Factors Associated with Medication Adherence to Long-Acting Injectable Antipsychotics: Results from the STAR Network Depot Study

Authors

Andrea Aguglia[1, 2*], Laura Fusar-Poli[3*], Antimo Natale[3], Andrea Amerio[1, 2], Irene Espa[1, 2], Veronica Villa[1, 2], Giovanni Martinotti[4], Giuseppe Carrà[5, 6], Francesco Bartoli[5], Armando D'Agostino[7], Gianluca Serafini[1, 2], Mario Amore[1, 2], Eugenio Aguglia[3], Giovanni Ostuzzi[8], Corrado Barbui[8]

Affiliations

1 Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health (DINOGMI), Section of Psychiatry, University of Genoa, Italy
2 IRCCS Ospedale Policlinico San Martino, Genoa, Italy
3 Department of Clinical and Experimental Medicine, Psychiatry Unit, University of Catania, Via Santa Sofia, Catania, Italy
4 Department of Neuroscience, Imaging and Clinical Sciences, "G. D'Annunzio" University of Chieti, Chieti, Italy
5 Department of Medicine and Surgery, University of Milano-Bicocca, via Cadore, Monza, Italy
6 Division of Psychiatry, University College London, Tottenham Court Rd, Bloomsbury, London, United Kingdom
7 Department of Health Sciences, University of Milan, Ospedale San Paolo, Blocco A, Via Antonio di Rudinì, Milan, Italy
8 WHO Collaborating Centre for Research and Training in Mental Health and Service Evaluation; Department of Neuroscience, Biomedicine and Movement Sciences, Section of Psychiatry, University of Verona, Verona, Italy

Key words

long-acting injectable, antipsychotics, adherence, schizophrenia, bipolar disorder

received 08.02.2022
revised 14.03.2022
accepted 16.03.2022
published online 25.04.2022

Bibliography

Pharmacopsychiatry 2022; 55: 281–289
DOI 10.1055/a-1804-6211
ISSN 0176-3679

Georg Thieme Verlag, Rüdigerstraße 14,
70469 Stuttgart, Germany

Correspondence

Prof. Andrea Aguglia, M.D., Ph.D.
Department of Neuroscience, Rehabilitation,
Ophthalmology, Genetics,
Maternal and Child Health (DINOGMI)
Section of Psychiatry, University of Genoa,
IRCCS Ospedale Policlinico San Martino
Largo Rosanna Benzi 10
16132 Genoa
Italy
andrea.aguglia@unige.it

ABSTRACT

Introduction Long-acting injectable (LAI) antipsychotics are prescribed to people with severe psychiatric disorders who show poor adherence to oral medication. The present paper examined factors potentially associated with medication adherence to LAI treatment.

Methods The STAR (Servizi Territoriali Associati per la Ricerca) Network Depot Study was a multicenter, observational, prospective study that enrolled 461 subjects initiating a LAI from 32 Italian centers. After 6 and 12 months of treatment, we evaluated differences between participants with high (≥ 5 points) and low (< 5 points) medication adherence using Kemp's 7-point scale in sociodemographic, clinical, psychopathological, and drug-related variables. Factors that differed significantly between the two groups were entered for multivariate logistic regression.

Results Six months after enrollment, participants with high medication adherence were younger, living with other people, had lower Brief Psychiatric Rating Scale (BPRS) total scores, lower adverse events, and a more positive attitude toward medication than participants with low adherence. Multivariate regression confirmed lower BPRS resistance and activation scores, absence of adverse events, and positive attitude toward medication as factors significantly associated with good adherence. After 12 months, all BPRS subscales were significantly lower in the high adherence group, which also showed a more positive attitude toward medication. BPRS resistance and attitude toward medication were confirmed as factors associated with medication adherence.

* Shared first-authors

Discussion Our findings suggest that adherence to LAI is principally related to attitude toward medication and traits of suspiciousness/hostility. Quality of patient-clinician relationship and tailored psychoeducational strategies may positively affect adherence in people undergoing psychopharmacological treatment, including LAI.

Introduction

In recent years, the term "compliance to treatment", defined as "the degree to which a person's behavior (taking medications, observing diets, lifestyle changes) follows passively the doctor's recommendations" [1], has been replaced, before with "adherence to treatment", defined as "an active and collaborative involvement of the patient in the planning of treatment, by elaborating a consensus based on the agreement was preferred" [2] and subsequently with "concordance to treatment", defined as "a medication-taking process achieved on the basis of effective communication between the doctor and the patient, taking into account the opinions of both, in which the patient is enabled to make an informed choice regarding treatment and have support during the entire course of the disease" [3]. In this way, the novel approach of shared decision-making, defined as "a process in which the doctor provides clear and complete clinical information to patients about their treatment, and patients provide information on his/her preferences", is the basis of the successful treatment, due to the potential reduction of the subjective patient's coercive pharmacological perception [4]. One of the main challenges in treating psychiatric disorders is the effectiveness of medications, which is influenced by several factors, including patient adherence. Reduced medication adherence may lead to higher recurrence and hospitalization rates, increased risk of suicide attempts, poor social and work functioning, and reduced quality of life [5, 6].

Adherence to pharmacological treatment, particularly in severe mental illnesses, such as bipolar disorder and schizophrenia, is influenced by several patient-, illness-, medication-, and environmental-related factors.

Among patient-related factors, several sociodemographic characteristics are associated with partial or total non-medication adherence, including male gender, younger age, low level of education and socioeconomic status. Also, single and unemployed people with no social activities, migrants, and individuals with non-Caucasian ethnicity appear to have poorer medication adherence, even if the evidence is still controversial [7]. Furthermore, several psychological patient-related factors, such as self-stigma, low overall life satisfaction, beliefs about treatment risks and benefits (including unawareness of medication effect and negative drug beliefs), a perceived need for treatment, and lack of family involvement (i. e., in psychoeducation programs, adherence monitoring, support, and supervision) appeared associated with low medication adherence [8–11]. Another important aspect is the environment surrounding patients that are often stigmatized by the general population due to negative and partial knowledge, beliefs, and perceptions of psychiatric disorders. Furthermore, the absence of extra-familial support system and the prejudice that all psychopharmacological treatments could provoke dependence or worsen the course of the disease are associated with partial adherence to pharmacological treatment [12–14].

Regarding illness-related factors, lower premorbid functioning, younger age at onset, diagnostic delay, longer duration of illness, number of previous hospitalizations, involuntary admissions, current inpatient status, suicide attempt in the past 12 months, longer duration of untreated illness, and lack of insight seem to play a role in medication adherence. Moreover, greater severity of illness (i. e., mixed episode, presence of delusions and hallucinations, negative symptoms, depression, and demoralization) and long-term course of illness (i. e., a higher number of episodes and recurrences, rapid cycling) are considered among the specific illness features related to this important issue. Other illness-related factors are represented by cognitive symptomatology (i. e., lower levels of memory and executive functions, concentration and attention, cognitive flexibility, abstraction, and problem-solving), psychiatric (i. e., alcohol and substance, particularly cannabis, use disorder, obsessive-compulsive disorder, or severe personality disorders) and medical comorbidities (i. e., metabolic syndrome, cardiovascular and endocrine diseases) with an overlap of mental illness symptoms and non-specific symptoms of physical illness [8, 11, 15–19].

Among medication-related factors, the evidence confirmed the role of adverse events (particularly metabolic, sexual, and extrapyramidal effects, depending on different receptor activity), inadequate efficacy of medications (depending on different clinical dimensions), delivery systems and formulations (drops *vs.* oral *vs.* intravenous *vs.* intramuscular, as long-acting injectable – LAI antipsychotics) as a cause of poor adherence to pharmacological treatment [6, 20–22].

Finally, difficulties of healthcare systems could have negative consequences on adherence due to the problematic access, continuity, and cohesion to care for the distance to mental health facilities, availability of trained psychosocial treatment specialists, poor communication between physicians, and lack of coordination of treatment activities, and concerns about reimbursement of medications [23–25]. Therefore, regular follow-up visits, quality of the therapeutic relationship between the patient and clinician, the organization of the mental healthcare system, and better communication should improve the adherence of patients to care [26, 27]. Lastly, a recent study reported a useful classification of non-adherence risk, identifying low risk of non-adherence (present insight of disease, good family support, and positive attitude to treatment by the patient and family members), vulnerability, and high risk for non-adherence [19].

LAI antipsychotics are used to improve medication adherence in populations with psychiatric disorders due to several advantages, including maintaining stable plasma levels and increased bioavailability, safety, and tolerability. Indeed, patients treated with LAI antipsychotics need regular visits with a specialist, monitoring the clinical condition and decreasing the risk of relapse [28]. Nonetheless, drop-out rates are observed in the real world [29]. While factors associated with poor adherence to oral medications have been

extensively studied, little is known about adherence to LAI antipsychotics [30, 31]. Therefore, the purpose of this study was to evaluate the potential sociodemographic and clinical characteristics associated with an overall good adherence to pharmacological treatment in patients with psychiatric disorders treated with LAI antipsychotics at 6- and 12- month follow-up.

Material and methods

Study design

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement [32] was applied for this multicenter, cross-sectional, and prospective study, involving in- and outpatients, starting any LAI antipsychotics, evaluated at 6- and 12-months follow-up. The protocol was approved by the Ethical Committees of the coordinating centers as well as each participating center, and it is available at the Open Science Framework (OSF) online repository (https://osf.io/wt8kx/).

All participants signed a written informed consent prior to their recruitment into the study. The study design was conducted in accordance with the guidelines provided in the current version of the Declaration of Helsinki [33]. The STAR (Servizi Territoriali Associati per la Ricerca) Network Depot Study was not supported by any funding and participants were not remunerated.

The inclusion and exclusion criteria, the sociodemographic and clinical characteristics investigated, and the assessment with several specific psychometric tools were reported on previously published articles from the STAR Network Depot Study [29, 34–38]. Baseline and follow-up data were periodically sent by mail or fax to the coordinating center (University of Verona), inserted into a computer database, and checked with the use of a double-entry technique, also applying manual and electronic checks. As the present paper aimed to investigate the factors associated with adherence to LAI antipsychotic' prescription, we considered only 6- and 12-month follow-up data.

Instruments

Main outcome: Kemp's 7-point scale

For this study, the adherence to LAI antipsychotics was assessed by clinicians using Kemp's 7-point scale [39]. In accordance with a previously published paper [36], medication adherence was defined as a total score ≥ 5, considering the following scores: 1 – complete refusal; 2 – partial refusal; 3 – frequent reluctance, requiring persuasion; 4 – occasional reluctance; 5 – passive acceptance; 6 – moderate participation; 7 – active participation.

Other variables

The following variables were included as potential predictors of adherence to LAI treatment:

1) Sociodemographic variables: age at recruitment, sex, living and marital status, employment, and educational level.
2) Clinical variables: diagnosis, years elapsed between the first contact to psychiatric services and enrollment into the study, presence of medical comorbidities, and alcohol and substance use disorder.
3) Psychopathological variables: the severity of the overall psychopathology was evaluated using the Italian version of the clinician-rated Brief Psychiatric Rating Scale (BPRS). The BPRS includes five symptom clusters: positive symptoms (unusual thought content, conceptual disorganization, hallucinations, grandiosity), negative symptoms (blunted affect, emotional withdrawal, motor retardation), affect (anxiety, guilt, depression, somatic concern), resistance (hostility, uncooperativeness, suspiciousness), and activation (excitement, tension, mannerisms-posturing) clusters [40].
4) Medication-related variables: type of LAI antipsychotic (first- or second-generation), frequency of injection (weekly/once every two weeks *vs.* once every three/four weeks), history of LAI prescription, adverse events reported, and attitude toward medication, evaluated using the Italian version of the self-administered Drug Attitude Inventory 10 items (DAI-10) [41, 42]. DAI-10 scores range between −10 and 10. A positive attitude was defined as a DAI-10 score > 0.

Statistical analyses

Sociodemographic and clinical characteristics of the total sample were summarized as means and standard deviations for continuous variables and counts and percentages for categorical variables. The total sample was divided into two subgroups at each time point: the first group was characterized by good medication adherence, according to a score ≥ 5 at Kemp's 7-point scale, while the second was characterized by the presence of a score < 5 at Kemp's 7-point scale (not overall good medication adherence) [36].

First, after the application of the Kolmogorov-Smirnov test to confirm the normal distribution, the Chi-square test and t-test were used to evaluate differences between the two groups in terms of adherence treatment to LAI antipsychotics at 6- and 12- month follow-up.

Second, a multivariate logistic regression analysis was used to explore the relationship between patients with an overall good medication adherence (dependent variable) and each of the independent variables previously found associated in the univariate analyses at 6- and 12- month follow-up. As for the BPRS, only the subscales were inserted in the multivariate models. Effect sizes in regression analyses were expressed as odds ratios (OR).

All statistical analyses were carried out using Stata for Windows, version 16 (StataCorp, College Station, Texas, USA), and statistical significance was set with a p-value < 0.05 (two-tailed).

Results

The sociodemographic and clinical characteristics at baseline were presented in the previously published studies [29, 34–38]. At baseline, 461 subjects were recruited. Participants were on average 41.72 years old, with ages ranging from 18 to 76 years. Of the total sample, 276 patients were males, mostly unemployed (49.24 %) and single (70.28 %), with a primary diagnosis of a schizophrenia spectrum disorder (71.80 %), starting treatment with a second-generation LAI antipsychotics (69.63 %).

Differences between patients with low and high medication adherence after 6 and 12 months of LAI treatment

Data were available for three hundred fifty-seven participants after 6 months of treatment with LAI antipsychotics and 332 participants after 12 months. As reported in ▶ **Table 1**, several significant differences were found in overall good medication adherence at 6-month follow-up: participants with higher medication adherence were younger (p = 0.01) and living with family members or in residential facilities (p = 0.02). Regarding psychopathological variables, patients with Kemp's 7-point scale ≥ 5 showed lower mean scores at BPRS total (p < 0.001), BPRS positive symptoms (p < 0.001), BPRS resistance (p < 0.001), and BPRS activation (p < 0.001). Considering medication-related variables, the absence of adverse events (p = 0.02) and a higher positive attitude toward medication (p < 0.001) were significantly associated with overall good medication adherence.

As reported in ▶ **Table 2**, the following characteristics were no longer different at 12-month follow-up: age (p = 0.17), living status (p = 0.36), and adverse events (p = 0.08). Patients with overall good medication adherence (Kemp's 7-point scale ≥ 5) reported lower mean scores to BPRS total and subscales (positive symptoms, negative symptoms, affect, resistance and activation) with medium to large effect sizes. Lastly, a positive attitude toward medication still differed significantly between the two groups at 12-month follow-up (p < 0.001).

▶ **Figure 1** displays the changes in BPRS subscales scores at baseline, 6- and 12-month follow-up in the two subgroups (low *vs.* high medication adherence).

Factors associated with medication adherence at 6- and 12-month follow-up: multivariate analyses

A multivariate logistic regression analysis was performed, taking into account only the variables regarded as significantly different at the univariate analyses. Younger age (OR = 0.97; 95 % CI 0.94–0.99), lower BPRS resistance (OR = 0.75; 95 % CI 0.64–0.87) and activation scores (OR = 0.83; 95 % CI 0.69–0.99), no adverse events reported (OR = 0.34; 95 % CI 0.15–0.75) and positive attitude to-

▶ **Table 1** Differences between participants with low (Kemp < 5) and high (Kemp ≥ 5) medication adherence at 6-month follow-up. Variables are expressed as mean ± SD or n (%) as appropriate.

Variables	Kemp < 5 N = 78	Kemp ≥ 5 N = 279	t/χ	d/φ	P-value
Sociodemographic variables					
Age	45.04 ± 13.24	40.90 ± 12.62	2.53	0.32	0.01*
Sex, male	43 (55.13)	177 (63.44)	1.78	−0.07	0.18
Living alone	23 (29.49)	49 (17.56)	5.38	0.12	0.02*
Married	11 (14.10)	40 (14.39)	0.004	0.003	0.95
Employed	18 (23.08)	79 (28.32)	0.84	0.05	0.36
Diploma or above	36 (46.75)	140 (50.54)	0.35	0.03	0.56
Clinical variables					
Diagnosis			0.67	0.04	0.72
Psychosis	57 (73.08)	191 (68.46)			
Mood disorders	13 (16.67)	57 (20.43)			
Others	8 (10.26)	31 (11.11)			
Years from first contact with services	12.29 ± 11.34	10.97 ± 9.59	1.03	0.13	0.30
Medical comorbidities	28 (35.90)	88 (31.65)	0.50	−0.04	0.48
Alcohol abuse	14 (17.95)	49 (17.56)	0.01	−0.004	0.94
Substance abuse	19 (24.36)	59 (21.15)	0.36	−0.03	0.54
Psychopathological variables					
BPRS total	41.83 ± 11.68	35.15 ± 10.52	4.79	0.62	< 0.001*
BPRS positive symptoms	9.28 ± 4.16	7.37 ± 3.45	4.08	0.53	< 0.001*
BPRS negative symptoms	7.13 ± 3.25	7.13 ± 3.16	0.01	0.001	0.99
BPRS affect	9.13 ± 3.48	8.67 ± 3.44	1.03	0.13	0.30
BPRS resistance	8.87 ± 3.78	5.69 ± 2.66	8.37	1.08	< 0.001*
BPRS activation	6.09 ± 2.72	5.09 ± 2.10	3.46	0.45	< 0.001
Medication-related variables					
Second-generation LAI antipsychotics	47 (60.26)	199 (71.33)	3.49	0.09	0.06
History of LAI prescription	29 (37.18)	82 (29.39)	1.73	−0.07	0.19
Injection twice monthly or more frequently	19 (24.36)	57 (20.43)	0.56	−0.04	0.45
Adverse events reported	23 (47.92)	65 (29.95)	5.72	−0.15	0.02*
Positive attitude toward medication	28 (37.33)	226 (81.59)	57.54	0.40	< 0.001*

Legend: BPRS = Brief Psychiatric Rating Scale LAI = long-acting injectable; * p < 0.05.

▶ **Table 2** Differences between participants with low (Kemp < 5) and high (Kemp ≥ 5) medication adherence at 12-month follow-up. Variables are expressed as mean ± SD or n (%) as appropriate.

Variables	Kemp < 5 N = 70	Kemp ≥ 5 N = 262	t/χ	d/φ	P-value
Sociodemographic variables					
Age	40.04 ± 13.63	42.39 ± 12.63	−1.36	−0.18	0.17
Sex, male	43 (61.43)	165 (62.98)	0.06	−0.01	0.81
Living alone	18 (25.71)	54 (20.61)	0.85	0.05	0.36
Married	7 (10.00)	38 (14.50)	0.96	0.05	0.33
Employed	16 (22.86)	74 (28.24)	0.81	0.05	0.37
Diploma or above	34 (49.28)	126 (48.65)	0.01	−0.005	0.93
Clinical variables					
Diagnosis			1.16	0.06	0.56
Psychosis	52 (74.29)	182 (69.47)			
Mood disorders	13 (18.57)	50 (19.08)			
Others	5 (7.14)	30 (11.45)			
Years from first contact with services	9.56 ± 9.21	12.02 ± 10.11	−1.83	−0.25	0.07
Medical comorbidities	23 (33.33)	88 (33.59)	0.002	0.002	0.97
Alcohol abuse	14 (20.00)	50 (19.08)	0.03	−0.01	0.86
Substance abuse	19 (27.14)	56 (21.37)	1.05	−0.06	0.30
Psychopathological variables					
BPRS total	42.93 ± 13.33	33.38 ± 9.24	6.92	0.93	< 0.001*
BPRS positive symptoms	9.19 ± 4.44	7.12 ± 3.00	4.57	0.62	< 0.001*
BPRS negative symptoms	7.89 ± 3.72	6.62 ± 2.72	3.18	0.43	0.002*
BPRS affect	9.67 ± 3.74	8.28 ± 3.15	3.15	0.42	0.002*
BPRS resistance	8.94 ± 3.88	5.28 ± 2.32	9.99	1.35	< 0.001*
BPRS activation	6.07 ± 2.81	4.93 ± 1.99	3.86	0.52	< 0.001*
Medication-related variables					
Second-generation LAI antipsychotics	45 (64.29)	180 (68.70)	0.49	0.04	0.48
History of LAI prescription	27 (38.57)	76 (29.01)	2.36	−0.08	0.12
Injection twice monthly or more frequently	5 (13.16)	28 (14.66)	0.06	0.02	0.81
Adverse events reported	20 (28.99)	50 (19.23)	3.10	−0.10	0.08
Positive attitude toward medication	21 (31.34)	217 (84.11)	75.54	0.48	< 0.001*

Legend: BPRS = Brief Psychiatric Rating Scale; LAI = long-acting injectable; * p < 0.05.

ward medication (OR = 6.54; 95 % CI 2.79–15.32) remained significantly associated with an overall good medication adherence at 6-month follow-up while only lower BPRS resistance scores (OR = 0.69; 95 % CI 0.59–0.80) and positive attitude toward medication (OR = 8.02; 95 % CI 4.01–16.02) remained significant at 12-month follow-up (see ▶ **Table 3**).

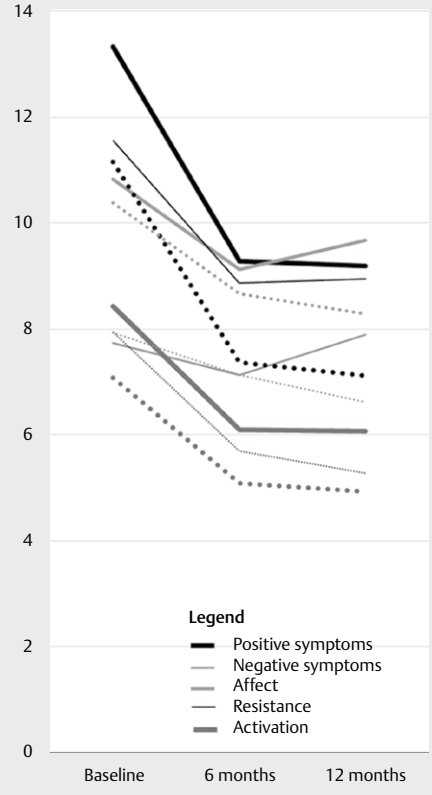
Discussion

In a large, unselected sample of everyday patients receiving LAI antipsychotics over a period of 12 months, patient attitude toward medication and scores at the BPRS resistance subscale appeared to be consistently associated with higher medication adherence.

Six and 12 months after initiating treatment with LAI antipsychotics, a positive attitude toward medication, as indicated by a DAI-10 higher than 0, predicted higher medication adherence after controlling for confounding variables. This substantially expands the results of a recent systematic review, reporting that perceived barriers and benefits represent the dimensions mostly influencing medication adherence in people with severe mental illness [43]. Moreover, this finding further underlines the importance of promoting a positive attitude toward medication in patients with psychiatric disorders [37]. More positive attitudes about medication and higher medication adherence have been found to be associated with more insight into the presence of a psychiatric disorder and a good relationship with the clinicians [19, 44]. In this respect, shared decision-making strategies represent a pillar in improving adherence to medication even in patients undergoing treatment with LAI antipsychotics [4]. Additionally, psychoeducational activities related to medication are important to explore and modify the feelings and thoughts perceived by the patients [45]. Indeed, recent papers have shown that combining LAI antipsychotics with customized interventions to address adherence barriers may improve outcomes both in individuals with bipolar disorder [46] and psychotic disorders [47].

Not surprisingly, the higher scores at the BPRS resistance subscale were also consistently associated with lower medication adherence at each considered time point in the multivariate analyses. This subscale explores the domains of hostility, uncooperativeness, and suspiciousness. Indeed, high severity of delusional symptoms

and suspiciousness are among the main risk factors for no medication adherence in schizophrenia and bipolar disorder [22]. Patients suspicious about the medication, believing that the medication may be harmful, or suffering from auditory hallucinations, telling them not to take the medication, are less likely to adhere [48]. Again, this finding highlights the importance of building a meaningful alliance between the patient and the clinician and the need for constant attention to the patients' experience with medication. Of note, assessing psychological factors, such as personality conflicts, needs, desires, dysfunctional beliefs, conscious and implicit attitudes about medications, could help clinicians to anticipate and deal with potential problems related to medications [49].



▶ **Fig. 1** Mean BPRS scores in patients with low (continuous lines) and high (broken lines) adherence to treatment at baseline, 6- and 12 months follow-up.

Other factors were associated with higher medication adherence at the multivariate analyses after 6, but not after 12 months of treatment, namely younger age, lower BPRS activation scores, and absence of adverse events. Our result about age is in contrast with past literature, showing that younger age is typically associated with poorer adherence to pharmacological treatment [19]. We could hypothesize that older patients in our sample have a longer history of the disorder and might feel discouraged and less propositional in following the prescribed therapy. On the contrary, younger people may have been more prone to adhere to pharmacological therapy with the hope of symptoms improvement. The subscale of BPRS activation measures excitement, tension, and mannerism-posturing. It is likely that people with activating symptomatology tend to be more inattentive and forget about medication. Finally, the presence of adverse events was strongly associated with lower medication adherence. The onset of side effects of psychotropic medication, including antipsychotics, may impair adherence [50]. However, the relationship between adverse events and non-adherence is quite complex, as, in the real-world, patients complain more about the lack of knowledge and management strategies rather than side effects per se [51]. Thus, it is crucial to implement shared decision-making and psychoeducational strategies. Of note, the presence of adverse events remains significant in the univariate but not in the multivariate analysis at 12-month follow-up. People with high rates of adverse events might have possibly discontinued the treatment with LAI antipsychotics. Indeed, adverse events represented the main cause of discontinuation in this naturalistic sample [29].

Other factors emerged as potentially influencing medication adherence. At 6-month follow-up, participants living alone were more likely to show lower adherence to pharmacological treatment. This underlines the crucial role of family support in psychiatric care [19, 52]. Moreover, besides the BPRS subscales discussed

▶ **Table 3** Multivariate logistic regression of the factors associated with low (Kemp < 5) and high (Kemp ≥ 5) medication adherence at 6- ($\chi^2 = 66.60$, $p = 0.001$, Pseudo $R^2 = 0.28$) and 12-month ($\chi^2 = 110.72$, $p < 0.001$, Pseudo $R^2 = 0.34$) follow-up.

Variables	6-month follow-up			12-month follow-up		
	OR	95 % CI	P	OR	95 % CI	P
Age	0.97	0.94, 0.99	0.04*	–	–	–
Living alone (ref: yes)	2.07	0.76, 5.59	0.15	–	–	–
BPRS positive symptoms	1.11	0.97, 1.27	0.14	1.07	0.95, 1.22	0.26
BPRS negative symptoms	–	–	–	1.05	0.93, 1.20	0.42
BPRS affect	–	–	–	0.94	0.84, 1.06	0.35
BPRS resistance	0.75	0.64, 0.87	<0.001*	0.69	0.59, 0.80	<0.001*
BPRS activation	0.83	0.69, 0.99	0.04*	0.97	0.81, 1.18	0.78
Adverse events reported (ref: no)	0.34	0.15, 0.75	0.007*	–	–	–
Positive attitude toward medication (ref: no)	6.54	2.79, 15.32	<0.001*	8.02	4.01, 16.02	<0.001*

Legend: BPRS = Brief psychiatric Rating Scale; * $p < 0.05$.

above, other domains related to medication adherence, specifically, people with low adherence have higher BPRS scores. It is possible that, on the one hand, people with increased severity of symptomatology tend to be less adherent to pharmacological treatment; on the other hand, taking medication irregularly does not guarantee symptoms improvement. A visual inspection of ▶ **Fig. 1** reveals interestingly that BPRS negative symptoms and affect domains tend to ameliorate in the group with high medication adherence, while patients with low adherence show an opposite trend. This result, even if not supported by statistical evidence, may suggest that improvements in non-positive symptoms of patients with severe mental disorders are seen in the longer-term after LAI antipsychotic' prescription. Therefore, it appears even more important to explain to the patients that medication adherence is fundamental for a good overall outcome.

Our findings are novel as literature has principally focused on factors related to adherence to oral medication or to characteristics of patients who discontinued LAI antipsychotics. Conversely, to our knowledge, little is known about the predictors of adherence to treatment with LAI antipsychotics. Although LAI antipsychotics are typically prescribed to improve treatment adherence, they are rarely prescribed in monotherapy. Indeed, a vast part of our sample (91.80 %) was also taking at least one concomitant oral medication [37]. Therefore, an evaluation of medication adherence and predictors remains fundamental.

Nevertheless, several shortcomings need to be mentioned to comprehensively discuss our results. First, we analyzed only the differences between patients who did not discontinue from the study. It is worth mentioning that reasons for discontinuation in the present cohort have been thoroughly described in a previous study [29]. Second, we could not evaluate some important factors associated with medication adherence, such as the level of insight [22], which is frequently lacking in patients with chronic psychiatric disorders. Third, we have dichotomized the outcome as well as many independent variables, with the risk of losing more detailed information. However, the limited dimension of our sample, which has been selected in a naturalistic manner, did not allow to introduce too many variability factors in our analyses.

In conclusion, our findings suggest that attitude toward medication and traits of suspiciousness/hostility appear to be related to medication adherence to LAI antipsychotics. Evidently, these factors are modifiable through adjustments in the patient-clinician relationship as well as the implementation of tailored psychoeducational strategies to better explain the importance of medication adherence and the prompt recognition and management of medication-related side effects.

Appendix

The STAR Network Depot Investigators are as follows: Corrado Barbui, Federico Bertolini, Filippo Boschello, Chiara Gastaldon, Maria Angela Mazzi, Michela Nosè, Giovanni Ostuzzi, Davide Papola, Giovanni Perini, Alberto Piccoli, Michela Pievani, Marianna Purgato, Mirella Ruggeri, Federico Tedeschi, Samira Terlizzi, and Giulia Turrini (Verona); Mariarita Caroleo, Pasquale De Fazio, Fabio Magliocco, and Gaetano Raffaele (Catanzaro); Simone Cavallotti, Margherita Chirico, Armando D'Agostino, Farida Ferrato, Ivan Limosani, Daniele Mastromo, Emiliano Monzani, Edoardo Giuseppe Ostinelli, Matteo Porcellana, and Francesco Restaino (Milano); Pasqua Maria Annese, Simone Bolognesi, Massimiliano Cerretini, Alberto De Capua, Sara Debolini, Maria Del Zanna, Francesco Fargnoli, Alessandra Giannini, Livia Luccarelli, Claudio Lucii, Elisa Pierantozzi, and Fiorella Tozzi (Siena); Francesco Bardicchia, Giuseppe Cardamone, Edvige Facchi, Nadia Magnani, and Federica Soscia (Grosseto); Bruno Biancosino, and Spyridon Zotos (Ferrara); Marzio Giacomin, Francesco Pompei, Mariangela Spano, and Filippo Zonta (Treviso); Aldo Buzzi, Camilla Callegari, Roberta Calzolari, Ivano Caselli, Marcello Diurni, Edoardo Luigi Giana, Marta Ielmini, Anna Milano, Nicola Poloni, Emanuele Sani, and Daniele Zizolfi (Varese); Gabrio Alberini, Paola Bortolaso, Sara Cazzamalli, Chiara Costantini, Angela Di Caro, Chiara Paronelli, Silvia Piantanida, and Marco Piccinelli (Varese Verbano); Papalini Alessandro, Silva Veronica Barbanti, Chiara D'Ippolito, Mauro Gozzi, and Valentina Moretti (Reggio Emilia); Ornella Campese, Mariangela Corbo, Lucia Di Capro, Massimo di Giannantonio, Federica Fiori, Marco Lorusso, Valerio Mancini, Giovanni Martinotti, and Daniela Viceconte (Chieti); Carmela Calandra, Maria Luca, Maria Salvina Signorelli, and Francesco Suraniti (Catania); Beatrice Balzarro, Giancarlo Boncompagni, Valentina Caretto, Roberta Emiliani, Pasqualino Lupoli, Marco Menchetti, Eugenio Rossi, Viviana Storbini, Ilaria Tarricone, and Laura Terzi (Bologna); Marianna Boso, Cristina Catania, Giuseppe De Paoli, and Paolo Risaro (Pavia); Flora Aspesi, Francesco Bartoli, Mattia Bava, Adele Bono, Giulia Brambilla, Giuseppe Carrà, Gloria Castagna, Sara Lucchi, Roberto Nava, Milena Provenzi, Tommaso Tabacchi, Martina Tremolada, and Enrica Verrengia (Monza); Michela Barchiesi and Maria Ginevra Oriani (Ancona); Monica Pacetti (Forlì); Andrea Aguglia, Maurizio Ferro, and Lucio Ghio (Genova); Rossella Beneduce, Laura Laffranchini, Laura Rosa Magni, Giuseppe Rossi, and Giovanni Battista Tura (Brescia); Lelio Addeo, Giovanni Balletta, Elisa De Vivo, Rossella Di Benedetto, and Vincenzo Fricchione Parise (Avellino); Bernardo Carpiniello and Federica Pinna (Cagliari); Damiano Pecile (Mantova); Chiara Mattei (Fermo); Tommaso Bonavigo, Elisabetta Pascolo Fabrici, Sofia Panarello, Giulia Peresson, and Claudio Vitucci (Trieste); Monica Pacetti (Forlì); Francesco Gardellin, and Stefania Strizzolo (Vicenza); Edoardo Cossetta, Carlo Fizzotti, and Daniele Moretti (Savona); Luana Di Gregorio and Francesca Sozzi (Trento); Giuseppe Colli and Daniele La Barbera (Palermo); Sabrina Laurenzi (Civitanova Marche).

Acknowledgments

This work was developed within the framework of the DINOGMI Department of Excellence of MIUR 2018–2022 (Law 232/2016).

Funding

This work has received no funding.

Conflict of Interest

GM has been a consultant and/or a speaker and/or has received research grants from Angelini, Doc Generici, Janssen, Lundbeck, Otsuka, and Pfizer. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

[1] Haynes RB. Compliance in health care. Baltimore, MD: Johns Hopkins University Press; 1979

[2] Myers LB, Midence K. Adherence to treatment in medical condition. Amsterdam: Harwood Academic Publisher; 1998

[3] Chakrabarti S. What's in a name? Compliance, adherence and concordance in chronic psychiatric disorders. World J Psychiatry 2014; 4: 30–36

[4] Fiorillo A, Barlati S, Bellomo A et al. The role of shared decision-making in improving adherence to pharmacological treatments in patients with schizophrenia: A clinical review. Ann Gen Psychiatry 2020; 19: 43

[5] Pacchiarotti I, Tiihonen J, Kotzalidis GD et al. Long-acting injectable antipsychotics (LAIs) for maintenance treatment of bipolar and schizoaffective disorders: A systematic review. Eur Neuropsychopharmacol 2019; 29: 457–470

[6] Velligan DI, Sajatovic M, Hatch A et al. Why do psychiatric patients stop antipsychotic medication? A systematic review of reasons for nonadherence to medication in patients with serious mental illness. Patient Prefer Adherence 2017; 11: 449–468

[7] Marazziti D, Mucci F, Avella MT et al. The increasing challenge of the possible impact of ethnicity on psychopharmacology. CNS Spectr 2021; 26: 222–231

[8] Fleck DE, Keck PE Jr, Corey KB et al. Factors associated with medication adherence in African American and white patients with bipolar disorder. J Clin Psychiatry 2005; 66: 646–652

[9] Kane JM, Kishimoto T, Correll CU. Non-adherence to medication in patients with psychotic disorders: Epidemiology, contributing factors and management strategies. World Psychiatry 2013; 12: 216–226

[10] Kretchy IA, Osafo J, Agyemang SA et al. Psychological burden and caregiver-reported non-adherence to psychotropic medications among patients with schizophrenia. Psychiatry Res 2018; 259: 289–294

[11] Yatham LN, Kennedy SH, Parikh SV et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. Bipolar Disord 2018; 20: 97–170

[12] Benkert O, Graf-Morgenstern M, Hillert A et al. Public opinion on psychotropic drugs: An analysis of the factors influencing acceptance or rejection. J Nerv Ment Dis 1997; 185: 151–158

[13] Helbling J, Ajdacic-Gross V, Lauber C et al. Attitudes to antipsychotic drugs and their side effects: A comparison between general practitioners and the general population. BMC Psychiatry 2006; 6: 42. doi: 10.1186/1471-244X-6-42

[14] Sajatovic M, Jenkins JH. Is antipsychotic medication stigmatizing for people with mental illness? Int Rev Psychiatry 2007; 19: 107–112

[15] Janssen B, Gaebel W, Haerter M et al. Evaluation of factors influencing medication compliance in inpatient treatment of psychotic disorders. Psychopharmacology (Berl) 2006; 187: 229–236

[16] Leclerc E, Mansur RB, Brietzke E. Determinants of adherence to treatment in bipolar disorder: A comprehensive review. J Affect Disord 2013; 149: 247–252

[17] El-Missiry A, Elbatrawy A, El Missiry M et al. Comparing cognitive functions in medication adherent and non-adherent patients with schizophrenia. J Psychiatr Res 2015; 70: 106–112

[18] Foglia E, Schoeler T, Klamerus E et al. Cannabis use and adherence to antipsychotic medication: A systematic review and meta-analysis. Psychol Med 2017; 47: 1691–1705

[19] El Abdellati K, De Picker L, Morrens M. Antipsychotic treatment failure: A systematic review on risk Factors and interventions for treatment adherence in psychosis. Front Neurosci 2020; 14: 531763

[20] Dibonaventura M, Gabriel S, Dupclay L et al. A patient perspective of the impact of medication side effects on adherence: Results of a cross-sectional nationwide survey of patients with schizophrenia. BMC Psychiatry 2012; 12: 20. doi: 10.1186/1471-244X-12-20

[21] Carbon M, Correll CU. Clinical predictors of therapeutic response to antipsychotics in schizophrenia. Dialogues Clin Neurosci 2014; 16: 505–524

[22] García S, Martínez-Cengotitabengoa M, López-Zurbano S et al. Adherence to antipsychotic medication in bipolar disorder and schizophrenic patients: A systematic review. J Clin Psychopharmacol 2016; 36: 355–371

[23] Perkins DO. Predictors of noncompliance in patients with schizophrenia. J Clin Psychiatry 2002; 63: 1121–1128

[24] McCann TV, Boardman G, Clark E et al. Risk profiles for non-adherence to antipsychotic medications. J Psychiatr Ment Health Nurs 2008; 15: 622–629

[25] Firth J, Siddiqi N, Koyanagi A et al. The Lancet Psychiatry Commission: A blueprint for protecting physical health in people with mental illness. Lancet Psychiatry 2019; 6: 675–712

[26] Day JC, Bentall RP, Roberts C et al. Attitudes toward antipsychotic medication: The impact of clinical variables and relationships with health professionals. Arch Gen Psychiatry 2005; 62: 717–724

[27] McCabe R, Healey PG, Priebe S et al. Shared understanding in psychiatrist-patient communication: Association with treatment adherence in schizophrenia. Patient Educ Couns 2013; 93: 73–79

[28] Correll CU, Kim E, Sliwa JK et al. Pharmacokinetic characteristics of long-acting injectable antipsychotics for schizophrenia: An overview. CNS Drugs 2021; 35: 39–59

[29] Bertolini F, Ostuzzi G, Pievani M et al. Comparing long-acting antipsychotic discontinuation rates under ordinary clinical circumstances: A survival analysis from an observational, pragmatic study. CNS Drugs 2021; 35: 655–665

[30] Peuskens J, Olivares JM, Pecenak J et al. Treatment retention with risperidone long-acting injection: 24-month results from the Electronic Schizophrenia Treatment Adherence Registry (e-STAR) in six countries. Curr Med Res Opin 2010; 26: 501–509

[31] Acosta FJ, Hernández JL, Pereira J et al. Medication adherence in schizophrenia. World J Psychiatry 2012; 2: 74–82

[32] von Elm E, Altman DG, Egger M et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: Guidelines for reporting observational studies. J Clin Epidemiol 2008; 61: 344–349

[33] World Medical Association World Medical Association Declaration of Helsinki: Ethical principles for medical research involving human subjects. JAMA 2013; 310: 2191–2194

[34] Ostuzzi G, Mazzi MA, Terlizzi S et al. Factors associated with first- versus second-generation long-acting antipsychotics prescribed under ordinary clinical practice in Italy. PLoS One 2018; 13: e0201371

[35] Barbui C, Bertolini F, Bartoli F et al. Reasons for initiating long-acting antipsychotics in psychiatric practice: Findings from the STAR Network Depot Study. Ther Adv Psychopharmacol 2020; 10: 2045125320978102

[36] Bartoli F, Ostuzzi G, Crocamo C et al. Clinical correlates of paliperidone palmitate and aripiprazole monohydrate prescription for subjects with schizophrenia-spectrum disorders: Findings from the STAR Network Depot Study. Int Clin Psychopharmacol 2020; 35: 214–220

[37] Aguglia A, Fusar-Poli L, Amerio A et al. The Role of attitudes toward medication and treatment adherence in the clinical response to LAIs: Findings from the STAR Network Depot Study. Front Psychiatry 2021; 12: 784366

[38] Bartoli F, Cavaleri D, Callovini T et al. Comparing 1-year effectiveness and acceptability of once-monthly paliperidone palmitate and aripiprazole monohydrate for schizophrenia spectrum disorders: Findings from the STAR Network Depot Study. Psychiatry Res 2022; 309: 114405

[39] Kemp R, Hayward P, Applewhaite G et al. Compliance therapy in psychotic patients: Randomised controlled trial. BMJ 1996; 312: 345–349

[40] Shafer A. Meta-analysis of the brief psychiatric rating scale factor structure. Psychol Assess 2005; 17: 324–335

[41] Hogan TP, Awad AG, Eastwood R. A self-report scale predictive of drug compliance in schizophrenics: Reliability and discriminative validity. Psychol Med 1983; 13: 177–183

[42] Rossi A, Arduini L, De Cataldo S et al. Subjective response to neuroleptic medication: A validation study of the Italian version of the Drug Attitude Inventory (DAI). Epidemiol Psichiatr Soc 2001; 10: 107–114

[43] Marrero RJ, Fumero A, de Miguel A et al. Psychological factors involved in psychopharmacological medication adherence in mental health patients: A systematic review. Patient Educ Couns 2020; 103: 2116–2131

[44] Wiesjahn M, Jung E, Lamster F et al. Explaining attitudes and adherence to antipsychotic medication: The development of a process model. Schizophr Res Treatment 2014; 2014: 341545

[45] Soria CG, Velasco CF, Martín LF et al. Attitude toward medication as a predictor of therapeutic adherence. Importance of psychoeducation on treatment. Eur Psychiatry 2016; 33: S565–S566

[46] Sajatovic M, Levin JB, Ramirez LF et al. Long-acting injectable antipsychotic medication plus customized adherence enhancement in poor adherence patients with bipolar disorder. Prim Care Companion CNS Disord 2021; 23: 20m02888

[47] Mbwambo J, Kaaya S, Lema I et al. An interventional pilot of customized adherence enhancement combined with long-acting injectable antipsychotic medication (CAE-L) for poorly adherent patients with chronic psychotic disorder in Tanzania. BMC Psychiatry 2022; 22: 62. doi: 10.1186/s12888-022-03695-8

[48] Kikkert MJ, Schene AH, Koeter MW et al. Medication adherence in schizophrenia: Exploring patients', carers' and professionals' views. Schizophr Bull 2006; 32: 786–794

[49] Mintz DL. Teaching the prescriber's role: The psychology of psychopharmacology. Acad Psychiatry 2005; 29: 187–194

[50] Velligan DI, Weiden PJ, Sajatovic M et al. The expert consensus guideline series: Adherence problems in patients with serious and persistent mental illness. J Clin Psychiatry 2009; 70: 1–46

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

[52] Rodolico A, Bighelli I, Avanzato C et al. Family interventions for relapse prevention in schizophrenia: A systematic review and network meta-analysis. Lancet Psychiatry 2022 S2215-0366(21)00437-5 [Epub ahead of print]