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RESEARCH ARTICLE

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Predictive factors of overall functioning improvement in patients with chronic schizophrenia and schizoaffective disorder treated with paliperidone palmitate and aripiprazole monohydrate

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Abstract

Background: Long-acting injectable (LAI) antipsychotics can improve medication adherence and reduce hospitalisation rates compared with oral treatments. Paliperidone palmitate (PAL) and aripiprazole monohydrate (ARI) LAI treatments were associated with improvements in global functioning in patients with schizophrenia.

Objective: The objective of this study was to assess the predictive factors of better overall functioning in patients with chronic schizophrenia and schizoaffective disorder treated with PAL and ARI.

Method: Enrolled were 143 (97 males, 46 females, mean age 38.24 years, *SD* = 12.65) patients with a diagnosis of schizophrenia or schizoaffective disorder, whom we allocated in two groups (PAL and ARI treatments). We assessed global functioning, amount of oral medications, adherence to oral treatment, and number of hospitalisations before LAI introduction and at assessment time point.

Results: Longer treatment time with LAIs ($p < .001$), lower number of oral drugs ($p < .001$), and hospitalisations ($p = .002$) before LAI introduction, and shorter duration of illness ($p = .038$) predicted better Global Assessment of Functioning scores in the whole sample ($R^2 = 0.337$).

Conclusion: Early administration and longer duration of ARI or PAL treatments could play a significant role in improving global functioning of patients with schizophrenia and schizoaffective disorder. Better improvement in functioning could be achieved with ARI in young individuals with recent illness onset and PAL in patients at risk for recurrent hospitalisations.

KEYWORDS

aripiprazole monohydrate, global assessment of functioning, long-acting injectable antipsychotics, paliperidone palmitate, schizoaffective disorder, schizophrenia

1 | INTRODUCTION

Schizophrenia and schizoaffective disorder are severe, chronic, and progressive disorders for many patients. One goal of long-term maintenance treatment is to optimise patient functioning and quality of life (Hasan et al., 2013). A key component in maintaining patient functioning is relapse prevention; this may reduce the socio-economic burden associated with the disorder, as psychotic episodes in schizophrenia may worsen psychopathology and social functioning (Awad & Voruganti, 2008; Harvey, Loewenstein, & Czaja, 2013; Hong, Windmeijer, Novick, Haro, & Brown, 2009; Kane, Kishimoto, & Correll, 2013). Reducing hospitalisation rates and improving medication adherence are key components for improving functional outcomes in patients with schizophrenia. Nonadherence to medication is a major issue in schizophrenia, constituting the most frequent cause of relapse and rehospitalisation (Kane, 2011; Keith & Kane, 2003). Despite the availability of effective antipsychotic treatment, long-term adherence to antipsychotic treatment is low (Kahn et al., 2008; Mullins, Obeidat, Cuffel, Naradzay, & Loebel, 2008). The rate of antipsychotic nonadherence early in the course of schizophrenia has been recently estimated to be about 60% (Offord, Lin, Mirski, & Wong, 2013). Antipsychotic drugs constitute the core of long-term management (Leucht et al., 2012), because they effectively treat psychosis and reduce the risk of relapse (Kahn & Keefe, 2013). Guidelines for the management of schizophrenia recommend improving medication adherence as a strategy to reduce hospitalisation rates and costs (Hasan et al., 2013).

Long-acting injectable (LAI) antipsychotic formulations allow patients to remain adherent to prescription and ensure regular contact with healthcare professionals; furthermore, the nature of the formulation prevents covert nonadherence (Leucht et al., 2011). LAI antipsychotics provide an opportunity to improve medication adherence (Hasan et al., 2013; Velligan et al., 2009) and reduce hospitalisation rates compared with oral formulations (Greene et al., 2017; Weiden et al., 2009).

The management of schizophrenia spectrum and other psychotic disorders primarily aims to reduce symptoms in the short- and long-term, to maintain physical and mental functioning, to improve quality of life, and to promote patient recovery (Hasan et al., 2013). Treatment with LAI antipsychotics has been followed by improved functioning with both paliperidone palmitate (PAL; Alphs, Fu, & Turkoz, 2016; Nussbaum & Stroup, 2012) and aripiprazole monohydrate (ARI) in patients with such disorders (Chue & Chue, 2016).

The aim of this study was to identify predictors of global functioning improvement in patients with chronic schizophrenia and schizoaffective disorder treated with PAL or ARI.

2 | METHODS

This study was a four-site investigation of the effects of LAI formulations of paliperidone and aripiprazole on global functioning that was conducted in psychiatric hospitals in Central Italy, namely, (a) Sant'Andrea University Hospital, Rome, (b) Villa von Siebenthal Neuropsychiatric Hospital, Genzano di Roma, (c) Belcolle Hospital, ASL Viterbo, and (d) Psychiatric Service of the Careggi University Hospital, Florence, Italy. The ethical committee of each site approved the study.

Inclusion criteria were DSM-5 diagnosis of schizophrenia or schizoaffective disorder, age between 18 and 70 years, and LAI atypical antipsychotic treatment with ARI or PAL. Exclusion criteria included pregnancy, recent brain injury, substance use, and severe neurological or medical illness.

2.1 | Clinical measures

Patients were subjected to the structured clinical interview for DSM-5, research version (First, Williams, Karg, & Spitzer, 2015) to confirm their diagnosis. Analysing the medical records of the participants, we recorded each patient's sociodemographic characteristics, diagnosis, age at onset, years of illness, type of LAI formulation and chlorpromazine equivalent daily dose, months of LAI administration, number of hospitalisations before LAI introduction and at assessment time point, number of oral medications taken before LAI introduction and at assessment time point, and number of missed LAI injections since their introduction. We assessed patients' global functioning at the beginning of the study through the Global Assessment of Functioning (GAF) scale (Endicott, Spitzer, Fleiss, & Cohen, 1976), that is, a "continuous" 1–100 scale subdivided in ten 10-point content layers; higher scores indicate better psycho-socio-occupational functioning.

2.2 | Participants

The recruitment period was from January 2016 to January 2017, during which we enrolled 143 (97 men and 46 women; mean age 38.24 years, *SD* = 12.65) consecutive patients, of whom 91 (68 men and 23 women; mean age 38.24 years, *SD* = 12.36) had a DSM-5 diagnosis of schizophrenia and 52 (29 men and 23 women; mean age, 38.23 years; *SD* = 13.28) schizoaffective disorder (American Psychiatric Association, 2013). We divided the whole sample in two groups, according to the prescribed LAI, that is, ARI (78 patients, 53 men and 25 women; mean age, 34 years; *SD* = 12.93) and PAL (65 patients, 44 men and 21 women; mean age, 41.77; *SD* = 11.33). The ARI group's mean long-acting treatment duration was 10.66 months (*SD* = 4.41), whereas the PAL group was on long-acting since a mean of 19.38 months (*SD* = 11.1). Patients after the interview were assigned to one of the two LAIs according to clinician's and patient's preference; the parties reached consensus when the clinician was explaining the patient the aims and design of the study, providing information on drug actions and on the mechanisms of the disorder, in the process of obtaining informed consent.

All patients were fully informed about the observational nature of the study, and each provided written informed consent.

2.3 | Oral drug treatment

All included patients received fixed doses of oral antipsychotic drugs at the time of LAI introduction; 67.4% of them were on typical antipsychotics, 94.3% on atypical antipsychotics, 74.3% on benzodiazepines, 80.9% on mood stabilisers, and 31.2% on antidepressants. At assessment time point, 7.7% of patients were on typical

antipsychotics, 53.8% on atypical antipsychotics, 60.8% on benzodiazepines, 58% on mood stabilisers, and 11.9% on antidepressants.

2.4 | Statistical analyses

We analysed the clinical characteristics of the samples with one-way analysis of variance for the continuous variables and used the chi-square (χ^2) test for categorical variables. We tested the distribution of GAF values in ARI and PAL samples with skewness, kurtosis, and the Shapiro–Wilk test for normality (ARI group, $W = 0.956$, $p = .263$; PAL group, $W = 0.928$, $p = .092$), which indicated a normal distribution in both groups.

We performed a stepwise multiple regression weighted by gender to identify predictors of improvement in global functioning, using mean GAF scores as the dependent variable, and diagnosis, illness years, number of oral drugs at LAI introduction, number of hospitalisations before LAI introduction, daily dosage of LAI in chlorpromazine equivalents, months of LAI administration, and number of missed LAI injections as the independent variables. Cut-off for statistical significance was set at $p < .05$. All p values were two-tailed. We used the software SPSS Statistics 24.0 (Armonk, NY: IBM Corp. 1989, 2016) for all analyses.

3 | RESULTS

3.1 | Descriptive statistics

There were significantly more men than women in the entire (ARI + PAL) sample ($\chi^2 = 18.189$; $p < .001$). ARI and PAL groups showed significant differences in gender composition ($\chi^2 = 5.449$; $p = .02$) and diagnosis ($\chi^2 = 6.609$; $p = .01$). One-way analysis of variance showed significant between-group differences in age ($F = 14.65$; $p < .001$), illness years ($F = 14.28$; $p < .001$), and months of LAI

TABLE 1 Demographic and clinical characteristics of samples

	LAI	N	Ratio		χ^2	p
Gender, M/F	PAL	78	53/25			
	ARI	65	44/21			
	TOT	143	97/46		5.449	**.02**
Diagnosis, SCZ/SAD	PAL	78	57/21			
	ARI	65	34/31			
	TOT	143	91/52		6.609	**.01**
	LAI	***N***	***M***	***SD***	***F***	***p***
Age, years	PAL	78	41.77	11.33		
	ARI	65	34.00	12.93		
	TOT	143	38.24	12.65	14.65	**<.001**
Age of illness onset, years	PAL	78	22.54	6.20		
	ARI	65	20.94	6.30		
	TOT	143	21.81	6.28	2.326	.129
Illness duration, years	PAL	78	19.23	9.71		
	ARI	65	13.06	9.73		
	TOT	143	16.43	10.17	14.28	**<.001**
GAF scores	PAL	78	59.05	9.98		
	ARI	65	58.46	9.55		
	TOT	143	58.78	9.76	0.129	.72
LAI treatment duration, months	PAL	78	19.38	11.10		
	ARI	65	10.66	4.41		
	TOT	143	15.42	9.73	35.415	**<.001**
Daily chlorpromazine equivalents, mg	PAL	78	412.39	100.41		
	ARI	65	389.61	26.67		
	TOT	143	402.04	76.93	3.157	.078
Number of missed injections	PAL	78	0.03	0.16		
	ARI	65	0.17	1.13		
	TOT	143	0.09	0.77	1.241	.267
Number of oral drugs before LAI introduction	PAL	76	5.01	2.73		
	ARI	65	4.75	2.14		
	TOT	141	4.89	2.47	0.385	.536
Number of oral drugs at assessment time	PAL	78	2.36	1.52		
	ARI	65	2.03	1.16		
	TOT	143	2.21	1.37	2.041	.155
Number of hospitalisations before LAI introduction	PAL	78	4.15	5.09		
	ARI	65	4.58	7.81		
	TOT	143	4.35	6.45	0.157	.692
Number of hospitalisations after LAI introduction	PAL	78	0.19	0.49		
	ARI	65	0.26	0.96		
	TOT	143	0.22	0.74	0.313	.577

Note. ARI = aripiprazole monohydrate; GAF = Global Assessment of Functioning; LAI = long-acting injectable; PAL = paliperidone palmitate; SAD = schizoaffective disorder; SCZ = schizophrenia; SD = standard deviation; TOT = total study sample.

Significant results in bold characters.

treatment (F = 35.415; p < .001). LAI groups did not differ in age at onset, number of oral drugs at LAI introduction, number of oral drugs during the study, number of hospitalisations before LAI introduction and at assessment timepoint, daily LAI dose in chlorpromazine equivalents, and number of missed LAI injections.

Table 1 summarises sociodemographic and clinical characteristics of study samples.

3.2 | Multiple regression

3.2.1 | Whole sample

Multiple regression showed that longer LAI treatment time (p < .001; Figure 1), lower number of prescribed oral drugs before LAI introduction (p < .001), fewer hospitalisations before LAI introduction (p = .002), and shorter illness duration (p = .038) were predictors of better GAF scores in the whole sample (R^2 = 0.337; Table 2).

3.2.2 | PAL group

In this group, longer PAL treatment time (p < .001; Figure 2), lower number of prescribed oral drugs before PAL introduction (p = .002), fewer hospitalisations before PAL introduction (p = .003), and lower number of missed injections (p = .028) were predictors of increased (improved) GAF scores (R^2 = 0.450; Table 3).

3.2.3 | ARI group

In this group, shorter illness duration (p = .005), lower number of prescribed oral drugs before ARI introduction (p = .01), and longer time of ARI treatment (p = .022; Figure 2) were predictors of increased GAF scores (R^2 = 0.282; Table 4).

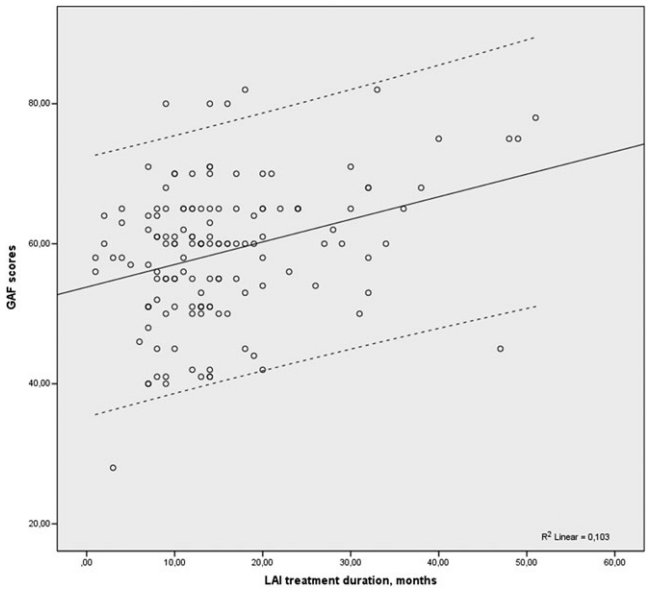

FIGURE 1 Correlation between Global Assessment of Functioning (GAF) scores and long-acting injectable (LAI) treatment duration for the whole sample

4 | DISCUSSION

This observational study examined the effects of long-acting ARI and PAL in patients with schizophrenia and schizoaffective disorder on overall functioning. Our findings suggest that early and longer treatment time with these LAIs in patients with lower number of prescribed oral drugs and fewer hospitalisations at LAI introduction could predict a better outcome in psycho-socio-occupational functioning.

Treatment with these LAI antipsychotics could affect patients' functioning in different ways. PAL therapy could improve functioning especially if given to patients with better adherence, to those with fewer hospitalisations prior to PAL introduction, to those with a lower oral drug load before PAL introduction, and if administered for a longer time. ARI could improve functioning especially if administered for a longer time to patients with shorter illness duration and lower number of prescribed oral drugs before its introduction.

Taken together, our data suggest that ARI and PAL LAI treatments could be introduced early in the course of psychotic illness, instead of adding oral medications. This could prevent a downward course of the illness that could ensue in further hospitalisations.

In our sample, patients on ARI were younger than those on PAL, which is consistent with the choice of aripiprazole for younger, first episode patients, who showed more benefit than multi-episode patients (Greene et al., 2017; Naber et al., 2015). Knowledge of literature and beliefs about therapeutic actions and side effects of the two drugs may have biased participating clinicians towards the use of ARI in younger patients. The fact that the PAL group had been treated with LAI for longer than the ARI group could be an artefact due to the longer availability of the former.

Our findings are consistent with studies showing that atypical long-acting LAIs were associated with lower rehospitalisation rates and improved treatment adherence in patients with schizophrenia (Biagi et al., 2017; Greene et al., 2017; Lafeuille et al., 2013; Lang et al., 2010; Marcus, Zummo, Pettit, Stoddard, & Doshi, 2015; Naber et al., 2015). Preventing relapse, improving quality of life and overall functioning of the patient, and maintaining recovery are key long-term goals of drug treatment for schizophrenia. Relapse itself represents an important predictor of subsequent relapses, whereas multiple relapses have been associated with poorer long-term outcome (Kahn et al., 2008). Fewer psychiatric hospitalisations may also contribute to substantial cost savings with LAI antipsychotic therapy, despite its higher costs (Lin, Wong, Offord, & Mirski, 2013).

The use of atypical antipsychotic LAIs early in the course of schizophrenia, namely, at the first psychotic episode, may improve outcome, given that it is associated with better cortical myelination (Bartzokis et al., 2011, 2012), whereas atypical oral formulations fare better than typical neuroleptic depot formulations at this respect (Bartzokis et al., 2007; Bartzokis et al., 2009). These results suggest that atypical LAIs are better than typical neuroleptics in restoring younger patients' myelination trajectories, thus preventing grey and white matter loss after psychosis onset. This could be related to the better maintenance of functioning with atypical LAIs, compared with their oral counterparts (Markowitz et al., 2013).

Our data are consistent with an early introduction of LAIs after psychoses onset, be it schizophrenia or schizoaffective disorder, but

TABLE 2 Least squares regression for both ARI and PAL treatments, weighted by gender

Model summary	R	R^2	Adjusted R^2	Standard error of the estimate
	0.581	0.337	0.318	9.35210

ANOVA	Sum of Squares	*df*	Mean square	*F*	*p*
Regression	6,058.332	4	1,514.583	17.317	<.001
Residual	11,894.808	136	87.462		
Total	17,953.140	140			

Coefficients Predictors	*B*	Standard error	β	*t*	*p*
Constant	63.501	2.070		30.678	<.001
Number of oral drugs at LAI introduction	−1.262	0.290	−0.307	−4.352	<.001
LAI treatment time (months)	0.360	0.072	0.364	4.997	<.001
Number of Hospitalisations before LAI introduction	−0.342	0.108	−0.232	−3.172	.002
Years of illness	−0.153	0.073	−0.159	−2.093	.038

Note. Dependent variable: mean Global Assessment of Functioning score.

Independent variables: diagnosis; illness years; number of oral drugs at LAI introduction; number of hospitalisations before LAI introduction; daily LAI dosage (chlorpromazine equivalents); LAI treatment time (months); number of missed LAI injections.

Predictors: number of oral drugs at LAI introduction; LAI treatment time (months); number of hospitalisations before LAI introduction; illness years.

ANOVA = analysis of variance; ARI = aripiprazole monohydrate; LAI = long-acting injectable; PAL = paliperidone palmitate.

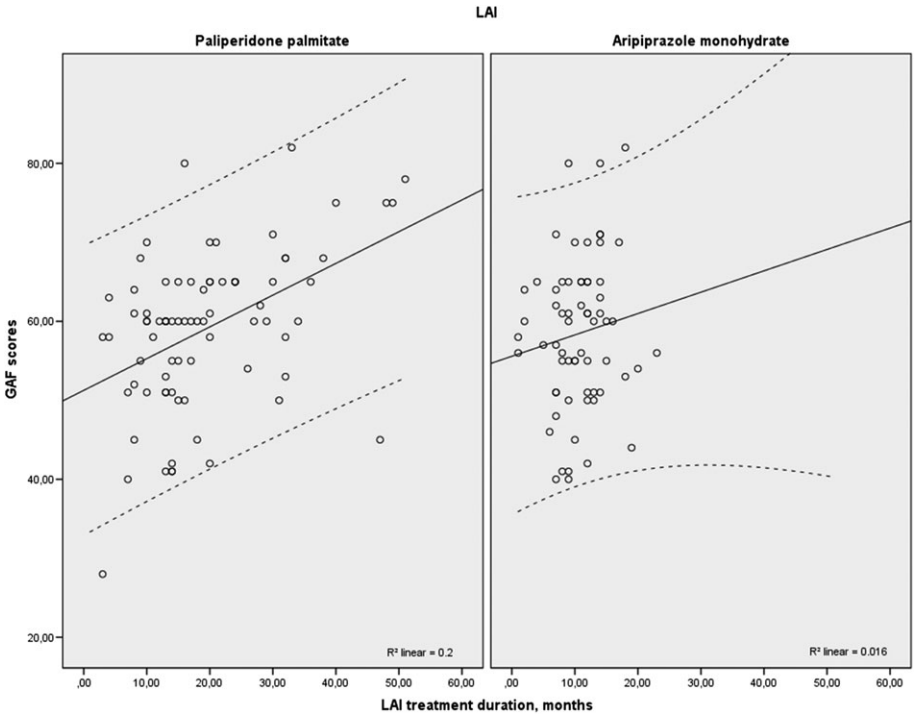

FIGURE 2 Correlations between Global Assessment of Functioning (GAF) scores and long-acting injectable (LAI) treatment duration for aripiprazole monohydrate and paliperidone palmitate groups

the same could be apply in the future for bipolar disorder, as ARI was found to delay time to relapse more than placebo (Calabrese et al., 2017). Since the first solicitations for using LAIs early in the course of schizophrenia (Stip, Abdel-Baki, Bloom, Grignon, & Roy, 2011; Zhornitsky & Stip, 2012), the appropriateness of starting young patients earlier on LAIs is increasingly advanced (Brugnoli et al., 2016; Karson, Duffy, Eramo, Nylander, & Offord, 2016; Lytle, McVoy, & Sajatovic, 2017; Manchanda et al., 2013; Stevens, Dawson, & Zummo, 2016).

4.1 | Limitations

Our study has the strengths and limitations of an open, naturalistic, real-world design; that is, it yields in scientific strength to gain in generalisability. The inclusion of control groups, consisting of patients on typical depot antipsychotics or the corresponding oral formulations of ARI and PAL, would have produced stronger results, as would a prospective, double-blind, placebo-controlled design. However, even without testing in our study the two LAIs against their oral

TABLE 3 Least squares regression for PAL treatment, weighted by gender

Model summary	R	R^2	Adjusted R^2	Standard error of the estimate	
	0.671	0.450	0.419	8.53264	
ANOVA	**Sum of squares**	***df***	**Mean square**	***F***	***p***
Regression	4,236.092	4	1,059.023	14.546	<.001
Residual	5,169.218	71	72.806		
Total	9,405.310	75			
Coefficients Predictors	***B***	**Standard error**	**β**	***t***	***p***
Constant	59.249	2.600		22.784	<.001
LAI treatment time (months)	0.366	0.076	0.428	4.821	<.001
Number of oral drugs at LAI introduction	−1.049	0.329	−0.285	−3.189	.002
Number of hospitalisations before LAI introduction	−0.459	0.147	−0.274	−3.112	.003
Number of missed LAI injections	−13.855	6.159	−0.200	−2.249	.028

Note. Dependent variable: mean Global Assessment of Functioning score.

Independent variables: diagnosis; illness years; number of oral drugs at PAL introduction; number of hospitalisations before PAL introduction; daily PAL dosage (chlorpromazine equivalents); PAL treatment time (months); number of missed PAL injections.

Predictors: PAL treatment time (months); number of oral drugs at PAL introduction; number of hospitalisations before PAL introduction; number of missed PAL injections.

ANOVA = analysis of variance; LAI = long-acting injectable; PAL = paliperidone palmitate.

TABLE 4 Least squares regression for ARI treatment, weighted by gender

Model summary	R	R^2	Adjusted R^2	Standard error of the estimate	
	0.531	0.282	0.246	10.03019	
ANOVA	**Sum of squares**	***df***	**Mean square**	***F***	***p***
Regression	2,404.61	3	801.537	7.967	<.001
Residual	6,136.89	61	100.605		
Total	8,541.5	64			
Coefficients Predictors	***B***	**Standard error**	**β**	***t***	***p***
Constant	63.312	3.819		16.578	<.001
Illness years	−0.335	0.114	−0.328	−2.932	.005
Number of oral drugs at LAI introduction	−1.435	0.543	−0.296	−2.641	.01
LAI treatment time (months)	0.618	0.263	0.257	2.352	.022

Note. Dependent Variable: mean Global Assessment of Functioning score.

Independent Variables: diagnosis; illness years; number of oral drugs at ARI introduction; number of hospitalisations before ARI introduction; daily ARI dosage (chlorpromazine equivalents); ARI treatment time (months); number of missed ARI injections.

Predictors: number of oral drugs at ARI introduction; ARI treatment time (months); number of hospitalisations before ARI introduction; years of illness.

ANOVA = analysis of variance; LAI = long-acting injectable; PAL = paliperidone palmitate.

counterparts or placebo, we may rely on previous studies showing overlap of clinical effects and functioning between oral formulations and LAI (Misawa, Kishimoto, Hagi, Kane, & Correll, 2016; Patel et al., 2013) and even slight advantages for the latter in meta-analyses, when quality of studies is taken into account (Ostuzzi, Bighelli, So, Furukawa, & Barbui, 2017). In addition, placebo-controlled studies showed the superiority of both medications over placebo (Fu et al., 2017; Kane et al., 2014; Kramer et al., 2010; Meltzer et al., 2015).

5 | CONCLUSIONS

LAI antipsychotics can play a key role in improving patient functioning. Early and longer treatment time with ARI or PAL in patients with lower number of prescribed oral drugs and fewer hospitalisations at their introduction could predict a better outcome in psycho-socio-occupational functioning. Our results advocate early use of LAI formulations during the course of schizophrenia or schizoaffective disorder.

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CONFLICT OF INTEREST

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