

Relationship of Long Acting Injectable Antipsychotics with Caregiver Burden, Quality of Life, Symptom Severity and Treatment Discontinuation in Schizophrenia



Feride UYSAL¹, Eren YILDIZHAN², Nesrin Buket TOMRUK³

SUMMARY

Objective: Regarding the patients using long acting injectable(LAI) antipsychotic treatment; we aimed to investigate the effect of attitude towards drugs, antipsychotic type and side effects on quality of life, caregiver burden and continuation of treatment.

Method: Our study sample consisted of 110 patients in the age range of 18-65 using LAI antipsychotics for at least 12 weeks with the diagnosis of schizophrenia according to DSM-5 criteria. Sociodemographic and Clinical Data Form, Drug Attitude Inventory 10 (DAI-10), Positive and Negative Syndrome Scale (PANSS), UKU Side Effect Rating Scale, Quality of Life for Schizophrenia Scale were used for evaluation of patients. Sociodemographic Data Form, Zarit Caregiver Burden Scale (ZCBS) were used for the caregivers.

Results: It is observed that the patients with positive attitude against the treatment had longer antipsychotic treatment duration (13.7+9.1 years) compared to patients with negative attitude (7.7 + 6.6 years) ($p<0.001$). PANSS total scores of patients who were considering about treatment discontinuation (44.0+14.3) were higher than the other patients (38.6+9.0) ($p=0.03$) and DAI-10 scores of patients who were considering about treatment discontinuation were lower (1.4+4.9; 5.2+3.4; $p<0.001$). Duration of illness were also shorter (10.3+9.3 year) for the patients who were considering about treatment discontinuation than the other group (15.7 + 9.0 year) ($p=0.01$). There was no significant difference in caregiver burden, side effects, quality of life and reasons for treatment discontinuation between typical and atypical antipsychotics. According to the regression analysis results, PANSS score ($\beta=0.553$, $p<0.001$) and male gender ($\beta=0.225$, $p=0.003$) were positive predictors of ZCBS scores.

Conclusion: It is observed that the attitude towards drugs and psychotic symptom severity were the most important factors for treatment discontinuation in patients with schizophrenia using LAI antipsychotics. Atypical and typical antipsychotics were not different with respect to quality of life and caregiver burden for the patients on regular treatment with LAI antipsychotics.

Keywords: schizophrenia, treatment discontinuation, quality of life, caregiver burden, long acting injectable antipsychotics

INTRODUCTION

Schizophrenia is a psychiatric disorder with 1% lifetime prevalence which can cause chronic disability (Köroğlu and Hocaoglu 2017). Periods of partial or full remission reflect, respectively, poor treatment compliance or frequent hospitalizations (Davis 1975, Schooler 2003). Incompliance with treatment, observed in both the early and the late stages of disease, is a serious problem in schizophrenia and other related psychotic disorders. Nearly %80 of the patients somehow discontinue their treatment in the long term. Treatment

discontinuation can be seen both in the early phases of the disorder and in the late phase. Reasons of discontinuation should be investigated and solved in order to maintain treatment adherence. Drug non-adherence causes symptom exacerbations and relapses, use of emergency psychiatric services and psychiatric hospitalizations, more frequent comorbid substance use disorder, poor cognitive functioning, decreases in quality of life, increases in the frequency of violence/aggression or victimizations and increases in suicide risk with a worse prognosis (Byerly et al. 2007, Haddad et al. 2014, Barkhof et al. 2012).

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¹MD., Dinar State Hospital, Department of Psychiatry, Afyon, ^{2,3}MD., Bakırköy Research and Training Hospital for Psychiatry, Neurology and Neurosurgery, Department of Psychiatry, İstanbul, Turkey.

e-posta: erenyildizhan@hotmail.com

Refusal of treatment or treatment discontinuation within a very short period of time is common for the patients with prejudices about psychiatric treatments of denial of the diagnosis. In these circumstances, long acting injectable antipsychotics (LAI) provide convenience (Taylor et al. 2012). LAI antipsychotics were developed in the 1960s and they are advantageous for patients with treatment adherence problems and history of severe relapses after treatment discontinuation (Fleischhacker and Miyamoto 2016). If a patient who is on LAI antipsychotic treatment for a long duration discontinues treatment, antipsychotic effect may continue for a period of 3-6 months depending on the time for steady state concentration of the drug (Meltzer and Bobo 2009). Advantages of the LAI antipsychotics include obviation of gut absorption and first pass metabolism, reduction of the administered dose to achieve the expected response and better treatment compliance.

Schizophrenia is one of the most burdensome psychiatric disorder for the families (Gülseren et al. 2010). Lefley (1997) was first to report on the relationship of caregiver burden with the loss or increase of functionality during treatment of schizophrenia. Aytur (2015) reported in her study that, within positive symptoms, delusions and hallucinations had more influence on burden and negative symptoms such as emotional withdrawal, poor rapport, passive/apathetic social withdrawal, lack of spontaneity and flow of conversation, Stereotyped thinking were related with increases in all aspects of burden. In addition to this, patients with history of suicide and violent behavior were constituting higher caregiver burden and female caregivers had higher levels of burden than males on psychological distress, personal strain and anger/frustration dimensions (Aytur 2015).

Despite this background, there are limited number of studies in the current literature on the comparison of the LAI APs and their effects on patient attitude, treatment compliance, quality of life and caregiver burden in contrast to the abundance of reports about the relationship of caregiver burden and quality of life with the side effects of oral antipsychotics and noncompliance with treatment. Therefore, we investigated the patient attitude to LAI APs, the side effects, treatment continuation, quality of life and caregiver burden in the management of schizophrenia.

METHOD

Participants

This cross sectional study was carried out with 110 patients aged 18-65 years and their respective caregivers, arriving consecutively between 08 April 2019 and-08 July 2019 at the outpatient clinics and the community mental healthcare centers (CMHCs) of the Health Sciences Prof. Dr. Mazhar

Osman Bakırköy Training and Research Hospital and treated on outpatient basis with LAI antipsychotics for at least 12 weeks for the diagnosis of schizophrenia on the DSM-V criteria. The study was given approval, dated 02.04.2019 and numbered 299, by the Medical Research and Practice Board of the hospital. The patients and their caregivers who accepted to participate in the study were explained the aims of the study, the rights of the participants for refusal to continue and withdraw their consents any time during the study and the confidentiality of the records on personal information, before obtaining signed consents.

After describing the aims of the study, oral and written consent was obtained from the patients and their caregivers. It was made clear that the participants had rights to refuse to participate or withdraw their consents any time during the study and the records of personal information would be kept with secrecy. Thus, informed consent was obtained from all the patients and the caregivers who accepted to participate in the study. The Clinical and Sociodemographic Data Form, Drug Attitude Inventory-10 (DAI), Positive and Negative Syndrome Scale (PANSS), UKU Side Effect Rating Scale (UKU), Quality of Life Scale for Schizophrenia (QLS) were filled for the patients and Zarit Caregiver Burden Scale (ZCBS) with Sociodemographic Data Form for Caregiver were filled for the caregivers.

Use of oral antipsychotics other than the primary LAI APs were restricted to eliminate the confounding effects. In accordance with the Maudsley Prescribing Guidelines (13th Edition), the minimum effective doses were accepted as 200 mg/day chlorpromazine or equivalent dose for first episode patients and 300 mg/day chlorpromazine or equivalent dose for patients with multiple episodes. Patients who were using oral antipsychotics above these doses were excluded from the study. The inclusion criteria for caregivers comprised being ≥ 18 years of age, literate and the family member who spends the longest time with the patient in comparison to other family members. Exclusion criteria for caregivers were having mental retardation, conditions such as hearing or speaking disability that disrupts interviews and the presence in the family of another member in need of caregiving for a mental or physical disorder.

Study Hypotheses were:

1. Patients with the intent to discontinue treatment have lower quality of life, higher symptom severity, and higher side effect scores.
2. Treatment discontinuation or change as a result of side effects is more frequent in patients using typical LAI antipsychotics.
3. Caregiver burden is lower in the families of patients using atypical LAI antipsychotics.

Data Collection Instruments

The Clinical and Sociodemographic Data Form: This form is created by the researchers according to the purpose of the study. Sociodemographic variables, family history, and questions regarding clinical state, count of hospitalizations, duration of hospitalizations, treatment continuation, treatment discontinuation and change with respect to side effects were included in this form. The Correll and colleagues' list of side effects associated with LAI antipsychotics were used in order to prepare the questionnaire for the reasons of treatment change or treatment discontinuation reasons (Rossi et al. 2012, Kishimoto et al. 2013, Correll et al. 2016).

Drug Attitude Inventory (DAI): Drug Attitude Inventory-10 was developed by Hogan and colleagues in 1983. This scale consists of 10 questions about the attitudes and subjective reactions of the patients against drugs. It includes 10 questions of which the expected answer is scored positive in 6 and negative in 4 of them. If the total score is above 0, the patient is accepted as being compliant with the given treatment. (Hogan and Awad 1992). The reliability and validity of the version adapted to the Turkish language was carried out by Aydın et al. (2018).

Positive and Negative Syndrome Scale (PANSS): The PANSS is a 30 item scale for evaluating positive symptoms, negative symptoms, and general psychopathology, with 7 points severity scoring in each item. It was developed by Kay and colleagues (1987). 7 items constitute positive symptoms subscale, 7 items constitute negative symptoms subscale and 16 items constitute the general psychopathology subscale (Kay et al. 1987). It is structured by Opfer and colleagues (1992) and Turkish adaptation was done by Kostakoğlu and colleagues in 1999.

UKU (Udvalg for Kliniske Undersøgelser) Side Effect Rating Scale (UKU): It consists of 48 items with 3 parts evaluating psychic, neurologic, autonomic and general side effects. Every item has 4 degrees with "0" corresponds no side effect and "3" corresponds serious side effect (Lingjaerde et al. 1987). Interrater reliability correlation coefficient of the Turkish version was 0.76 ($p < 0.001$) (Kostakoğlu et al. 2001).

Quality of Life Scale for Schizophrenia (QLS): It is developed by Heinrichs and colleagues (1984) for the evaluation of quality of life for the last one month of the patients with schizophrenia under maintenance treatment. Turkish adaptation was made by Soygür and colleagues (2020). It evaluates the richness of personal experience, quality of interpersonal relationships and occupational productivity. It is a semi-structured form consisting of 21 items and 4 subscales. The subscales are as follows: interpersonal relations, instrumental role, intrapsychic foundations, common objects and activities. Every item consists of three parts. First part, there is a brief description for focusing the parameter to be evaluated. Second part

consists of questions for the initiation of investigation. Third part consists of a 7 degree scale for every item (Heinrichs et al. 1984, Soygür et al. 2000).

Sociodemographic Data Form for Caregiver: It is a form developed for the purpose of the study by the researchers which is consisting of the age, gender, level of education, marital state, occupational state, relation to the patient, level of income and presence of any physical illness of the caregiver.

Zarit Caregiver Burden Scale (ZCBS): The scale was first developed for evaluating the caregiver burden of the relatives of patients with dementia by Zarit and colleagues (1980), but it was used also for the evaluation of burden of the relatives of patients with schizophrenia in other studies (Setsuko Hanzawa et al. 2008). Original scale consists of 22 items, but in the reliability and validity study which was conducted for the relatives of patients with the diagnosis of schizophrenia in Turkish language, 3 items were excluded and the Turkish version consists of 19 items (Özlü et al. 2009). The scale consists of Likert type 5 points evaluation corresponding the frequencies of never, seldom, sometimes, frequently and always. Higher scores shows higher caregiver burden.

Statistical Analysis

The SPSS Version 22.0 for Mac (IBM) was used for the statistical analyses of the data to assess the frequencies of the basic clinical and demographic variables. The Chi-square test was used for the categorical variable and the Independent Sample's t-test was used for the continuous variables. Minimum sample size was calculated by G*Power 3.0.10 program for statistical power. Two sided t test for targeted effect size was determined with the α error probability of 0.05 and $1-\beta$ error probability of 0.95. For two sided comparisons of two groups in defined level of significance with power of 0.950129 (critical $F=1.971$); minimum sample size was calculated as 108 patients and sample size of the study was finalized according to these analyses. In our study consisting of 110 patients. The p value of 0.05 was accepted to represent statistical significance.

RESULTS

The schizophrenia patients meeting the inclusion criteria of our study cited under the participants section above, were under follow up at the outpatient clinics of our hospital and at the attached 3 CHMCs in Bakırköy, Güngören and Bağcılar-Meydan where 85, 70 and 38 patients, respectively, had been treated with LAI antipsychotics for at least 12 weeks. On grounds of using additional oral antipsychotics over the minimum effective dose of 200 mg/day for first episode patients and 300 mg/day for patients with multiple episodes, 37 patients were excluded from the study. Also 8 more

Table 1. Comparative Distribution of the Use of Typical and Atypical LAI Antipsychotics According to the Demographic and Clinical Data of the Patients

N		Atypical		Typical		P
		(%)	N	(%)		
Gender	Female	29	43.6	15	40.9	0.471
	Male	39	57.4	27	59.1	
Marital Status	Single	51	75.0	32	75.5	0.888
	Married	17	25.0	10	24.5	
Medical Comorbidity	Yes	15	22.1	9	21.4	0.938
	None	53	77.9	33	78.6	
History of Suicide	Yes	20	29.4	5	11.9	0.033
	None	48	70.6	37	88.1	
Nicotine Use	Yes	33	48.5	25	59.5	0.262
	None	35	51.5	17	40.5	
Alcohol Use	Yes	3	4.4	1	2.4	0.506
	None	65	95.6	41	97.6	
Substance Use	Yes	2	2.9	0	0	0.380
	None	66	97.1	42	100	
Familial History of Psychiatric Disorder	Yes	31	45.6	20	47.6	0.836
	None	37	54.4	22	52.4	
Criminal History	Yes	13	19.1	12	28.6	0.250
	None	55	80.9	30	70.4	
CMHC Follow-up	Yes	50	73.5	20	47.6	0.006
	None	18	26.5	22	52.4	

For the comparison of categorical variables between two groups, Xi-Square analysis was used, level of significance was accepted as $p < 0.05$ p^* : X^2 degree of significance
 CMHC: Community Mental Healthcare Center; LAI: Long Acting Injectable

patients were excluded, 2 for reasons of refusal to continue participating, 3 for inaccessibility of their relations, 2 for the inability of caregivers to understand the self-report psychometric test and 1 for the death of the caregiver after the initial interviews, such that 110 patients arriving with respective caregivers made up the participants of this research. The demographic and clinical details of the participating patients are given in Table 1.

61 (55.5%) of the caregivers in our study were female and 49 (45.5%) were male. Educational level of the caregivers was primary school for 55 (50%), secondary school for 12 (11.8%), high school for 12 (10.9%), and higher education for 14 (12.7%) of them. Most of the caregivers (64.5%, $n=71$) were married, 12.7% ($n=14$) were single and 22.7% ($n=25$) were divorced. 35.4% of the caregivers ($n=39$) were unemployed, 32.7% were employed ($n=36$) and 31.8% were retired ($n=35$). 48.2% of the caregivers were parents ($n=53$) of the patients, 21.8% ($n=24$) were brothers or sisters, 18.2% ($n=20$) were spouse, 5.5% ($n=6$) were daughter or son and 6.4% ($n=7$) were in other family members (Table 2).

70 of the patients in our study sample were attending CMHCs and 40 patients were attending outpatient clinics of our hospital. Comparisons of patients who were being followed up from CMHCs or outpatient clinics are given in Table

3. Mean ZCBS scores of the patients attending CMHCs were 45.2 ± 3.9 and they were higher from scores of patients attending outpatient clinics (39.1 ± 15.2) significantly ($t=2.129$, $p=0.036$). There were no other differences in other scores for the comparison of CMHC and outpatient clinic.

With respect to LAI treatment, 16 (14.5%) patients were on Aripiprazole, 16 (14.5%) on Risperidone, 25 (22.7%) on monthly Paliperidone Palmitate, 11 (10.0%) on 3 monthly Paliperidone Palmitate, 22 (20.0%) on Zuclopenthixol, 5 (4.5%) on Flupentixol, 1 (0.9%) on Fluphenazine and 14 (12.7%) on Haloperidol. Of the 65 patients using oral antipsychotics limited by the minimum effective dose together with the LAI antipsychotics, 8 (12.3%) were on Risperidone, 27 (41.5%) on Quetiapine, 4 (6.1%) on Amisulpride, 4 (6.1%) on Olanzapine, 7 (10.7%) on Clozapine, 5 (7.6%) on Haloperidol, 5 (7.6%) on Chlorpromazine and 5 (7.6%) were on Aripiprazole.

Whereas 20 (18.2%) patients declared their intention to discontinue drug treatment, 90 (81.8%) patients did not. The comparisons of the psychometry scores of patients with and without decision to discontinue treatment is presented in Table 4.

Table 2. Demographic Data of the Caregivers

		Numbers	(%)
Gender	Female	61	55.5
	Male	49	44.5
Level of Education	Literate	16	15.5
	Primary	55	50
	Secondary	13	11.8
	High School	12	10.9
	University	14	12.7
Marital Status	Single	14	12.7
	Married	71	64.5
	Divorced	25	22.7
Employment Status	Unemployed	39	35.4
	Employed	36	32.7
	Retired	35	31.8
Relationship with the Patient	Parent	53	48.2
	Sibling	24	21.8
	Partner	20	18.2
	Offspring	6	5.5
	Other	7	6.4
Monthly Income Level (TL: Turkish Lira)	Less than 500 TL	21	19.1
	Between 500- 1000 TL	4	3.6
	Between 1000-1500 TL	20	18.2
	1500 TL and over	65	59.1

Independent Samples' t-test was used for comparing the DAI, QLS, ZCBS, UKU and the PANSS scores and the clinical variables of the CMHC follow-up duration, the disorder duration, number of hospitalizations, duration of LAI use, total duration of antipsychotic use) according to the type of antipsychotic used. 68 patients were using atypical, 42 were

using typical LAI antipsychotic. Mean duration of CMHC follow-up were significantly longer for patients using atypical LAI antipsychotics (23.81 months) than patients using typical LAI antipsychotics (10.46 months) significantly [$t(108)=3.197$, $p=0.002$, $p<0.001$]. There were no significant differences for other variables (Table 5).

The frequency and duration of hospitalizations decreased after starting treatment with LAI APs, irrespective of the AP being typical or atypical as shown by independent samples t-test analysis ($p<0.001$). Comparisons of the number of hospitalizations and duration of hospitalizations according to the type of antipsychotics are given in Table 6.

57 patients (51.8%) had never changed the LAI antipsychotic they used, 53 patients (48.2%) had discontinued or changed the LAI antipsychotic that first prescribed to them and started using the LAI antipsychotic they use currently. Reasons for the switch in LAI antipsychotics to the current LAI were side effects in 20 patients (18.2%), relapse in 20 patients (18.2%) and other reasons in 13 patients (11.8%). Comparisons of the typical and atypical LAI antipsychotics for the reasons of change in treatment are given in Table 7.

Standard multiple regression analyses were carried out to assess the prediction of the caregiver ZCBS scores by the variables of caregiver age and gender - by categorically coding 1 for the male and 0 for the female gender, atypical/typical type of the AP used, disease duration and the patient PANSS total score. In these analyses, the ZCBS score was the dependent variable and the other demographic/clinical parameters and the PANSS scores were the independent variables. The linear regression model was significant for predicting the ZCBS scores [$F(5,104)=17.910$, $p<0.001$] with the inclusion of all the independent variables in the equation, This

Table 3. Comparison of the Clinical Data of Patients followed up at CMHCs and at Outpatient Clinic

	CMHC (n=70) Mean \pm SD	Outpatient Clinic (n=40) Mean \pm SD	t(p)*
Age	41.2 \pm 11.3	44.0 \pm 11.7	-1.234 (0.220)
Duration of Disorder (year)	15.6 \pm 9.2	13.2 \pm 9.1	1.321 (0.189)
Duration of LAI Use (year)	3.1 \pm 4.0	3.9 \pm 4.4	-0.925 (0.357)
Total Duration of Antipsychotic Use (year)	13.4 \pm 9.2	11.4 \pm 8.7	1.108 (0.270)
PANSS Positive Score	8.3 \pm 2.6	7.9 \pm 2.3	0.853 (0.395)
PANSS Negative Score	11.1 \pm 4.4	9.7 \pm 4.7	1.561 (0.121)
PANSS General Score	21.0 \pm 4.4	20.2 \pm 5.6	0.805 (0.422)
PANSS Total Score	40.5 \pm 9.8	37.9 \pm 11.0	1.292 (0.199)
DAI-10 Total Score	4.8 \pm 2.9	4.2 \pm 4.1	0.755 (0.452)
UKU Side Effects Scale Total	11.1 \pm 7.3	10.2 \pm 6.3	0.696 (0.488)
ZCBS Total score	45.2 \pm 13.9	39.1 \pm 15.2	2.129 (0.036)

*Independent Samples t-test result for the comparisons; * $p<0.05$: accepted level of significance

DAI-10: Drug Attitude Inventory-10; PANSS: Positive and Negative Syndrome Scale; CMHC: Community Mental Healthcare Center; LAI: Long Acting Injectable, SD: Standard Deviation, UKU: UKU Side Effect Rating Scale; ZCBS: Zarit Caregiver Burden Scale

Table 4. Comparisons of Scale Scores According to the Presence of the Intent for Drug Discontinuation

		Drug Discontinuation	N	Mean.	SD	t (p)*
DAI-10 Total Score		Yes	20	1.40	4.94	-4.222(0.000)
		No	90	5.28	3.40	
PANSS Total Score		Yes	20	44.00	14.33	2.127 (0.036)
		No	90	38.65	9.02	
ZCBS Total Score		Yes	20	43.62	16.91	0.200 (0.842)
		No	90	42.90	14.19	
Quality of Life for Schizophrenia	Interpersonal Relations	Yes	20	26.35	9.54	-0.910 (0.365)
		No	90	28.33	8.65	
	Instrumental Role	Yes	20	11.20	5.23	0.701 (0.485)
		No	90	10.40	4.47	
	Intrapsychic Foundations	Yes	20	24.40	7.41	-0.800 (0.425)
		No	90	25.62	5.88	
	Common Objects And Activities	Yes	20	8.90	2.48	-1.356 (0.178)
		No	90	9.63	2.11	
	Total	Yes	20	70.85	23.06	-0.648 (0.518)
		No	90	73.98	18.77	
UKU Side Effects Scale	Psychic	Yes	20	4.80	3.98	0.440 (0.661)
		No	90	4.41	3.48	
	Neurologic	Yes	20	1.05	0.88	-0.702 (0.484)
		No	90	1.24	1.16	
	Autonomic	Yes	20	1.55	1.63	-0.738 (0.462)
		No	90	1.86	1.75	
	Other	Yes	20	3.90	2.65	1.085 (0.280)
		No	90	3.18	2.65	
	Total	Yes	20	11.30	7.59	0.338 (0.736)
		No	90	10.71	6.92	
Duration of CMHC Follow-up (month)		Yes	20	17.94	19.73	-0.147 (0.884)
		No	90	18.76	22.61	
Duration of Disorder (year)		Yes	20	10.37	9.32	-2.398 (0.018)
		No	90	15.75	9.02	
Number of Hospitalizations		Yes	20	3.50	6.50	0.155 (0.877)
		No	90	3.34	3.30	
Duration of LAI Use (year)		Yes	20	3.66	6.40	0.227 (0.821)
		No	90	3.42	3.60	
Total Duration of Antipsychotic Use (year)		Yes	20	9.20	9.52	-1.924 (0.057)
		No	90	13.45	8.80	

*Independent Samples t-test result for the comparisons; *p<0.05: the accepted level of significance

DAI-10: The Drug Attitude Inventory-10; PANSS: The Positive and Negative Syndrome Scale; CMHC: Community Mental Healthcare Center; LAI: Long Acting Injectable; SD: Standard Deviation; ZCBS: The Zarit Caregiver Burden Scale

Table 5. Comparison of Clinical Variables and Scale Scores According to the Use of Typical and Atypical LAI Antipsychotic Agents

		LAI Antipsychotic	N	Mean	SD	t (p)*
Duration of CMHC Follow-up (month)		Atypical	50	23.81	23.08	3.197 (0.002)
		Typical	20	10.46	17.68	
Duration of Disorder (year)		Atypical	68	14.56	9.81	-0.303 (0.763)
		Typical	42	15.11	8.41	
Number of Hospitalizations		Atypical	68	3.20	4.69	-0.549 (0.584)
		Typical	42	3.64	2.69	
Duration of LAI Use (year)		Atypical	68	2.91	2.68	-1.747 (0.084)
		Typical	42	4.35	5.84	
Total Duration of Antipsychotic Use (year)		Atypical	68	12.28	9.37	0.573 (0.568)
		Typical	42	13.30	8.55	
DAI Total Score		Atypical	68	4.17	4.29	-1.356 (0.178)
		Typical	42	5.23	3.42	
PANSS Total Score		Atypical	68	39.89	9.31	0.347 (0.729)
		Typical	42	39.19	11.87	
ZCBS Total Score		Atypical	68	42.04	13.91	-0.900 (0.370)
		Typical	42	44.63	15.78	
Quality of Life for Schizophrenia	Interpersonal Relations	Atypical	68	27.57	9.06	-0.603 (0.548)
		Typical	42	28.61	8.44	
	Instrumental Role	Atypical	68	10.33	4.54	-0.598 (0.551)
		Typical	42	10.88	4.74	
	Intrapsychic Foundations	Atypical	68	25.00	6.07	-0.864 (0.369)
		Typical	42	26.04	6.34	
	Common Objects And Activities	Atypical	68	9.52	1.97	0.178 (0.859)
		Typical	42	9.45	2.53	
	Total	Atypical	68	72.44	19.55	-0.665 (0.507)
		Typical	42	75.00	19.68	
UKU Side Effects Scale	Psychic	Atypical	68	4.82	3.45	1.284 (0.202)
		Typical	42	3.92	3.71	
	Neurologic	Atypical	68	1.05	1.06	-1.813 (0.073)
		Typical	42	1.45	1.17	
	Autonomic	Atypical	68	1.83	1.83	0.224 (0.824)
		Typical	42	1.76	1.57	
	Other	Atypical	68	3.60	2.55	1.439 (0.153)
		Typical	42	2.85	2.77	
	Total	Atypical	68	11.32	6.94	0.960 (0.339)
		Typical	42	10.00	7.14	

*Independent Samples t-test result for the comparisons; *p<0.05: the accepted level of significance

LAI: Long Acting Injectable DAI-10: The Drug Attitude Inventory-10; PANSS: The Positive and Negative Syndrome Scale ; ZCBS: The Zarit Caregiver Burden Scale; CMHC: Community Mental Healthcare Center; SD: Standard Deviation ; N: Number

Table 6. Comparisons of the Number and Duration of Hospitalizations According to the Use of Typical and Atypical Antipsychotic Agents used

	LAI	N	Mean	SD	t (p)*
Number of hospitalizations during 1 year before initiation of the LAI treatment	Atypical	67	0.71	0.75	-0.328 (0.744)
	Typical	42	0.76	0.61	
Number of hospitalizations during 1 year after initiation of the LAI treatment	Atypical	68	0.08	0.28	-0.519 (0.605)
	Typical	42	0.11	0.32	
Yearly hospitalization incidence before initiation of the LAI treatment	Atypical	68	0.86	0.71	-0.537 (0.692)
	Typical	42	0.95	0.93	
Yearly hospitalization incidence after initiation of the LAI treatment	Atypical	68	0.11	0.32	-0.382 (0.703)
	Typical	42	0.14	0.35	
Duration of hospitalizations in a year before initiation of LAI treatment (days)	Atypical	68	13.08	10.98	-1.345 (0.181)
	Typical	42	16.16	12.68	
Duration of hospitalizations in a year after initiation of LAI treatment (days)	Atypical	68	1.76	6.14	-0.308 (0.759)
	Typical	42	2.11	5.35	

*Independent Samples t-test result for the comparisons; *p<0.05: the accepted level of significance

DAI-10: The Drug Attitude Inventory-10; PANSS: The Positive and Negative Syndrome Scale; UKU: The UKU Side Effect Rating Scale; ZCBS: The Zarit Caregiver Burden Scale; CMHC: Community Mental Healthcare Center; LAI: Long Acting Injectable; SD: Standard Deviation; N: Number

Table 7. Comparison of the Reasons for Previous LAI Discontinuation or Change According to the Use Typical and Atypical Antipsychotic Agents

			Reason for Changing or Discontinuing LAI treatment			Total	X ² (p)*
			Side Effects	Relapse	Other		
Previously used LAI Antipsychotic Type	Atypical	Number	13	6	5	24	0.518 (0.772)
		Percent	54.2%	25.0%	20.8%	100.0%	
	Typical	Number	13	6	8	27	
		Percent	48.1%	22.2%	29.6%	100.0%	
	Total	Number	26	12	13	51	
		Percent	51.0%	23.5%	25.5%	100.0%	

*Chi-Square analysis was used for comparison of categorical variables between the two groups, *p<0.05: the accepted level of significance

LAI: Long Acting Injectable

Table 8. The Results of the Regression Analysis for the Prediction of Caregiver Burden by the Clinical Variables of the Patients

	B	B	T	P*	Paired r	Partial r	95% Confidence Interval	
							Lower	Upper
Constant	4.344		0.518	0.605			-12.272	20.960
Age	-0.192	-0.151	-1.644	0.103	-0.159	-0.118	2.289	11.089
Gender#	6.689	0.225	3.015	0.003	0.283	0.117	-0.424	0.040
Type of Antipsychotic	3.234	0.108	1.478	0.143	0.143	0.106	-1.106	7.574
Duration of Disorder	0.036	0.023	0.270	0.788	0.026	0.019	-0.231	0.304
PANSS Total Score	0.785	0.553	7.306	0.000	0.582	0.525	0.572	0.998

R=0.680 R²=0.463 R²_{adj}=0.437 F (5,104)=17.910 p<0.000; *p<0.05: the accepted level of significance

Dependent Variable: The Zarit Caregiver Burden Scale Total Score

PANSS: The Positive and Negative Syndrome Scale

#: Categorical coding for female:0, male:1. Positive direction signifies prediction for male gender.

model describes 43% of the variance in the ZCBS scores (R²=0.437). The standardized regression coefficients indicated that the significant positive predictors of the ZCBS scores were the PANSS total score (β =0.553, p < 0.001), and gender (β =0.225, p =0.003) with the predictivity being positive in the direction of the male gender (Table 8).

DISCUSSION

Duration of treatment adherence, caregiver burden, side effects and quality of life scores were similar for patients using typical or atypical antipsychotics according to our study in

which the patients with positive attitudes towards drugs had longer duration of treatment with the same medication and not side effects or quality of life, but symptom severity had effect on the intent of treatment discontinuation.

Primary caregivers in our study were usually the parents (48%) of the patients, followed by brothers or sisters (21%) and spouses (18%). According to reports from other studies in different countries in the world, caregivers were usually parents, and most frequently the mothers (Awad et al. 2008, Nasr et al. 2009, Velligan et al. 2019). Female to male ratio similar to the literature, with slightly favoring for females (%55) (Caqueo-Urizar et al. 2006, Yazici et al. 2016). Most

of the caregivers had primary school level of education. It was previously reported in Turkey that 47.6% of the caregivers were at the primary school grade, while 20.4% and 10.7% had had, respectively, high school and university diplomas. These results should be taken into account when planning education and activity for the caregivers of patients with schizophrenia.

In our study, there were patients from CMHC and from outpatient clinics of our hospital and the characteristics of these patients were mostly similar with the exception that caregiver burden scores of patients from CMHC were higher. There were studies from our country reporting the opposite as caregiver burden scores of patients from outpatient clinics being higher than CMHC (Ayhan et al. 2019, Özdemir et al. 2017). There were such patients in our study that their treatment adherence could only be maintained by home visits from CMHC team. In the CMHC, for the patient who refuse to come to the hospital or who has low treatment motivation, home visits are planned for treatment adherence. That's why, the patients with low treatment motivation and high caregiver burden might be more frequent in the CMHC sample. Patients who would drop out of treatment in outpatient clinic system could be able to attend treatment by the help of the capabilities of CMHCs.

Attitude towards treatment is a factor associated with treatment discontinuation and treatment non-adherence, for this reason, it is suggested as a predictor for effectiveness (Lacro et al. 2002, Gaebel et al. 2010). Since Non-adherence and drug discontinuation is an important issue in the long term treatment of schizophrenia, defining early signs and maintaining safe and effective treatment is a primary concern. Non-adherence to psychotropics is also a factor increasing the burden and anxiety of the caregiver (Kretchy et al. 2018). In our study, attitude towards drugs was measured with DAI and 20 patients had negative attitude whereas 90 patients had positive attitude towards drugs. Treatment adherence duration was longer for patients with positive attitude, and this was in line with previous studies. In his study consisting 228 first episode patients, Gaebel and colleagues (2010) decided that DAI was a significant and valid predictor of effectiveness. In a study of schizophrenia from Czech Republic, attitude towards drugs was positively correlated with treatment duration and drug attitude was substantially negative for patients who had history of drug discontinuation without consulting with their clinician. Results of this study were also in line with our study, reporting a strong relationship between duration of treatment adherence and attitude towards drugs (Kondratova et al. 2019). Patients who were using the same treatment for a long time had also higher scores on DAI scale; thus, DAI has been an effective instrument for measuring treatment adherence.

Comparison of DAI scores were similar for the two groups of patient groups using typical or atypical antipsychotics. This

result is similar to other studies in the literature. Comparing the 12-month follow-up results on patients using typical or atypical LAI antipsychotics, the STAR network multicenter "Depot" study at 35 centers in Italy showed that treatment compliance and attitude to drugs were similar in both groups (Ostuzzi et al. 2018). The results of a 6-month observational follow up on patients using LAI risperidone or typical LAI APs also proved similarly positive attitude to the prescribed drugs in both groups (Singh et al. 2016).

In our study, there were 20 patients who declared the intent of drug discontinuation and there were 90 patients who declared that they had no intent of drug discontinuation. PANSS scores of patients with the intent of drug discontinuation were significantly higher. In a similar way, the patients with the intent of drug discontinuation had negative attitude towards drugs. Between these two groups of patients there were no difference for the comparison of drug side effects and quality of life. There was also no difference between the patients using typical or atypical antipsychotics for the comparison of reasons for treatment change which are side effects, relapse or other reasons. In agreement with the previous studies, it is presumable that patients' perception of the effectiveness of treatment is a factor favoring treatment continuation. In a retrospective study of three LAI antipsychotics (haloperidol decanoate, paliperidone palmitate, LAI aripiprazole) consisting of 217 patients with the diagnosis of schizophrenia, the most frequent reason for drug discontinuation was ineffectiveness of treatment and the least frequent reason was side effects. For these three groups using different LAI antipsychotics, there were no significant difference for the presence of side effects (Di Lorenzo et al. 2019). In another retrospective study investigating treatment adherence ratios of 82 schizophrenia patients using LAI antipsychotics, 63.4% of the patients were found to be still on treatment in 6 months. The most common reason for treatment discontinuation was inadequate effectiveness or lack of effectiveness (Taniguchi et al. 2019). On the other hand, in the CATIE study that investigates the effectiveness of antipsychotics in schizophrenia, the primary reasons for drug discontinuation were ineffectiveness (continuing symptoms) and side effects (Lieberman et al. 2005). Side effects were not associated with the intent of treatment discontinuation in our study, but our study consists of a sample of patients who tolerated the drug they used and continued to use it regularly. The reason for the low impact of side effects in our study is probably our study design investigating patients with schizophrenia who were using their medications regularly for a while. It should not be forgotten that there may be treatment non-adherent patients who could not tolerate to use their medication with adequate duration and dose because of side effects, or who discontinued their medication in the beginning phases of the

treatment; but these patients were outside of the purview of our analyses because of the study design.

Similar to our study, in two retrospective studies of Paliperidone LAI, the most frequent reason for drug discontinuation was ineffectiveness (Deslandes et al. 2018, Attard et al. 2014). In a study consisting one year follow-up of first episode psychosis, attitudes to drugs were negative and the PANSS total scores were high for patients who discontinued their medication. In addition to this quality of life of the patients were similar, and the side effect scores were also similar except slight significant difference for akathisia and sexual side effects (Gaebel et al. 2010).

There are studies reporting severity of side effects to be effective in discontinuing drug therapy. Higher incidence of discontinuation during treatment with typical as compared to atypical antipsychotics has been reported (Ascher-Svanum et al. 2006). Reasons given for discontinuing oral antipsychotics were reported to include 60.5%, 51.9% and 44.4% incidences of, respectively, non-life threatening side effects, deficits in functional recovery and inadequate improvement of the positive symptoms (Matza et al. 2012). There is, however, a paucity of similar research with the LAI antipsychotics.

In a review consisting of studies conducted between January 2002- May 2013 with the aim of comparing LAI Aripiprazole with other LAI antipsychotics for effectiveness, tolerability and safety; treatment discontinuation ratios for the reason of side effects were reported to be similar between LAI Aripiprazole and other LAI antipsychotics (Majer et al. 2015). Excluding exceptional situations, the oral form of an antipsychotic is given initially to a patient for assessing tolerability and side effects before proceeding to treatment with the LAI form. This may be a factor diminishing the influence of side effects in the studies of LAI antipsychotics with regard to studies of oral antipsychotics. Another factor could be that there is less fluctuation in the blood levels of LAI forms than with oral medications.

In our study, schizophrenia patients who were using Typical and atypical LAI antipsychotics were similar for the comparison of quality of life. In a study comparing LAI Aripiprazole and other LAI antipsychotics, there were no difference for the comparison of brief psychiatric rating scale and quality of life scores (Kane et al. 2020). This result was explained by the probable similarity of symptom severity when working with patients in remission and not in acute psychotic episode.

Caregiver burden was similar in our study for the comparison of typical and atypical LAI antipsychotics. Perlick and colleagues (2010) did not find any evidence of decreasing caregiver burden in favor of atypicals in their comparison of typical and atypical oral antipsychotics. LAI antipsychotics decrease the risk of relapses and with this way decrease the distress of the caregivers (Tiihonen et al. 2017, Taipale et al. 2018). Also in

our study, there was decrease in the duration and frequency of hospitalizations after LAI treatment. Although there are studies underlining that LAI antipsychotics are superior from oral antipsychotics for decreasing caregiver burden, studies comparing different LAI antipsychotics for their effect on caregiver burden are rare (Li et al. 2018, Gopal et al. 2017).

A study investigating the difference between LAI risperidone with LAI typical antipsychotics and oral typical and atypical antipsychotics found that caregiver burden scores were lower and better quality of life was more frequent in patients using LAI risperidone (Odds Ratio: 1.654, 95% confidence interval: 1.126-2.431) (Bravo-Ortiz et al. 2011). The study sample of Bravo-Ortiz was consisting of patients whose treatment were changed because of treatment non-adherence, side effects or treatment ineffectiveness, for this reason; the study sample consisted patients who stopped their oral antipsychotics and started LAI treatment. It was a factor in the favor of LAI risperidone that there were patients who switched from oral treatment to LAI treatment in the LAI risperidone group. It is well known that LAI treatment is advantageous over oral treatment because it eliminates the need for caregivers' continuous monitoring for treatment adherence and by this way relieves the anxiety of the parents (Lerner et al. 2018). In our study, the similarity of the clinical and caregiver burden results with both the typical and atypical LAI antipsychotics may be due to working with patients on regular maintenance treatment.

Although the ZCBS has been frequently used for measuring caregiver burden, it has been considered to be problematic for reasons cited as having been originally developed for dementia patients, not having a specified recall period and the related difficulty of answering the questions in relation to a particular period, scoring observable behaviors and not adequately reflecting emotional evaluations and tendencies and the possibility of being given socially desirable answers in a self-report scale with the inclusion of the expression "caregiver burden" in its heading. Therefore, the Schizophrenia Caregiver Questionnaire (SCQ) was developed by improvements on the ZCBS (Gater et al. 2015). The SCQ has not yet been adapted to the Turkish language but may be useful for accentuating the differences not detected by the ZCBS. There may be other ways of observing the effect of schizophrenia on the families of the patients: Investigating the data on 10883 patients and their caregivers between 2006 and 2013 showed that the risk of needing long term sickness leave was lower for caregivers of patients using both typical and atypical LAI APs, and that the risk of seeking psychiatric service was lower for caregivers of patients on atypical LAI APs and higher for caregivers of patients on oral APs (Taipale et al. 2020).

Regression analysis for investigating the prediction of the ZCBS scores by factors of disease duration, the use of typical and atypical LAI APs, gender and the PANSS total scores

showed that the PANSS total scores and gender correlated with caregiver burden, and that the higher PANSS scores and the male gender increased caregiver burden. Given the traditional Turkish family construct that expects the male to be the income provider, disabling and unemployment of male patients by schizophrenia may underlie the increased correlation of the caregiver burden with the male gender. Other explanations may be the more frequent propensity to aggression in males and the worse prognosis among male schizophrenia patients. Association of high caregiver burden with male gender is supported by previous research (Roick et al. 2007, Atar 2018). Two studies investigating schizophrenia with respect to psychotic symptom severity also concluded that high PANSS total scores were associated with increased caregiver burden (Uygur & Esen 2019, Angermeyer & Dietrich 2006). In cases of treatment resistant schizophrenia, caregiver burden correlated with the severity of positive symptoms (Velligan et al. 2019). These findings emphasize the primary treatment target should be to relieve the positive symptoms of schizophrenia.

Limitations and Challenges

A primary limitation of the study is the cross-sectional design which has not allowed comparative measurements between the periods before and after the initiation of LAI antipsychotics. The results only give information about the patients who tolerated the prescribed LAI antipsychotic and maintained it with regularity.

The use by some of the patients of oral antipsychotics at the minimum effective dose together with the LAI antipsychotics, an approach although not ideal but frequent in clinical practice, might have interfered with the results on the comparisons of the effects of the typical and atypical LAI antipsychotics. Presence of this possible confounder should be kept in mind while interpreting the results of our naturalistic study with distinct aim to describe the general clinical practice with the LAI APs. These problems can be solved by randomized controlled prospective trials with definitive exclusion criteria.

In this study, the data on the presence of an intention to discontinue drug therapy were based on the self-report by the patient. There may have been patients who were hesitant to declare this intention.

CONCLUSIONS

According to our results, medications side effects and quality of life were similar between patients for the comparison of presence of the intent of treatment discontinuation, but symptom severity were higher in patients who were thinking of discontinuing treatment. The incidences of drug change or treatment discontinuation were similar between patients on

typical or atypical LAI antipsychotics and did not change on grounds of the side effects of using typical LAI antipsychotics. Also, the caregiver burden of the families did not differ significantly in relation to the use of typical and atypical LAI antipsychotics by the patients.

The decreases observed in the number and duration of hospitalizations after starting maintenance therapy with typical and atypical LAI antipsychotics were similar. In addition, type of antipsychotic was not related with longer treatment duration. However, it was observed that patients who had positive attitude towards drugs had longer treatment duration.

According to the observation that the presence of the intent of drug discontinuation were related not with side effect severity but with higher symptom severity and shorter disorder duration of disorder, it can be suggested that patients in the early psychosis period and with higher symptom severity had increased risks of treatment discontinuation.

The factors related with increased caregiver burden were psychotic symptom severity, as also reported by others, and the male gender, irrespective of the use of typical or atypical LAI antipsychotics. Therefore, it is concluded that decreasing symptom severity should be the primary treatment target which has the potential of decreasing caregiver burden of the family.

Our study was designed to compare typical and atypical LAI APs. Comparisons between generic antipsychotics could be possible in future studies with larger numbers of patients. Moreover, population database studies can report data on the entire national subpopulation with schizophrenia diagnosis. Such studies, although very difficult to carry out in the past, can be feasible in our country with the development of informatics and electronic prescribing systems recording all patient data in a single database.

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