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Comparison of Typical and Atypical Long-Acting Antipsychotics in a Real-World Sample in terms of Treatment Adherence and Factors Influencing Treatment Choice: A One-Year Follow-Up Study

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ABSTRACT

Introduction: Non-adherence to antipsychotics, which plays a critical role in the treatment of individuals with severe mental disorders, is the most significant predictor of relapse. The effectiveness of long-acting injectable antipsychotics (LAIs) in ensuring treatment adherence and preventing relapse is well established. However, studies examining the factors influencing the clinical choice between first-generation and second-generation LAIs and the adherence differences between them are limited. This study aimed to compare patients with schizophrenia and bipolar disorder, who were hospitalized and discharged on either a first– or second-generation LAI, in terms of LAI choice, factors influencing adherence to LAIs, and adherence differences between the two groups of LAIs.

Methods: Our study is a naturalistic, follow-up study. The sample consists of 187 patients (99 females, 88 males) who were hospitalized, initiated on LAI treatment, and discharged. Sociodemographic and clinical information was obtained from patient records. Patients and/or their relatives were contacted by phone at 3, 6, and 12 months after discharge to assess treatment continuation, and this information was verified through health system records.

Results: First-generation LAIs were more frequently chosen for patients who were unemployed, diagnosed with schizophrenia, had a longer illness duration, had a higher number of prior hospitalizations, exhibited homicidal behavior, or had a history of electroconvulsive therapy ($p<0.05$). Patients with alcohol or substance-use developed non-adherence to treatment earlier ($p<0.05$). Treatment adherence was higher in patients with bipolar disorder ($p=0.025$). Adherence to second-generation LAIs at 12 months was higher compared to first-generation LAIs. Adherence was particularly higher with long-acting (LA) aripiprazole and LA paliperidone compared to the other three LAIs (haloperidol, risperidone, and zuclopenthixol) ($p<0.05$). Adherence to treatment prior to hospitalization significantly predicted LAI adherence at 12 months ($p<0.001$). Adherence to LAIs administered every four weeks was higher than those administered every two weeks ($p=0.014$).

Conclusion: For patients expected to face challenges with adherence to LAIs, second-generation agents with longer administration intervals may be preferred.

Keywords: Aripiprazole, bipolar disorder, depot antipsychotic, long-acting injectable antipsychotic, paliperidone, schizophrenia

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INTRODUCTION

Antipsychotics are included as the main pharmacological treatment for schizophrenia and bipolar disorder in all treatment guidelines (1,2). Although there is a high level of evidence for the efficacy of antipsychotics in both disorders (1,2), it is known that treatment adherence is generally low, and this nonadherence is among the strongest predictors of relapse, hospitalization, self-harm behavior, and functional impairment in schizophrenia and bipolar disorder (3). The effectiveness of long-acting injectable antipsychotics (LAIs) in improving treatment adherence and preventing relapses is a frequently reported finding in studies (4). Additionally, LAIs not only allow for precise monitoring of whether the patient is taking the medication but also prevent self-medication or misuse of the drug. The advantages of LAIs also include stable plasma drug levels, high bioavailability, and being safe and tolerable. Alongside these advantages, they also have disadvantages such as causing pain at the injection site in some patients, limited dosing flexibility, and the inability to quickly reduce the dose or discontinue the drug rapidly in case of side effects (5,6).

In the early years of depot antipsychotic use –when only first-generation LAIs were available– these agents were used in clinical practice mostly

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- **Adherence is higher to second- than first-generation long-acting antipsychotics (LAI).**
- **Adherence is higher to LAIs given every 4 weeks than those given every 2 weeks.**
- **Adherence to LAIs is better in bipolar disorder than in schizophrenia patients.**
- **Noncompliance appears earlier when alcohol or substance use disorder is present.**
- **The LAIs with the highest treatment adherence rates are aripiprazole and paliperidone.**
- **Good treatment adherence before starting LAIs, predicts adherence to LAIs.**

for patients who had frequent relapses, chronic illness, repeated hospitalizations, lack of insight, aggressive behavioral patterns, and clearly established nonadherence, at least confirmed by several hospitalizations due to treatment discontinuation; and treatment guidelines recommended LAIs only in cases of "nonadherence to treatment" at the time (7). However, since the early 2000 s, with the introduction of second-generation LAIs, this trend began to change, and especially following the positive results of studies on the use of second-generation LAIs in the early stages of schizophrenia—even during the first episode—early use of LAIs began to increase. Promising study results led to the addition of "patient preference" as an indication in treatment guidelines for LAI use (8,9). Around the same period, the number of studies showing positive outcomes resulting from LAIs use in bipolar disorder began to increase as well (4,10). Observing the facilitative effects of LAIs on patients' lives and studies reporting patients' positive perspectives toward these agents, the stigmatizing views regarding LAIs in clinical practice began to decrease (11).

Along with these recent developments, it has been observed that attitudes and practices related to LAI use are changing. However, so far only a few studies have investigated the factors influencing the choice between first or second-generation LAIs, the factors affecting adherence to the selected LAI, and whether there is a difference in adherence between different LAIs (12,13), real-world patient data remains limited. In a retrospective study in our country examining the factors affecting the choice of LAI (first– or second-generation) and differences in treatment adherence between LAIs in schizophrenia spectrum disorders, first-generation LAIs and risperidone LAI were compared; although treatment persistence was found to be longer in first-generation LAIs, risperidone LAI was found to be superior in terms of side effects and ongoing use of the same drug (14). In a retrospective study comparing LAI use in bipolar disorder, LAIs were found to prevent manic episodes; and second-generation LAIs were found to reduce both mania recurrence and illness severity scores (15).

The aim of this study is to compare patients who were hospitalized with schizophrenia or bipolar disorder diagnosed at a tertiary psychiatric hospital and discharged with a first– or second-generation LAI, in terms of LAI selection and to examine differences in treatment adherence among different LAIs. We hypothesized that second-generation LAIs would be preferred more than first-generation LAIs; that second-generation LAIs would be preferred in patients diagnosed with bipolar disorder, younger patients, and those with lower illness severity; and that treatment adherence would be better with second-generation LAIs.

METHODS

Study Sample and Procedure

This study is a naturalistic follow-up study. The population of the study consists of patients hospitalized in two closed psychiatric wards (one ward reserved for female patients and one ward for male patients) with a diagnosis of schizophrenia or bipolar disorder at the Bakirköy Prof. Dr. Mazhar Osman Training and Research Hospital for Psychiatry, Neurology and Neurosurgery from November 2023 to November 2024. Patients diagnosed with bipolar disorder (type 1) and schizophrenia were identified through the hospital's medical record system, and their treatment files were reviewed. The sample size of the study was calculated based on the 12-month continuation rates for five different LAI options included in the study. The parameters used in the analysis were as follows: effect size w=0.3 (medium effect), significance level α=0.05, power value 1–β=0.95, df (degrees of freedom)=2. Based on this power analysis, the required sample size was calculated to be 172. Considering the possibility of missing data or dropouts, the total sample size was planned to be 220 participants, consisting of 110 women and 110 men. Data collection ceased once the target sample size was reached.

Patients who started LAI treatment were identified from medical records, and a sociodemographic and clinical data form created by the researchers was filled out. The clinical characteristics of the participants were derived from existing medical records and, when applicable, from previous hospitalization files. The presence of homicidal behavior was operationally defined based on documented risk of homicide as an indication for admission, as well as the identification of violent or aggressive behavior toward others reported in the anamnesis obtained from the patient and/or their relatives. Due to missing data in 10 male and 1 female participant records, and the inability to contact participants or not consenting to the study at the 3rd, 6th, and 12th follow-up points (12 male and 10 female participants), 99 women and 88 men were included in the final analysis. Participants were grouped based on the LAI they received (first or second-generation). After discharge, participants were contacted by phone on the 3rd, 6th, and 12th months for verbal consent to participate and information regarding their treatment adherence. The date of the last LAI injection was also recorded, and this information was verified via the hospitals or the national medical data system. Consent was obtained from the participant and the legal guardian of the participant when applicable for the collection and verification of data in the 3rd, 6th, and 12th months. Non-adherence to treatment was defined as no LAI administration for 8 weeks after the last injection for drugs administered every 4 weeks, and 4 weeks after the last injection for drugs administered every 2 weeks.

Inclusion criteria for the study were: Being 18 years of age and above, having a diagnosis of bipolar disorder or schizophrenia, being treated with LAIs and a history of psychiatric hospitalization in the past year. Exclusion criteria for the study were: Not consenting to be part of the study, incomplete data or missing follow-up information at specified time points.

The study was approved by the Ethical Committee of Bakirkoy Dr. Sadi Konuk Training and Research Hospital (Decision No: 2023-22-13/Date: 20.11.2023).

Statistical Analysis

Data were analyzed using the IBM Statistical Package for Social Sciences (SPSS) program version 26.0 for Windows. The normality of data distribution was assessed using the Kolmogorov-Smirnov test. Descriptive statistics included means, standard deviations, percentage rates, and frequency values. After descriptive analysis, independent t-tests were performed for normally distributed variables. Chi-square tests were used

to assess differences in categorical variables. Logistic regression analysis was performed to identify factors predicting treatment adherence. A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 187 participants were included in the study. The mean age of the participants was 43.43±10.82 years, with 56.7% being female (n=99) and 43.3% male (n=88). Of the participants, 68.4% (n=128) had a diagnosis of schizophrenia and 31.6% (n=59) had bipolar disorder. The majority of participants were unemployed (81.8%, n=153), lived in urban areas (88.7%, n=166), and had a history of smoking (66.8%, n=125), alcohol use percentage was 13.3% (n=25), and psychoactive substance-use disorders percentage was 16.6%, (n=31).

Among the participants, 36.7% (n=68) received first-generation LAIs and 63.3% (n=119) received second-generation LAIs. Specific medications included 16.6% (n=31) aripiprazole, 32.1% (n=60) paliperidone, 15% (n=28) risperidone, 21.9% (n=41) haloperidol, and 14.4% (n=27) zuclopenthixol. No significant differences in LAI selection were found regarding age or gender (p=0.064 and p=0.76, respectively). However, among unemployed participants, 41.8% were prescribed first-generation LAIs, compared to 8.3% in employed participants (p=0.004). There were no significant differences in LAI choice based on smoking, alcohol, or substance abuse (p>0.05).

According to analysis made comparing disorders, 45.3% of schizophrenia patients, received first-generation LAIs, while only 16.9% of bipolar disorder patients received first generational LAIs (p<0.001). Those prescribed first-generation LAIs had a longer disease duration and more hospitalizations compared to those receiving second-generation LAIs (p=0.032 and p=0.005, respectively). A history of homicidal behavior or electroconvulsive therapy was associated with a higher likelihood of receiving first-generation LAIs (p<0.05) (Table 1).

The continuation rates for LAI treatment were 70.1% (n=131) in the 3rd month, this rate dropped to 50.8% (n=95) in the 6th month, and 39.0% (n=73) in the 12th month (Table 2).

When the relationship between sociodemographic characteristics and treatment adherence was evaluated, no significant difference was found in terms of age, gender, and employment status when compared (p>0.05). However, it was determined that patients with alcohol and substance-use disorders had lower treatment adherence in the 3rd and 6th months

Table 1. Comparison of sociodemographic and clinical characteristics associated with the preference for first- and second-generation long-acting injectable antipsychotics

		First generation LAIs (n=68)	Second generation LAIs (n=119)	
		Mean ± SD, n (%)		p
Age* (years)		45.3±10.3	42.3±10.9	0.064
Gender**	Female	35 (35.4)	64 (64.6)	0.763
	Male	33 (48.5)	55 (46.2)	
Employment status**	Unemployed	64 (41.8)	89 (58.2)	0.004
	Employed	2 (8.3)	22 (91.7)	
	Retired	2 (20.0)	8 (80.0)	
Tobacco use**	No	24 (38.7)	38 (61.3)	0.747
	Yes	44 (35.2)	81 (64.8)	
Alcohol use disorder**	No	60 (37.0)	102 (63.0)	0.824
	Yes	8 (32.0)	17 (68.0)	
Psychoactive substance-use disorder**	No	58 (37.2)	98 (62.8)	0.686
	Yes	10 (32.3)	21 (67.7)	
Diagnosis**	Schizophrenia	58 (45.3)	70 (54.7)	**<0.001**
	Bipolar Disorder	10 (16.9)	49 (83.1)	
Age of illness onset* (years)		25.6±7.7	26.2±8.7	0.652
Duration of illness* (years)		15.9±10.7	12.5±10.2	**0.032**
Number of hospitalizations*		7.5±6.9	4.8±3.9	**0.005**
Good treatment adherence before hospitalization**	No	58 (39.2)	90 (60.8)	0.137
	Yes	10 (25.6)	24 (74.4)	
Hospitalization history in the last year before the index hospitalization**	No	27 (40.3)	40 (59.7)	0.431
	Yes	41 (34.2)	79 (65.8)	
History of suicide attempt **	No	50 (33.1)	101 (66.9)	0.082
	Yes	18 (50.0)	18 (50.0)	
History of homicidal behavior**	No	21 (26.6)	58 (73.4)	**0.021**
	Yes	47 (43.5)	61 (56.5)	
History of ECT**	No	41 (31.5)	89 (47.4)	**0.048**
	Yes	27 (68.5)	30 (52.6)	

ECT: electroconvulsive treatment; LAI:long-acting antipsychotic injection; SD: standard deviation; * Independent variable t test; **Chi-square analysis; statistical significance was p<0.05.

Table 2. Comparison of continuation of LAI use at months 3, 6, and 12 according to various variables

		3. month control			6. month control			12. month control		
		Non-adherence (n=56)	Adherence (n=131)	p	Non adherence (n=92)	Adherence (n=95)	p	Non-adherence (n=114)	Adherence (n=73)	p
		Mean ± SD, n (%)								
Age* (years)		41.9±11.0	44.1±10.7	0.219	43.1±11.3	43.8±10.3	0.662	43.3±11.1	43.6±10.3	0.862
Gender**	Female	24 (24.2)	75 (75.8)	0.071	48 (48.5)	51 (51.5)	0.863	61 (61.6)	38 (38.4)	0.846
	Male	32 (36.4)	56 (63.6)		44 (50.0)	44 (50.0)		53 (60.2)	35 (39.8)	
Employment Status **	Unemployed	46 (30.1)	107 (69.9)	0.683	74 (48.4)	79 (51.6)	0.773	94 (61.4)	59 (38.6)	0.253
	Employed	6 (25.0)	18 (75.0)		12 (50.0)	12 (50.0)		12 (50.0)	12 (50.0)	
	Retired	4 (40.0)	6 (60.0)		6 (60.0)	4 (40.0)		8 (80.0)	2 (20.0)	
Alcohol use disorder**	Yes	12 (48.0)	13 (52.0)	**0.034**	17 (68.0)	8 (32.0)	**0.043**	18 (72.0)	7 (28.0)	0.224
	No	44 (27.2)	118 (72.8)		75 (46.3)	87 (53.7)		96 (59.3)	66 (40.7)	
Psychoactive substance-use disorder**	Yes	15 (48.4)	16 (51.6)	**0.014**	19 (61.3)	12 (38.7)	0.140	21 (67.7)	10 (32.3)	0.397
	No	41 (26.3)	115 (73.7)		73 (46.8)	83 (53.2)		93 (59.6)	63 (40.4)	
Diagnosis**	Schizophrenia	42 (32.8)	86 (67.2)	0.208	70 (54.7)	58 (45.3)	**0.027**	85 (66.4)	43 (33.6)	**0.025**
	Bipolar Disorder	14 (23.7)	45 (76.3)		22 (37.3)	37 (62.7)		29 (49.2)	30 (50.8)	
Age of illness onset* (years)		27.1±7.9	25.6±8.5	0.256	26.6±8.0	25.5±8.6	0.377	26.3±8.3	25.7±8.5	0.630
Duration of illness* (years)		12.0±10.2	14.6±10.6	0.125	13.1±10.4	14.5±10.6	0.348	13.4±10.5	14.3±10.6	0.572
Number of hospitalizations*		7.0±6.4	5.3±4.8	0.055	6.8±6.0	4.9±4.5	**0.013**	6.4±5.6	4.9±4.8	0.065
Good treatment adherence before hospitalization**	Yes	4 (10.0.3)	35 (89.7)	**0.003**	8 (20.5)	31 (79.5)	**<0.001**	12 (30.8)	27 (69.2)	**<0.001**
	No	52 (35.1)	96 (64.9)		84 (56.8)	64 (43.2)		102 (68.9)	46 (31.1)	
Hospitalization history in the last year before the index hospitalization**	Yes	33 (27.5)	87 (72.5)	0.328	65 (54.2)	55 (45.8)	0.069	80 (66.7)	40 (33.3)	**0.032**
	No	23 (34.3)	44 (65.7)		27 (40.3)	40 (59.7)		34 (50.7)	33 (49.3)	
History of homicidal behavior**	Yes	37 (34.3)	71 (65.7)	0.132	59 (54.6)	49 (45.4)	0.082	72 (66.7)	36 (33.3)	0.062
	No	19 (24.1)	60 (75.9)		33 (41.8)	46 (58.2)		42 (53.2)	37 (46.8)	
LAI group**	First generation	22 (32.4)	46 (67.6)	0.587	37 (54.4)	31 (45.6)	0.281	49 (72.1)	19 (27.9)	**0.019**
	Second generation	34 (28.6)	85 (71.4)		55 (46.2)	64 (53.8)		65 (54.6)	54 (45.4)	
History of LAI use**	Yes	34 (35.8)	61 (64.2)	0.076	54 (56.8)	41 (43.2)	0.108	65 (68.4)	30 (31.6)	**0.034**
	No	22 (23.9)	70 (76.1)		38 (41.3)	54 (58.7)		49 (53.3)	43 (46.7)	
LAI administration interval**	15 days	21 (38.2)	34 (61.8)	0.119	29 (52.7)	26 (47.3)	0.630	41 (74.5)	14 (25.5)	**0.014**
	30 days	35 (26.5)	97 (73.5)		63 (47.7)	69 (52.3)		73 (55.3)	59 (44.7)	

LAI: Long-acting Antipsychotic Injection; SD: Standard deviation; * Independent variable t test; **Chi-square analysis; statistical significance was p<0.05.

compared to those without (p<0.05), while the statistical difference disappeared in the 12th month (Table 2).

When evaluated based on diagnosis, no significant difference in treatment adherence was found between patients with bipolar disorder and schizophrenia in the 3rd month, while it was determined that patients with bipolar disorder had higher treatment adherence than those with schizophrenia in the 6th and 12th months (6th month: χ^2=4.89, p=0.027; 12th month: χ^2=5.05, p=0.025). When examined in terms of disease onset age and disease duration, no significant difference was found between those with and without treatment adherence; however, it was determined that patients who adhered to treatment had fewer hospitalizations than those who did not, and this difference was statistically significant only in the 6th month (t=2.50, p=0.013). In terms of regular medication use before hospitalization, 89.7% (n=35) of patients using regular medication continued treatment in the 3rd month, while this rate dropped to 79.5% (n=31) in the 6th month and 69.2% (n=27) in the 12th month. It was found that the treatment adherence rates of patients using regular medication were significantly higher than those of patients not using regular medication in all follow-up periods (3rd month: p=0.003; 6th month: p<0.001; 12th month: p<0.001) (Table 2).

When the impact of first- and second-generation antipsychotics on treatment adherence rates was examined, it was seen that 67.6% of patients using first-generation antipsychotics and 71.4% of patients using second-generation antipsychotics continued treatment in the 3rd month, and no significant difference was found between the two groups in terms of treatment adherence (χ^2=0.29, p=0.58). In the 6th month, 45.6% of patients using first-generation antipsychotics and 53.8% of patients using second-generation antipsychotics continued treatment, and again no significant difference was found between the groups (χ^2=1.16, p=0.28). However, in the 12th month, 27.9% of patients using first-generation antipsychotics and 45.4% of patients using second-generation antipsychotics continued treatment, and it was determined that the treatment adherence rate for patients using second-generation antipsychotics was significantly higher than for those using first-generation antipsychotics in the long run (χ^2=5.52, p=0.019) (Table 2 and Figure 1).

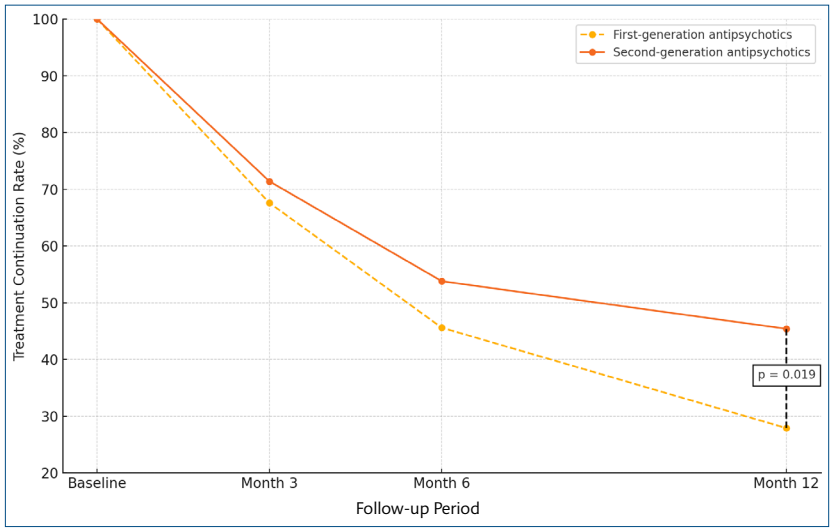

Figure 1. Comparison of treatment adherence rates of first- and second-generation long-acting antipsychotic groups.

Table 3. Comparison of continuation of different LAI types at months 3, 6, and 12 according to the post-hoc analysis results

	3. month control			6. month control			12. month control		
	Non-adherence (n=56)	Adherence (n=131)	p	Non-adherence (n=92)	Adherence (n=95)	p	Non-adherence (n=114)	Adherence (n=73)	p
Aripiprazole	7 (22.6)	24 (77.4)		14 (45.2)	17 (54.8)		15 (48.4) a	16 (51.6) a	
Paliperidone	17 (28.3)	43 (71.7)		28 (46.7)	32 (53.3)		32 (53.3) a	28 (46.7) a	
Risperidone	10 (35.7)	18 (64.3)	0.556	13 (46.4)	15 (53.6)	0.808	18 (64.3) b	10 (35.7) b	**0.034**
Zuclopenthixole	11 (40.7)	16 (59.3)		16 (59.3)	11 (40.7)		23 (85.2) c	4 (14.8) c	
Haloperidol	11 (26.8)	30 (73.2)		21 (51.2)	20 (48.8)		26 (63.4) b	15 (36.6) b	

The levels of statistical significance were: a > b > c, with p <0.05 considered statistically significant.
LAI: Long-Acting Antipsychotic.

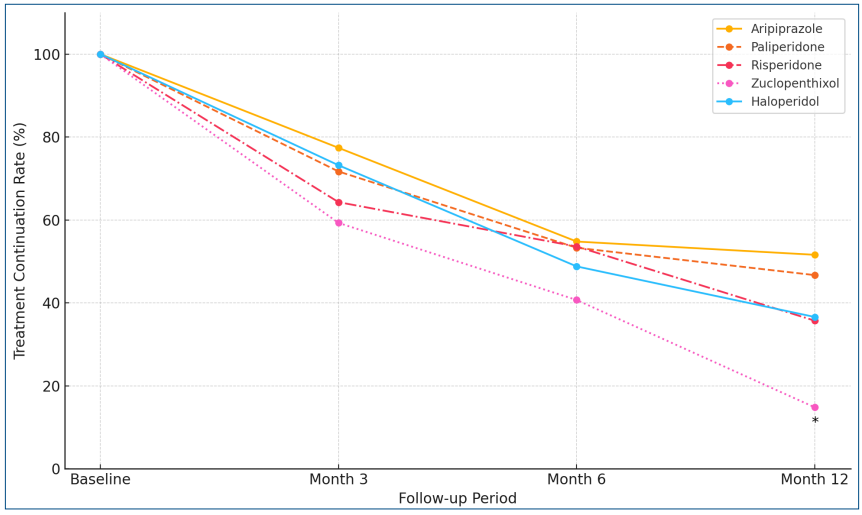

Figure 2. Comparison of treatment adherence rates of long-acting antipsychotics.

*At month 12, continuation rates were significantly different: Paliperidone=Aripiprazole>Haloperidol=Risperidone>Zuclopenthixol

When the relationship between antipsychotics and treatment adherence was examined separately, it was found that in all three time points, the highest treatment adherence was with aripiprazole, and the lowest treatment adherence was with zuclopenthixol. The treatment adherence rates in the 12th month were 51.6% for aripiprazole, 46.7% for paliperidone, 35.7% for risperidone, 36.6% for haloperidol, and 14.8% for zuclopenthixol (p=0.034) (Table 3 and Fig. 2). When comparing the treatment adherence rates of five different LAIs in the 12th month, it was found that treatment adherence with aripiprazole and paliperidone was higher than with the other three LAIs (haloperidol, risperidone, and zuclopenthixol) (p<0.05); and, treatment adherence with risperidone and haloperidol was significantly higher than with zuclopenthixol (p<0.05) (Figure 2).

Logistic regression analysis was used to examine the factors predicting treatment continuation in the 12th month. Independent variables included in the analysis were disease diagnosis, type of long-acting antipsychotic (first and second generation), previous use of long-acting antipsychotics, number of hospitalizations, regular medication use before hospitalization, and long-acting antipsychotic administration interval (2 and 4 weeks). The model was found to be statistically significant

Table 4. Logistic regression analysis identifying factors predicting medication adherence at 12 months

	Odds Ratio	95% CI, for EXP (B)	p
Diagnosis (bipolar disorder)	1.765	0.872 – 3.572	0.114
LAI group (second generation)	1.37	0.655 – 2.731	0.425
History of LAI use	0.790	0.378 – 1.648	0.529
Number of hospitalizations	0.949	0.876 – 1.028	0.199
Good treatment adherence before hospitalization	2.804	1.155 – 6.805	**0.023**
LAI administration interval (once in 4 weeks)	2.118	1.006 – 4.461	**0.048**

Dependent variable, 12. month treatment adherence $\chi^2(6)=22.556$, p <0.001, Nagelkare R^2=0.154, Hosmer and Lemeshow $\chi^2(8)=6.152$, p >0.05.
Reference categories: Diagnosis: schizophrenia; LAI group: 1. Generation; History of LAI use: None; Good treatment adherence before hospitalization: No; LAI administration interval: once every 2 weeks; CI: confidence interval; LAI: long acting antipsychotic injection.

($\chi^2(6)=22.556$, p<0.001), and the Nagelkerke R2 value was calculated to be 0.154. The Hosmer and Lemeshow test indicated that the model showed good fit ($\chi^2(8)=6.152$, p>0.05). According to the analysis results, receiving regular treatment before hospitalization and having a 4-week administration interval for long-acting antipsychotics significantly increased the likelihood of continuing treatment in the 12th month (Odds Ratio [OR]=2.80, 95% Confidence Interval [CI] [1.15–6.80], p=0.023 and OR=2.11, 95% CI [1.00–4.46], p=0.048) (Table 4).

DISCUSSION

The results of our study draw attention to the fact that second-generation LAIs are preferred more than first-generation ones (63.3% vs. 36.7%, respectively). It was observed that second-generation LAIs were started in younger patients, but no statistical significance was found in terms of patient age (p: 0.064). First-generation LAIs were preferred more often in patients who were unemployed, had a diagnosis of schizophrenia, had longer disease duration and more hospitalizations, and had a history of homicidal behavior and ECT. In terms of treatment adherence, patients with alcohol and substance-use disorders showed earlier non-adherence patterns. In the 6th and 12th months, treatment adherence was higher in patients with bipolar disorder compared to schizophrenia. The treatment adherence of patients using second-generation LAIs was higher than those using first-generation LAIs in the 12th month. When comparing the treatment adherence rates of five different LAIs in the 12th month, it was found that treatment adherence with aripiprazole and paliperidone was higher than with the other three LAIs (haloperidol, risperidone, and zuclopenthixol). Receiving regular treatment before hospitalization and having a 4-week administration interval for LAIs (compared to a two-week interval) were other factors that significantly predicted the likelihood of continuing treatment in the 12th month.

A study conducted in Italy examining the factors affecting the preference of first– and second-generation LAIs in standard clinical practice, found similar results to our study, where 65% of participants had schizophrenia and 18% had bipolar disorder. Second-generation LAIs were found to be preferred over first-generation ones (n: 316 vs. n: 135) (13). Second-generation LAIs seem to be preferred more in clinical practice. The underlying reasons might include the higher tolerability of second-generation antipsychotics, causing fewer extrapyramidal symptoms (EPS), and having a longer administration interval (16). In the study mentioned above, as in ours, second-generation LAIs were preferred more often in patients who were employed; although it has been reported that there is no overall cost increase with second-generation LAIs when hospitalization costs are considered (17), it is generally thought that second-generation LAIs are more costly in outpatient treatments. Unemployment also indicates a higher disease severity. Studies have reported that in older, unemployed, and lower-functioning patients, first-generation LAIs are preferred more often (13). In our study, first-generation LAIs were prescribed more often to patients with clinical characteristics indicating disease severity and treatment resistance, such as having a history of ECT (18), long disease duration, number of hospitalizations, and a history of homicidal behavior (19,20). A recent study examining factors affecting the choice of first- and second-generation LAIs also reported that factors such as male gender, being Black, advanced age, and living in rural areas increase the preference for first-generation LAIs for treatment (21). Therefore, it can be said that in addition to patient, clinician, and disease-related clinical characteristics, there may be many other factors, such as ethnicity, that can affect the choice of first- and second-generation LAIs. A study examining the factors associated with off-label LAI use reported that off-label use was most common in patients with bipolar disorder and that first-generation LAIs were preferred more in patients with high hostility scores (22). A study examining the use of LAIs in schizophrenia patients in 15 Asian countries found that the number of hospitalizations and incidence of verbal aggression predicted the use of first-generation LAIs (23). The higher preference for first-generation LAIs in patients with homicidal behavior and high hostility traits may be related to the fact that first-generation antipsychotics achieve more dopamine D2 receptor blockade (24). Another reason for the higher preference for first-generation LAIs in patients with high hostility risk may be that clinicians associate first-generation antipsychotics with neurolepsis, and consider first generation antipsychotics to be better for aggression control (24).

According to the results of our study, first-generation LAIs are preferred more in schizophrenia compared to bipolar disorder. This is thought to be related to treatment guidelines, which recommend second-generation LAIs for the treatment of bipolar disorder (2,4). In addition to this general information, there are studies in the literature indicating that second-generation LAIs reduce hospitalization rates in bipolar disorder (25). A recent study came up with the same finding, that the diagnosis of bipolar disorder predicted the preference for second-generation LAIs (12).

In our study, it was observed that treatment noncompliance developed earlier (at the 3rd and 6th months) in patients with alcohol and substance-use disorders compared to those without. Although there are studies that point in the opposite direction (26), it is known that alcohol and/or substance-use disorders are an important factor in predicting noncompliance with treatment, symptom severity, homelessness, and incarceration in schizophrenia. A study investigating the factors predicting noncompliance with antipsychotics reported that in cases of early noncompliance, alcohol/substance abuse was more frequent, but at the 24th month, the only factor predicting noncompliance was the duration of untreated psychosis (27). In cases where alcohol or substance-use disorders accompanies severe mental disorders, prioritizing the severe mental condition for treatment and delaying intervention for alcohol or substance-use may be a cause of early treatment noncompliance. Therefore, the presence of alcohol and substance-use negatively impacts treatment adherence and the course of the disease (28). In a study by Auxilia et al. (29), reasons for discontinuing long-acting antipsychotics were investigated, and alcohol and substance-use disorders were found to be associated with discontinuation of treatment. Although there are studies recommending long-acting

antipsychotics for patients with alcohol and substance-use disorders in schizophrenia (28), it is suggested that these patients may benefit more from community-based mental health interventions, considering the potential issues with adherence to long-acting antipsychotics in individuals with alcohol and/or substance-use disorders.

When comparing patients diagnosed with schizophrenia and bipolar disorder, it is frequently reported that individuals with bipolar disorder have better treatment adherence (30). Our study supports this finding. Specifically, in the 6th and 12th months, participants diagnosed with bipolar disorder were found to be more compliant with treatment compared to those diagnosed with schizophrenia. This may be related to better insight into bipolar disorder, the prominence of negative symptoms in schizophrenia, more functional impairment and less social support in schizophrenia, and more frequent use of second-generation long-acting antipsychotics in participants with bipolar disorder.

In our study, the rates of continuing long-acting antipsychotic treatment at the 3rd, 6th, and 12th months were 70.1%, 50.8%, and 39%, respectively; however, for those without a history of treatment noncompliance prior to hospitalization, this rate was 69.2% at the 12th month. Although noncompliance has long been an indication for the use of long-acting antipsychotics (4), in the noncompliant group, even long-acting antipsychotics may not meet expectations. Therefore, especially when recent studies are considered, supporting the use of long-acting antipsychotics in the first episode or early stages of the illness (31) and the importance of preventing relapses in severe mental disorders in terms of functionality and preventing structural brain changes (32), it may be recommended to start long-acting antipsychotic treatment before patients stop their medication multiple times and experience relapses in order to ensure better treatment adherence. In a study by Correll et al. (33), when comparing strategies for initiating long-acting antipsychotics in patients diagnosed with schizophrenia, better outcomes were observed in the group where long-acting antipsychotics were started earlier. Again, considering that noncompliance is still considerable despite the use of long-acting antipsychotics, it suggests that interventions in other areas, such as the healthcare system, social support, substance-use, psychoeducation and psychotherapy, and online solutions (34), may be necessary to ensure treatment adherence.

According to our study results, treatment adherence to second-generation long-acting antipsychotics was better than first-generation LAIs, and adherence to injections applied every 4 weeks was better than those applied every 2 weeks. At the end of one year, when considering antipsychotics individually, the treatment adherence rates were 51.6% for aripiprazole LAI, 46.7% for paliperidone LAI, 35.7% for risperidone LAI, 36.6% for haloperidol LAI, and 14.8% for zuclopenthixol LAI. When comparing antipsychotics, adherence was highest for aripiprazole and paliperidone, while adherence to zuclopenthixol was the lowest. Adherence to haloperidol and risperidone was the same, but lower than aripiprazole and paliperidone, and higher than zuclopenthixol. Although it is known that long-acting antipsychotics increase treatment adherence compared to oral agents (4), one of the few studies comparing long-acting antipsychotics, by Aguglia et al. (26), found that adherence was numerically higher in patients using second-generation long-acting antipsychotics, however the difference was not statistically significant (p=0.06). Another study reported that treatment adherence to second-generation long-acting antipsychotics such as olanzapine and aripiprazole was better compared to the first-generation long-acting antipsychotic zuclopenthixol (28). The less frequent occurrence of motor side effects with second-generation antipsychotics (35), the availability of different administration alternatives such as deltoid injection, and the availability of different dosage options may be reasons contributing to increased adherence. In a systematic review and meta-analysis comparing first– and second-generation long-acting antipsychotics (paliperidone, risperidone, haloperidol, and fluphenazine), it was found that first-generation long-acting antipsychotics were associated with more use of antiparkinsonian agents, but no difference in terms of treatment adherence and efficacy was detected (35). In a study by Yang et al. (17), it was found that emergency service visits were significantly lower with second-generation long-acting antipsychotics compared to first-generation ones. In a study comparing the most frequently used second-generation long-acting antipsychotics, paliperidone and aripiprazole, no significant difference in treatment response, relapse, or treatment adherence was found between the two agents, similar to our study (36). A recent review reported that increasing the application interval of long-acting antipsychotics enhances treatment adherence, reduces treatment refusal, reduces labeling, and increases self-esteem, and allows the time spent by both the patient and physician in visits to be more focused on psychotherapeutic interventions rather than medication adherence (37). In our study, we believe that the higher adherence to second-generation long-acting antipsychotics may also be related to the longer administration interval of these agents.

The strengths of our study include its naturalistic design, its longitudinal follow-up approach, and the fact that it is one of the few studies in our country evaluating factors influencing the choice between first– and second-generation antipsychotics (FGAs and SGAs), as well as adherence to these agents. Since the patients included in the study were not assessed cross-sectionally, we could not obtain disease severity scores that could affect long-acting antipsychotic selection and adherence patterns because severity scales could not be applied. Also, since sociodemographic and clinical data were obtained from file records, detailed sociodemographic data collection for the research could not be conducted and recall bias may have occurred. Since the diagnoses and records of the participants were made by psychiatrists working in the clinics where the patients were treated, bias may have occurred regarding the interviewers. Since no cross-sectional assessment was made, other diagnoses that could affect treatment adherence, such as personality disorders, intelligence level, attention deficit hyperactivity disorder, and anxiety disorders, were not evaluated. The lack of a focused evaluation of the reasons for treatment noncompliance (e.g., medication side effects, insight, physician recommendations, inefficacy) seems to have limited the assessment of the underlying cause of noncompliance. The severity of alcohol and substance-use disorders in individuals with alcohol and substance-use disorders were also not evaluated. Additionally, other medications that participants may have used in combination with long-acting antipsychotics were not assessed.

In conclusion, our study found that first-generation long-acting antipsychotics were preferred for participants with more severe and resistant disease features, such as a history of homicide or ECT, second-generation long-acting antipsychotics were preferred more for employed patients, alcohol and substance-use disorders reduced adherence to long-acting antipsychotics, first-generation long-acting antipsychotics were preferred more in schizophrenia compared to bipolar disorder, adherence to second-generation long-acting antipsychotics was better than first-generation ones, and adherence to injections applied every four weeks was better than those applied every two weeks. As a final point, individual differences in long-acting antipsychotic selection should always be considered, and additional interventions to increase adherence should be included for groups where noncompliance may be higher. In patients with prominent adherence issues, agents are administered every four weeks and second-generation long-acting antipsychotics may be preferred. Studies that assess the severity of the disease and symptoms cross-sectionally and examine clinical features in more detail are needed regarding LAI use.

Ethics Committee Approval: This study was conducted in accordance with the latest version of the Helsinki Declaration and approved by the Clinical Research Ethics Committee of Bakirkoy Dr. Sadi Konuk Training and Research Hospital (Decision No: 2023-22-13/Date: 20.11.2023).

Informed Consent: Consent was obtained from the patients.

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