects with a first episode of psychosis. Ther Adv Psychopharmacol 3(2), 89-99.

Kirson NY; Weiden PJ; Yermakov S; Huang W; Samuelson T; Offord SJ (2013): Efficacy and effectiveness of depot versus oral antipsychotics in schizophrenia: synthesizing results across different research designs. J Clin Psychiatry 74 (6), 568–575.

Kishi T, Oya K, Iwata N (2016): Long-Acting Injectable Antipsychotics for Prevention of Relapse in Bipolar Disorder: A Systematic Review and Meta-Analyses of Randomized Controlled Trials. Int J Neuropsychopharmacol 19(9), pii: pyw038

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. The Journal of clinical psychiatry 74 (10), 957–965.

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

Lammers L; Zehm B; Williams R (2013): Risperidone long-acting injection in Schizophrenia Spectrum Illnesses compared to first generation depot antipsychotics in an outpatient setting in Canada. BMC Psychiatry 13, 155.

Lee SJ; de Castella A; Stafrace S; Keppich-Arnold S; Kulkarni J (2017): Retrospective audit of people treated with long-acting antipsychotic injectable medications: Usage patterns and outcomes. Schizophr Res. pii: S0920-9964(17)30709-0.

Leucht C; Heres S; Kane JM; Kissling W; Davis JM; Leucht S (2011): Oral versus depot antipsychotic drugs for schizophrenia--a critical systematic review and meta-analysis of randomised long-term trials. Schizophr Res 127 (1-3), 83–92.

Leucht S; Cipriani A; Spinelli L; Mavridis D; Orey D; Richter F; Samara M; Barbui C; Engel RR; Geddes JR; Kissling W; Stapf MP; Lässig B; Salanti G; Davis JM (2013): Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia. A multiple-treatments meta-analysis. Lancet 382:951-62.

Leucht S; Kane JM; Kissling W; Hamann J; Etschel E; Engel R (2005): Clinical implications of Brief Psychiatric Rating Scale Scores. British Journal Of Psychiatry 187, 366-71.

Li H; Rui Q; Ning X; Xu H; Gu N (2011): A comparative study of paliperidone palmitate and risperidone long-acting injectable therapy in schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 35(4), 1002-8.

Lieb K; Völlm B; Rücker G; Timmer A; Stoffers JM (2010): Pharmacotherapy for borderline personality disorder: Cochrane systematic review of randomised trials. Br J Psychiatry 196(1),: 4-12.

Lieb, Klaus; Völlm, Birgit; Rücker, Gerta; Timmer, Antje; Stoffers, Jutta M. (2010): Pharmacotherapy for borderline personality disorder: Cochrane systematic review of randomised trials. In: The British journal of psychiatry : the journal of mental science 196 (1), S. 4–12.

Maia-de-Oliveira JP; Bressan RA; Elkis H; Machado-de-Sousa JP; Hallak JE (2013): Why we should use long-acting injectable antipsychotics more frequently. Rev Bras. Psiquiatr. 35(3), 217-8.

Mannaert E; Vermeulen A; Remmerie B; Bouhours P; Levron JC (2005): Pharmacokinetic profile of long-acting injectable risperidone at steady-state: comparison with oral administration. L'Encéphale 31 (5 Pt 1), 609–615.

Marcus SC; Zummo J; Pettit AR; Stoddard J; Doshi J (2015): Antipsychotic Adherence and Rehospitalization in Schizophrenia Patients Receiving Oral Versus Long-Acting Injectable Antipsychotics Following Hospital Discharge. Journal of managed care & specialty pharmacy 21 (9),754–768.

Masan PS (2004): Atypical antipsychotics in the treatment of affective symptoms: a review. Annals of clinical psychiatry: official journal of the American Academy of Clinical Psychiatrists 16 (1),3–13.

Maust, Donovan T.; Kim, Hyungjin Myra; Seyfried, Lisa S.; Chiang, Claire; Kavanagh, Janet; Schneider, Lon S.; Kales, Helen C. (2015): Antipsychotics, other psychotropics, and the risk of death in patients with dementia: number needed to harm. In: JAMA Psychiatry 72 (5), S. 438–445. DOI: 10.1001/jamapsychiatry.2014.3018.

McCreath J; Larson E; Bharatiya P; Labanieh HA; Weiss Z; Lozovatsky M (2017): Long-Acting Injectable Antipsychotics for Schizophrenia: Sociodemographic Characteristics and Treatment Adherence. Prim Care Companion CNS Disord 19(1).

McEvoy JP; Byerly M; Hamer RM; Dominik R; Swartz MS; Rosenheck RA et al. (2014): Effectiveness of paliperidone palmitate vs haloperidol decanoate for maintenance treatment of schizophrenia: a randomized clinical trial. JAMA 311 (19), 1978–1987.

Mitchell AJ; Vancampfort D; Sweers K; van Winkel R; Yu W; de Hert M (2013): Prevalence of metabolic syndrome and metabolic abnormalities in schizophrenia and related disorders--a systematic review and meta-analysis. Schizophrenia bulletin 39 (2),306–318.

Moncrieff J (2006): Does antipsychotic withdrawal provoke psychosis? Review of the literature on rapid onset psychosis (supersensitivity psychosis) and withdrawal-related relapse. Acta Psychiatr Scand 114 (1), 3–13.

Montemagni C; Frieri T; Rocca P (2016): Second-generation long-acting injectable antipsychotics in schizophrenia: patient functioning and quality of life. Neuropsychiatr Dis Treat 12, 917-29.

Morrato EH; Parks J; Campagna EJ; Muser E; Thomas DS; Fang H; Doshi D (2015): Comparative effectiveness of injectable paliperidone palmitate versus oral atypical antipsychotics: early postmarketing evidence. J Comp Eff Res 4(2), 89-99.

Morrens M, Destoop M, Cleymans S, van der Spek S, Dom G (2015): Evolution of First-generation and Second-generation Antipsychotic Prescribing Patterns in Belgium Between 1997 and 2012: A Population-based Study. J Psychiatr Pract 21(4), 248-58.

Müller-Spahn F (2002): Current use of atypical antipsychotics. European psychiatry:the journal of the Association of European Psychiatrists 17 Suppl 4,377s-384s.

Naber D; Hansen K; Forray C; Baker RA; Sapin C; Beillat M; Peters-Strickland T; Nylander AG; Hertel P; Andersen HS; Eramo A; Loze JY; Potkin SG (2015):

Qualify: a randomized head-to-head study of aripiprazole once-monthly and paliperidone palmitate in the treatment of schizophrenia. Schizophr Res 168(1-2), 498-504.

Naber D; Karow A; Lambert M (2005): Subjective well-being under the neuroleptic treatment and its relevance for compliance. In Acta psychiatrica Scandinavica. Supplementum (427), 29–34.

Narasimhan M; Un Pae C; Masand N; Masand P (2007): Partial compliance with antipsychotics and its impact on patient outcomes. Int J Psychiatry Clin Pract 11 (2), 102–111.

National Institute for Health and Care Excellence (NICE) (2014): Psychosis and schizophrenia in adults: prevention and management. Clinical guideline [CG178]. Available: https://www.nice.org.uk/guidance/cg178

Nielsen J; Jensen SOW; Friis RB; Valentin JB; Correll CU (2015): Comparative effectiveness of risperidone long-acting injectable vs first-generation antipsychotic long-acting injectables in schizophrenia: results from a nationwide, retrospective inception cohort study. Schizophrenia bulletin 41 (3),627–636.

Nosé M; Barbui C; Tansella M (2003): How often do patients with psychosis fail to adhere to treatment programmes? A systematic review. Psychol Med 33 (7), 1149–1160.

Nosè M; Bighelli I; Castellazzi M; Martinotti G; Carrà G; Lucii C; Ostuzzi G; Sozzi F; Barbui C; STAR NETWORK GROUP (2016): Prevalence and correlates of QTc prolongation in Italian psychiatric care: cross-sectional multicentre study. Epidemiol Psychiatr Sci 25(6), 532-540.

Nosè M; Mazzi MA; Esposito E; Bianchini M; Petrosemolo P; Ostuzzi G; Tansella M; Barbui C (2012): Adverse effects of antipsychotic drugs: survey of doctors' versus patients' perspective. Soc Psychiatry Psychiatr Epidemiol 47 (1), 157–164.

Nosè M; Tansella M; Thornicroft G; Schene A; Becker T; Veronese A; Leese M; Koeter M; Angermeyer M; Barbui C (2008): Is the Defined Daily Dose system a reliable tool for standardizing antipsychotic dosages? Int Clin Psychopharmacol 23(5), 287-90.

Nunes V; Neilson J; O'Flynn N; Calvert N; Kuntze S; Smithson H; Benson J; Blair J; Bowser A; Clyne W; Crome P; Haddad P; Hemingway S; Horne R; Johnson S; Kelly S; Packham B; Patel M; Steel J (2009). Clinical Guidelines and Evidence Review for Medicines Adherence: involving patients in decisions about prescribed medicines and supporting adherence. London: National Collaborating Centre for Primary Care and Royal College of General Practitioners. Available: https://www.nice.org.uk/guidance/cg76/evidence/full-guideline-242062957

Ostuzzi G; Barbui C (2016): Comparative effectiveness of long-acting antipsychotics: issues and challenges from a pragmatic randomised study. Epidemiol Psychiatr Sci 25(1), 21-3.

Ostuzzi G; Bighelli I; So R; Furukawa TA; Barbui C (2017a): Does formulation matter? A systematic review and meta-analysis of oral versus long-acting antipsychotic studies. Schizophr Res 183, 10-21.

Ostuzzi G; Papola D; Gastaldon C; Barbui C (2017b): New EMA report on paliperidone 3-month injections: taking clinical and policy decisions without an adequate evidence base. Epidemiol Psychiatr Sci 26(3), 231-233.

Overall JE; Gorham DR (1962): The Brief Psychiatric Rating Scale. Psychological Reports 10 (3), 799–812.

Pandina G; Lane R; Gopal S; Gassmann-Mayer C; Hough D; Remmerie B;, Simpson G (2011): A double-blind study of paliperidone palmitate and risperidone long-acting injectable in adults with schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 35(1), 218-26.

Patel MX; David AS (2005). Why aren't depot antipsychotics prescribed more often and what can be done about it? Advances in Psychiatric Treatment 11 (3), 203-211.

Patel MX; Haddad PM; Chaudhry IB; McLoughlin S; Husain N; David AS (2010): Psychiatrists' use, knowledge and attitudes to first- and second-generation antipsychotic long-acting injections: comparisons over 5 years. J Psychopharmacol. (Oxford) 24 (10), 1473–1482.

Patel MX; Taylor M; David AS (2009): Antipsychotic long-acting injections: mind the gap. Br J Psychiatry Suppl 52, S1-4.

Piccinni C; Piazza A; Poluzzi E; Tarricone I; Koci A; Berardi D; Fioritti A; de Ponti F (2015): Social and clinical descriptors of antipsychotic prescription. Int J Psychiatry Med 49(1), 45-62.

Pietrini F; Spadafora M; Tatini L; Talamba GA; Andrisano C; Boncompagni G; Manetti M; Ricca V; Ballerini A (2016): LAI versus oral: A case-control study on subjective experience of antipsychotic maintenance treatment. Eur Psychiatry 37, 35-42.

Pilon D; Joshi K; Tandon N; Lafeuille MH; Kamstra RL; Emond B; Lefebvre P (2017). Treatment patterns in Medicaid patients with schizophrenia initiated on a first- or second-generation long-acting injectable versus oral antipsychotic. Patient Prefer Adherence 11, 619-629.

Regier DA; Farmer ME; Rae DS; Locke BZ; Keith SJ; Judd LL; Goodwin FK (1990): Comorbidity of mental disorders with alcohol and other drug abuse. Results from the Epidemiologic Catchment Area (ECA) Study. JAMA 264 (19), 2511–2518.

Roncone R; Tozzini C; Mazza M; De Risio A; Giosuè P; Morosini P; Casacchia M (2003): Validation of the Italian version of the self report Insight Scale. Epidemiol Psichiatr Soc 12 (01), 63–75.

Roncone R; Ventura J; Impallomeni M; Falloon IR; Morosini PL; Chiaravalle E; Casacchia M (1999): Reliability of an Italian standardized and expanded Brief Psychiatric Rating Scale (BPRS 4.0) in raters with high vs. low clinical experience. Acta Psychiatr Scand 100 (3), 229–236.

Rossi A; Arduini L; De Cataldo S; Stratta P (2001): Gli aspetti soggettivi del trattamento con farmaci antipsicotici: studio di validazione della versione italiana della Drug Attitude Inventory (DAI). Epidemiol Psichiatr Soc 10 (2), 107–114.

Rossi G; Frediani S; Rossi R; Rossi A (2012): Long-acting antipsychotic drugs for the treatment of schizophrenia: use in daily practice from naturalistic observations. BMC Psychiatry 12, 122.

Schooler NR (1994): Deficit symptoms in schizophrenia: negative symptoms versus neuroleptic-induced deficits. Acta Psychiatr Scand Suppl 380, 21-6.

Scottish Intercollegiate Guidelines Network (SIGN) (2013). Management of schizophrenia. 2013. Available: http://www.sign.ac.uk/sign-131-management-of-schizophrenia.html

Shi L; Ascher-Svanum H; Zhu B; Faries D; Montgomery W; Marder SR (2007): Characteristics and use patterns of patients taking first-generation depot antipsychotics or oral antipsychotics for schizophrenia. Psychiatr Serv 58(4), 482-8.

Singh SM; Haddad PM; Husain N; Heaney E; Tomenson B; Chaudhry IB (2016): Cross-sectional comparison of first-generation antipsychotic long-acting injections vs risperidone long-acting injection: patient-rated attitudes, satisfaction and tolerability. Ther Adv Psychopharmacol 6(3), 162-71.

Stahl SM (2014): Long-acting injectable antipsychotics: shall the last be first? CNS Spectr. 19(1), :3-5.

Stevens GL; Dawson G; Zummo J (2016): Clinical benefits and impact of early use of long-acting injectable antipsychotics for schizophrenia. Early Interv Psychiatry 10(5), 365-77.

Stip E (2017): Physician Characteristics Associated With Prescription of Long-Acting Injectable Antipsychotics. J Clin Psychiatry 78(8), e1060.

Svedberg B; Backenroth-Ohsako G; Lützén K (2003): On the path to recovery: patients' experiences of treatment with long-acting injections of antipsychotic medication. Int J Ment Health Nurs 12(2), 110-8.

Waddell L; Taylor M (2009): Attitudes of patients and mental health staff to antipsychotic long-acting injections: systematic review. Br J Psychiatry Suppl 52, S43-50.

Walburn J; Gray R; Gournay K; Quraishi S; David AS (2001): Systematic review of patient and nurse attitudes to depot antipsychotic medication. Br J Psychiatry 179, 300–307.

Whyte A; Parker C (2016). A review of the efficacy and tolerability of antipsychotic long-acting injections. Progress in Neurology and Psychiatry 20. Available:

http://www.progressnp.com/article/review-efficacy-tolerability-antipsychotic-long-acting-injections/

Williams RL (2000): A note on robust variance estimation for cluster-correlated data. Biometrics 56, 645–646.

Wu HE; Okusaga OO (2015): Antipsychotic medication-induced dysphoria: its meaning, association with typical vs. atypical medications and impact on adherence. The Psychiatric quarterly 86 (2), 199–205.

Zhou X; Keitner GI; Qin B; Ravindran AV; Bauer M; Del Giovane C; Zhao J, Liu Y, Fang Y, Zhang Y, Xie P (2015): Atypical Antipsychotic Augmentation for Treatment-Resistant Depression: A Systematic Review and Network Meta-Analysis. The international journal of neuropsychopharmacology 18 (11),pyv060.

Appendix 1 – Enrolment Form

Studio DEPOT

SCHEDA DI RECLUTAMENTO

Data compilazione: ____ / ____ / _____

Nome del reclutatore: _____

Centro reclutante: _____

_____

_____

Numero identificativo del paziente
Inserire un numero progressivo per ogni paziente reclutato dal centro

|___|___|___|

Si raccomanda di tenere traccia della corrispondenza tra il numero identificativo e il nome del paziente, in modo da facilitare la successiva compilazione della scheda di follow-up

Data di nascita: ____ / ____ / _____

Sesso: ☐ **M** ☐ **F**

Nazionalità: _____

Con chi vive:
- ☐ Da solo
- ☐ Con il coniuge (o partner)
- ☐ Da solo con i figli
- ☐ Con il coniuge (o partner) e figli
- ☐ Con altri familiari
- ☐ Comunità
- ☐ Appartamento protetto
- ☐ Casa di riposo
- ☐ R.E.M.S.
- ☐ R.S.A.
- ☐ Struttura residenziale (es. CTRP, ecc.)
- ☐ Altra condizione

Stato civile:
- ☐ celibe/nubile
- ☐ coniugato/a
- ☐ vedovo/a
- ☐ separato/a
- ☐ libero/a di stato

Scolarità:
- ☐ Analfabeta
- ☐ Alfabeta senza titolo di studio
- ☐ Licenza elementare
- ☐ Licenza media inferiore
- ☐ Diploma
- ☐ Laurea

Condizione lavorativa:
- ☐ Occupato
- ☐ Disoccupato
- ☐ Casalinga
- ☐ Studente
- ☐ Ritirato dal lavoro o pensionato
- ☐ Altro (lavoro protetto...)

Anno 1° contatto psichiatrico: |___|___|___|___|

Diagnosi psichiatrica: _____

_____

Condizioni mediche rilevanti: _____

_____

Abuso/dipendenza da alcol ☐ **No** ☐ **Sì**

Abuso/dipendenza da sostanze ☐ **No** ☐ **Sì** Se sì, quali? 1. _____
2. _____
3. _____
4. _____

Luogo di reclutamento:
☐ SPDC
☐ strutture residenziali
☐ ambulatorio (CPS-CSM)

Il paziente è stato ricoverato nei 12 mesi precedenti alla data del reclutamento? ☐ **No** ☐ **Sì** Se sì, quante volte? _____

Caratteristiche dei ricoveri avvenuti nei 12 mesi precedenti alla data di reclutamento

(N.B. barrare TSO qualora questo sia stato attivo almeno una volta nel corso del ricovero)

	Volontario	**TSO**	**Durata complessiva (giorni)**	**Quali motivazioni hanno portato al ricovero?**		
				Scompenso clinico	*Motivi ambientali (sociali, familiari, ecc.)*	*Altro (specificare)*
1° ricovero	☐	☐	_____	☐	☐	☐ _____
2° ricovero	☐	☐	_____	☐	☐	☐ _____
3° ricovero	☐	☐	_____	☐	☐	☐ _____
4° ricovero	☐	☐	_____	☐	☐	☐ _____

Terapia farmacologica in atto:

(riportare tutti i farmaci assunti al momento del reclutamento)

Antipsicotico LONG-ACTING di nuova prescrizione per cui il paziente è stato reclutato nello studio:

Principio attivo (nome commerciale) _____ (_____)

Posologia _____ mg / _____ giorni

Data prima somministrazione _____ / _____ / _____

È questa la prima assunzione di LONG-ACTING nella vita?

☐ **Si**

☐ **No** → In questo caso il paziente ha già assunto antipsicotici LONG-ACTING in passato.

Il LONG-ACTING assunto attualmente è stato introdotto dopo che **il precedente è stato interrotto da almeno 3 mesi?**

☐ **No → ATTENZIONE! In questo caso il paziente non può essere incluso nello studio!**

☐ **Si** → elencare quali antipsicotici LONG-ACTING sono stati assunti in passato e quando sono stati sospesi:

1. _____ data sospensione _____
2. _____ data sospensione _____
3. _____ data sospensione _____
4. _____ data sospensione _____

(se non si dispone di informazioni più dettagliate indicare semplicemente l'anno)

Altri psicofarmaci

riportare l'ultima terapia assunta prima dell'inizio della terapia long-acting

Nome farmaco (principio attivo)	Posologia
1. _____	_____ mg / die
2. _____	_____ mg / die
3. _____	_____ mg / die
4. _____	_____ mg / die
5. _____	_____ mg / die
6. _____	_____ mg / die

Farmaci prescritti per problematiche mediche

Nome farmaco (principio attivo)	Posologia
1. _____	_____ mg / die
2. _____	_____ mg / die
3. _____	_____ mg / die
4. _____	_____ mg / die
5. _____	_____ mg / die
6. _____	_____ mg / die

Negli ultimi 12 mesi, il paziente ha assunto farmaci antipsicotici per bocca? ☐ **No** ☐ **Sì**

Se **SI**, quali? 1. _____ 4. _____
2. _____ 5. _____
3. _____ 6. _____

Negli ultimi 12 mesi, il paziente ha sofferto di effetti collaterali da antipsicotici? ☐ **No** ☐ **Sì**

Se **SI**, indicare i più rilevanti: 1. _____
2. _____
3. _____
4. _____

Caratteristiche del medico che ha prescritto il LONG-ACTING per cui il paziente è entrato nello studio:

Anno di nascita: |__|__|__|__| **Sesso:** ☐ **M** ☐ **F**

Ruolo:
☐ Medico Specializzando in Psichiatria
☐ Medico Specialista in Psichiatria
☐ Altro (es. neurologo, MMG, etc.)

Da quanti anni pratica la professione? _____
(contare anche gli anni di specializzazione)

Considerazioni che hanno contribuito alla scelta di introdurre un LONG-ACTING

Indicare se ciascuna delle seguenti considerazioni ha contribuito o meno alla scelta dell'attuale terapia long-acting da parte del medico che ha effettuato la prescrizione

		SI	**NO**
1.	La scelta della formulazione long-acting è stata considerata come ultima opzione dopo il fallimento di altri interventi, con lo scopo di favorire una maggiore aderenza alle terapie.	☐	☐
2.	Il paziente è ad alto rischio di non assumere autonomamente la terapia per bocca, o di assumerla a dosaggi minori rispetto a quelli prescritti.	☐	☐
3.	Il paziente è ad alto rischio di assumere la terapia in modo incongruo (es. sovradosaggio, assunzione disorganizzata).	☐	☐
4.	Anche se attualmente aderente alla terapia orale, rimane un elevato rischio di interruzione improvvisa in occasione di esacerbazioni psicopatologiche.	☐	☐
5.	Il paziente riferisce come maggiormente stigmatizzante l'assunzione quotidiana della terapia orale (per es. questa gli ricorda quotidianamente del suo problema, oppure la gestione della stessa lo pone in conflitto	☐	☐

	con i familiari, ecc.).		
6.	Il paziente riferisce come maggiormente stigmatizzanti gli effetti acuti associati alla formulazione orale dell'antipsicotico (es. tremore, rigidità, sonnolenza).	☐	☐
7.	La somministrazione del long-acting potrebbe consentire una migliore gestione degli effetti collaterali rispetto alla terapia orale.	☐	☐
8.	Il paziente considera più "pratico" assumere la terapia antipsicotica in formulazione long-acting (es. per ragioni quali la difficoltà a rispettare gli orari di assunzione della terapia orale, ecc.).	☐	☐
9.	La somministrazione del long-acting potrebbe favorire un monitoraggio più continuativo del paziente presso il Servizio.	☐	☐
10.	La somministrazione del long-acting potrebbe consentire una migliore gestione delle condotte aggressive e/o impulsive del paziente.	☐	☐
11.	Nonostante il paziente abbia manifestato resistenza verso la terapia long-acting, si è valutato che i benefici di questa superassero gli effetti negativi sul piano della relazione terapeutica.	☐	☐
12.	La prescrizione del long-acting è stata pienamente condivisa dal paziente e non ha impatto significativo sulla relazione terapeutica.	☐	☐
13.	Altro (specificare) _____ _____ _____ _____		

Considerazioni aggiuntive

_____

_____

_____

_____

Compilata la scheda, si prega di inviarla presso la **Segreteria dello STAR network:**

e-mail: giovanni.ostuzzi@gmail.com

Fax: 045 8124155

Posta: Ospedale Policlinico "G.B. Rossi", Piazzale L.A. Scuro 10, 37134 Verona

Appendix 2 – Follow-up Form

Studio DEPOT

SCHEDA DI FOLLOW-UP

Indicare se somministrata a **6 mesi** ☐ oppure a **12 mesi** ☐

Data compilazione: ____ / ____ / _____

Nome del reclutatore: _____

Centro reclutante: _____

_____

_____

Numero identificativo del paziente
Inserire il numero progressivo assegnato al paziente al momento del reclutamento

|___|___|___|

Si raccomanda di tenere traccia della corrispondenza tra il numero identificativo e il nome del paziente, in modo da facilitare la successiva compilazione della scheda di follow-up

Data di nascita: ____ / ____ / _____ **Sesso:** ☐ **M** ☐ **F**

Il paziente è ancora in carico al Servizio? ☐ **Si** ☐ **No**

Se **NO**, per quale motivo non è più in carico?

- ☐ decesso
- ☐ cambio residenza e Servizio di cura
- ☐ prosecuzione delle cure presso altro specialista o presso il MMG
- ☐ interruzione dei contatti; paziente non rintracciabile
- ☐ altro (specificare) _____

_____

Eventuali modifiche della diagnosi psichiatrica: _____

_____

Eventuali nuove condizioni mediche rilevanti: _____

_____

Abuso/dipendenza da alcol negli ultimi 6 mesi ☐ **No** ☐ **Sì**

Abuso/dipendenza da sostanze negli ultimi 6 mesi ☐ **No** ☐ **Sì** Se sì, quali? 1. _____
2. _____
3. _____
4. _____

Il paziente è stato ricoverato negli ultimi 6 mesi? ☐ **No** ☐ **Sì** Se sì, quante volte? _____

Caratteristiche dei ricoveri avvenuti negli ultimi 6 mesi

(N.B. barrare TSO qualora questo sia stato attivo almeno una volta nel corso del ricovero)

	Volontario	**TSO**	**Durata complessiva (giorni)**	**Quali motivazioni hanno portato al ricovero?**		
				Scompenso clinico	*Motivi ambientali (sociali, familiari, ecc.)*	*Altro (specificare)*
1° ricovero	☐	☐	_____	☐	☐	☐ _____
2° ricovero	☐	☐	_____	☐	☐	☐ _____
3° ricovero	☐	☐	_____	☐	☐	☐ _____
4° ricovero	☐	☐	_____	☐	☐	☐ _____

Il paziente è in terapia con l'antipsicotico LONG-ACTING riportato nella valutazione precedente? ☐ **Si** ☐ **No**

Se **SI**, specificare gli eventuali principali **effetti collaterali** attribuiti al LONG-ACTING: 1. _____
2. _____
3. _____

Se **NO**, specificare la data dell'ultima somministrazione _____ / _____ / _____

Se nell'attualità il paziente non è più in terapia con antipsicotici LONG-ACTING e assume solo antipsicotici orali, o non assume affatto antipsicotici, specificare qual è stato il **motivo della sospensione del LONG-ACTING:**

☐ Passaggio a terapia orale

☐ Rifiuto della modalità iniettiva da parte del paziente

☐ Inefficacia del LONG-ACTING

☐ Effetti collaterali del LONG-ACTING

In tal caso specificare i più rilevanti: 1. _____

2. _____

3. _____

altro: _____

È stato introdotto un nuovo antipsicotico LONG-ACTING in sostituzione del precedente (switch)? ☐ **Si** ☐ **No**

Se **SI**, specificare:

Principio attivo (nome commerciale) _____ (_____)

Posologia _____ mg / _____ giorni

Data prima somministrazione _____ / _____ / _____

Data somministrazione più recente _____ / _____ / _____

Per quale motivo è stato effettuato tale **switch**?

☐ Inefficacia del precedente LONG-ACTING

☐ Effetti collaterali del precedente LONG-ACTING

In tal caso specificare i più rilevanti: 1. _____

2. _____

3. _____

☐ altro: _____

Il nuovo farmaco LONG-ACTING ha consentito di superare le problematiche precedentemente emerse?

☐ Completamente

☐ In buona parte

☐ In minima parte

☐ Per nulla

☐ Non valutabile (es. se introdotto da poco tempo)

Altri trattamenti farmacologici in atto:

(riportare tutti i farmaci assunti al momento della valutazione di follow-up)

Altri psicofarmaci	
Nome farmaco (principio attivo)	Posologia
1. _____	_____ mg / die
2. _____	_____ mg / die
3. _____	_____ mg / die
4. _____	_____ mg / die
5. _____	_____ mg / die
6. _____	_____ mg / die

Farmaci prescritti per problematiche mediche	
Nome farmaco (principio attivo)	Posologia
1. _____	_____ mg / die
2. _____	_____ mg / die
3. _____	_____ mg / die
4. _____	_____ mg / die
5. _____	_____ mg / die
6. _____	_____ mg / die

Commenti aggiuntivi

_____

_____

_____

_____

_____

_____

_____

_____

_____

Compilata la scheda, si prega di inviarla presso la **Segreteria dello STAR network:**

e-mail: giovanni.ostuzzi@gmail.com

Fax: 045 8124155

Posta: Ospedale Policlinico "G.B. Rossi", Piazzale L.A. Scuro 10, 37134 Verona

Appendix 3 – Brief Psychiatry Rating Scale (BPRS)

Studio Depot
2016

BPRS

Brief Psychiatric Rating Scale

Data compilazione ___/____/_____ Numero identificativo paziente _____

Nome reclutatore _____

Centro reclutante _____

Indicare l'eventuale presenza e intensità di ciascun item nel corso dell'ultimo mese

	SINTOMI	Non valutato	Non presente	Molto lieve	Lieve	Moderato	Moderato severo	Severo	Estrem. severo
		0	1	2	3	4	5	6	7
1	Preoccupazione somatica								
2	Ansietà								
3	Ritiro emotivo								
4	Disorganizzazione concettuale								
5	Sentimenti di colpa								
6	Tensione								
7	Manierismi								
8	Grandiosità								
9	Umore depresso								
10	Ostilità								
11	Sospettosità								
12	Allucinazioni								
13	Rallentamento motorio								
14	Mancanza di cooperazione								
15	Contenuti insoliti del pensiero								
16	Appiattimento affettivo								
17	Eccitamento								
18	Disorientamento								

Punteggio totale _____

1. **Preoccupazione somatica:** preoccupazione per la salute fisica, paura di malattia fisica, ipocondria
2. **Ansietà:** Apprensione, paura, iperpreoccupazione per il presente o il futuro, mancanza di serenità
3. **Ritiro emotivo:** mancanza di interazione spontanea, isolamento, incapacità nella relazione con gli altri.
4. **Disorganizzazione Concettuale:** processi di pensiero confusi, sconnessi, disorganizzati.
5. **Sentimenti di colpa:** biasimo di se stessi, vergogna, rimorso per il comportamento passato.
6. **Tensione:** manifestazioni fisiche e motorie di nervosismo, iper-attivazione.
7. **Manierismi e postura:** comportamento motorio innaturale, particolare, bizzarro(esclusi i tic)
8. **Grandiosità:** opinione di sé esagerata, arroganza, convinzione di poteri e abilità straordinari.
9. **Umore depresso:** dolore, tristezza, disappunto, pessimismo.
10. **Ostilità:** animosità, ira, belligeranza, sdegno per gli altri.
11. **Sospettosità:** sfiducia, credenza che gli altri agiscano malvagiamente o con intento discriminatorio.
12. **Comportamento allucinatorio:** percezione senza la normale corrispondenza con lo stimolo esterno.
13. **Rallentamento motorio:** movimento o eloquio rallentato ed indebolito, riduzione del tono corporeo.
14. **Assenza di cooperazione:** resistenza, chiusura, rigetto dell'autorità.
15. **Contenuti di pensiero inusuali:** contenuto del pensiero inusuale, strano, particolare, bizzarro.
16. **Appiattimento affettivo:** tono emotivo ridotto, riduzione della normale intensità dei sentimenti.
17. **Eccitamento:** tono emotivo innalzato, agitazione, reattività aumentata.
18. **Disorientamento:** confusione o mancanza di associazioni appropriate alla persona, al luogo o al tempo.

Da compilare alla fine:

Giudizio di validità della valutazione(1=per niente; 5=molto attendibile)

Motivi di un'eventuale difficoltà nella valutazione(segnare tutti i motivi presenti):
☐ Sintomi indotti da farmaci
☐ Possibile sottostima dei sintomi per mancanza di una buona relazione
☐ Possibile sottostima dei sintomi per la presenza di un quadro di tipo negativo
☐ Mancanza di collaborazione da parte del paziente
☐ Presenza di disturbi formali del pensiero
☐ Altro(da specificare)…….

In caso di difficoltà nella compilazione della scheda contattare:
Giovanni Ostuzzi: giovanni.ostuzzi@gmail.com; 045 8124063
Mariasole Castellazzi: mariasole.castellazzi@univr.it; 045 8124884

Appendix 4 – Drug Attitude Inventory 10-items (DAI-10)

Studio Depot
2016

DAI-10

Drug Attitude Inventory, 10 item

Data compilazione ___/____/_____ Numero identificativo paziente _____

Nome reclutatore _____

Centro reclutante _____

Da compilare da parte del paziente

Indichi quali delle seguenti affermazioni risultano vere o false nella sua esperienza

1. Per me i vantaggi dell'uso dei farmaci superano gli svantaggi	❑ VERO	❑ FALSO
2. Mi sento strano, come uno zombie, quando prendo i farmaci	❑ VERO	❑ FALSO
3. Prendo i farmaci di mia spontanea volontà	❑ VERO	❑ FALSO
4. I farmaci mi fanno sentire più rilassato	❑ VERO	❑ FALSO
5. I farmaci mi fanno sentire più stanco e spossato	❑ VERO	❑ FALSO
6. Prendo i farmaci solo quando sto male	❑ VERO	❑ FALSO
7. Quando prendo i farmaci mi sento più normale	❑ VERO	❑ FALSO
8. Non è naturale per la mia mente e per il mio corpo essere sotto il controllo dei farmaci	❑ VERO	❑ FALSO
9. I miei pensieri sono più chiari quando prendo i farmaci	❑ VERO	❑ FALSO
10. Prendo i farmaci per evitare di stare male	❑ VERO	❑ FALSO

Da compilare da parte del centro coordinatore

Punteggio totale _____

Appendix 5 – Kemp's 7-point scale

Kemp's 7-point scale

Data compilazione ___/____/_____ Numero identificativo paziente _____

Nome reclutatore _____

Centro reclutante _____

Indichi quali delle seguenti affermazioni descrive con maggior precisione il grado di aderenza alle cure del paziente

Item	Definizione	Punteggio
Rifiuto totale		❑ 1
Rifiuto parziale	Rifiuta farmaci depot o accetta solo un dosaggio minimo	❑ 2
Accetta con riluttanza	Accetta solo perchè il trattamento è imposto o mette in discussione spesso la necessità del trattamento (ogni due giorni)	❑ 3
Occasionale riluttanza	Mette in discussione la necessità del trattamento una volta a settimana	❑ 4
Accettazione passiva		❑ 5
Partecipazione moderata	Ha qualche conoscenza ed interesse per il trattamento e non ha bisogno di essere stimolato per assumere I farmaci	❑ 6
Partecipazione attiva	Accetta prontamente il trattamento e lo assume con senso di responsabilità	❑ 7

In caso di difficoltà nella compilazione della scheda contattare:
Giovanni Ostuzzi: giovanni.ostuzzi@gmail.com; 045 8124063
Mariasole Castellazzi: mariasole.castellazzi@univr.it; 045 8124884