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Relationships between Use of Long Acting Antipsychotics and Sociodemographic and Clinical Characteristics of Patients with Schizophrenia

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ÖZET:

Uzun etkili antipsikotik kullanımı ile şizofrenili hastaların sosyodemografik ve klinik özellikleri arasındaki ilişkiler

Amaç: Şizofreni ciddi sosyal ve mesleki özürlülüğe neden olan kronik bir psikiyatrik bozukluktur. Tedavinin birincil amacı relapsı önlemek ve sosyal ve mesleki işlevselliği hastalık öncesi duruma geri çevirmektir. Ancak hastalık süresince verilen medikal tedavilere yetersiz uyum nedeniyle yüksek oranda relapslar görülebilmektedir. Uzun etkili enjeksiyon antipsikotiklerin kullanımı ile ciddi mental hastalıkları olan bireylerde tedaviye uyumun sağlanması ve dolayısıyla relapsların önlenmesi amaçlanmaktadır. Literatürde uzun etkili enjeksiyon antipsikotikler ile şizofreni hastalarının sosyodemografik ve klinik özellikleri arasındaki ilişkiyi inceleyen çalışma sayısı kısıtlıdır. Bu çalışmada şizofreni hastalarının sosyodemografik ve klinik özellikleri ile uzun etkili antipsikotik kullanımı arasındaki ilişkileri belirlemeyi amaçladık.

Yöntemler: Bu çalışma retrospektif bir kohort çalışmasıdır. Şizofreni tanılı iki yüz elli hastanın bilgileri Kırklareli Devlet Hastanesi ve Gölbaşı Devlet Hastanesinin tıbbi kayıtlarından elde edildi. Hastalar uzun etkili enjeksiyon antipsikotik kullanıp kullanmamalarına göre gruplandırıldı. Uzun etkili enjeksiyon antipsikotik kullanımı olan ve olmayan hastaların sosyodemografik ve klinik özellikleri karşılaştırıldı.

Bulgular: Uzun etkili enjeksiyon antipsikotik grubunda (n=96) hastalığın başlangıç yaşı daha erken ve hastalık süresi daha uzundu. Şiddet davranışı, intihar girişimi öyküleri ve ailede şizofreni hastalığı öyküsü uzun etkili enjeksiyon antipsikotik grubunda anlamlı olarak yüksekti. Hastalığın daha erken yaşta başlaması, şiddet davranışı, intihar girişimi öyküleri ve ailede şizofreni hastalığı öyküsü uzun etkili enjeksiyon antipsikotik kullanımı için anlamlı prediktörler olarak bulundu.

Sonuç: Tedaviye uyumun zayıf olmasına bağlı relapslar uzun etkili enjeksiyon antipsikotiklerin kullanılması ile engellenebilir. Tedaviye uyumsuzluk nedenlerinin belirlenmesi ve uzun etkili enjeksiyon antipsikotik kullanımını gerektiren olguların öngörülebilmesi ile uygun hastalara hastalığın erken dönemlerinde dahi uzun etkili enjeksiyon antipsikotikler verilebilir.

Anahtar sözcükler: Antipsikotikler, şizofreni, tedavi uyumu

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ABSTRACT:

Relationships between use of long acting antipsychotics and sociodemographic and clinical characteristics of patients with schizophrenia

Objective: Schizophrenia is a chronic psychiatric disorder that causes severe sociooccupational disability. The primary goal of treatment is to prevent a subsequent relapse and restore sociooccupational functioning to the premorbid level. However, high rates of relapses can be seen during the illness due to inadequate adherence to drug therapy. Long acting injectable (LAI) antipsychotics aim to promote compliance in individuals with particularly severe mental illnesses, thereby enhancing relapse prevention. In the literature, there are limited numbers of studies, which have investigated the relationships between use of LAI antipsychotics and sociodemographical and clinical characteristics of schizophrenic patients. In this study, we aimed to identify the association between sociodemographic and clinical characteristics of patients with schizophrenia and use of long acting antipsychotics.

Methods: This was a retrospective cohort study. The data of 252 patients with a diagnosis of schizophrenia were obtained from the medical records of the psychiatry departments of Kırklareli State Hospital and Gölbaşı State Hospital. The patients were grouped according to whether they had used LAI antipsychotics or not. The sociodemographic and clinical characteristics were compared between patients with and without use of long acting antipsychotics.

Results: In the LAI antipsychotic group (n=96), onset of illness was earlier and duration of schizophrenia was longer. The percentage of history of violent behaviour, suicide attempts and family history of schizophrenia were significantly higher in the LAI antipsychotic group. An earlier age of onset, a more significant history of suicide attempts, a history of violent behaviour and a family history of schizophrenia were found to be predictors of LAI antipsychotic use.

Conclusion: Relapses due to poor adherence to treatment can be overcome by LAI antipsychotics. In addition to the familiar causes of nonadherence, the specific predictors of use of LAI antipsychotics should be carefully noted and patients should be initiated on LAI antipsychotics even when they are in the early phases of illness.

Key words: Antipsychotics, schizophrenia, medication adherence

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INTRODUCTION

Schizophrenia is a chronic disabling psychiatric disorder characterized by hallucinations, delusions, cognitive deficits, poor insight, and comorbid substance use disorder. Most individuals who developed schizophrenia will have chronic illness. The severity of positive, negative, cognitive and mood symptoms is highly variable, as is the severity of social and vocational disability (1-4). The primary goal of treatment during the critical period is to prevent a subsequent relapse and to restore sociooccupational functioning to the premorbid level and reduce disability (5). The relapse rate in patients with first episode schizophrenia is relatively low during the first year of the illness but substantially increases to rates of 53.7% and 74%-81.9% after 2 and 5 years, respectively (6,7). There are many potential causes of relapse in chronic schizophrenic patients; however, inadequate adherence to prescribed medication regimens always should be considered as a strong contributing factor (8). The discontinuation of antipsychotics in patients with first-episode schizophrenia or schizoaffective disorder increases the risk of relapse by approximately five times (6,8). The rate of medication discontinuation in individuals with first-episode schizophrenia ranges from 26% (7) to 44% (9,10) during the first year. Coldham et al. (11) have reported a rate of poor adherence of 59% (39% nonadherent and 20% inadequately adherent) within the first year after the first episode. None of the interventions currently used to improve the nonadherence problem have been completely reliable in the treatment of schizophrenia.

Several authors have identified a "predictable checklist" of features associated with nonadherence, including being young, male, and unemployed or socially isolated; a past history of nonadherence; and, possibly, current use of illicit substances. However a meta-analysis by Lacro et al. (12) found no association between adherence and either age or gender. The factors which have been commonly associated with adherence problemsare poor insight, negative attitude or subjective response to medication, previous nonadherence, substance abuse, short illness duration, inadequate discharge planning or aftercare environment, and a poor therapeutic alliance. Neverthless, the severity of psychotic symptoms or medication side effects did not have notable effects (13). A recent review by Narasimhan et al. (14) concluded that symptomatology, cognitive function, disease insight, and presence of substance abuse were the most important features.

The aim of using long acting injectable (LAI) antipsychotics is to promote compliance in people with particularly severe mental illnesses, thereby enhancing relapse prevention (15-20). Several studies have showed advantages of LAI antipsychotics regarding rates and durations of rehospitalization, compared with oral antipsychotics (15) Guidelines recommend considering LAI antipsychotics in patients with repeated nonadherence. Previous studies have suggested that LAI antipsychotics might be more effective for maintaining medication adherence (21,22) and preventing relapse (23) in first-episode schizophrenia compared with oral antipsychotics (OA) (24,25). However, most psychiatrists use LAI antipsychotics very conservatively (26-28). There is limited data, which has investigated the predictors of using LAI antipsychotics in patients, who suffered from schizophrenia. Furthermore, to our knowledge there is no study conducted in Turkey which describes the clinical and sociodemographical predictors of using LAI antipsychotics. We aimed to determine the sociodemograpical and clinical predictors of using LAI antipsychotics in patients with schizophrenia. We suggest that determining the predictors of using of LAI antipsychotics may be useful for clinicians in terms of the reduction of relapses, increasing the quality of life and functioning and reduction of disability in patients with schizophrenia.

METHODS

This was a retrospective cohort study. The data were obtained from the medical records of the psychiatry departments of Kırklareli State Hospital and Gölbaşı State Hospital. Three hundred and sixty

patients, who were admitted to the outpatient and inpatient clinics of the psychiatry departments of Kırklareli State Hospital and Gölbaşı State Hospital or who were admitted to the Community Mental Health Service of Kırklareli State Hospital with a diagnosis of schizophrenia according to the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) (29) between the dates of October 2010 and January 2013 were included in the present study. Sociodemographic data were collected from each subject including age, sex, marital status, employment status, economic status and living accomodation. The clinical data consist of age at illness onset, duration of illness, numbers of relapses, numbers of hospitalization, use of long acting antipsychotics, type of long acting antipsychotics (conventional or second generation), scale for the assessment of negative symptoms (SANS) (30), scale for the assessment of positive symptoms (SAPS) (31), brief psychiatric rating scale (BPRS) (32), status of substance, alcohol and tobacco abuse, history of violence and suicide attempts, family history of schizophrenia and family history of suicide attempts. The patients were divided into two groups according to whether they were treated with LAI antipsychotics or not. Because the medical records of 108 patients were insufficient for our research, the final study included 252 schizophrenic patients. The study was approved by our local ethics committee.

Statistical Methods

Data were analyzed using the Statistical Package for the Social Sciences—PC version 16.0 (SPSS, Chicago, IL). A confidence interval (CI) of 95% and a 2-tailed P value less than 0.05 were considered to be statistically significant for all analyses. Variables were tested for homogeneity of variance by using the Levene test and for normality of distribution by utilizing the Kolmogorov-Smirnov test. Between age groups, differences in length of education were tested with independent sample t-tests, whereas duration of illness, age at illness onset, scores of SANS, SAPS and BPRS were evaluated with the Mann Whitney U test because of nonparametric distributions. Differences in, numbers of relapse, numbers of hospitalization, type of oral antipsychotics used, status of substance, alcohol and tobacco abuse, history of violence and suicide attempts, family history of schizophrenia, family history of suicide attempts and comorbid medical illness were tested by a χ^2 test.

A series of logistic regressions examined the strength of associations between use of LAI antipsychotics (dependent variable) and the SANS, SAPS and BPRS scores, age at illness onset, duration of illness, sex, history of violence and suicide attempts and family history of schizophrenia. Results are presented as odds ratios (ORs) for independent variables of interest with associated 95% confidence intervals (CIs).

RESULTS

A total of 252 patients were included in the study. The mean age of all patients was 36.1±10.7 years. The number of male patients was 134 (53.2%) and the number of female patients was 118 (43.8%). 96 patients (30.5%) were treated with LAI antipsychotics. The percentage of second generation LAI antipsychotic (risperidone long acting injection) was 72.9% (72 patients) and conventional antipsychotics (zuclopenthixol decanoate or flupentixol decanoate) was 27.1% (24 patients). Among LAI antipsychotic treated patients, there were no significant differences in terms of sociodemographical and clinical characteristics between patients who were treated with risperidone long acting injection and patients who were treated with zuclopenthixol decanoate or flupentixol decanoate, with the exception of a higher percentage of male patients in the conventional LAI antipsychotic group (χ^2=12.4, P=0.032). The mean age of patients who received LAI antipsychotics was 36.44±10.66 years which was comparable with patients who were treated with OA. (t=-0.427, P=0.66). Both groups were similar in terms of gender, family status, employment status, economic status, length of education and living accomodation (P=0.05) (Table 1).

Among clinical characteristics, both groups were similar in terms of number of relapses, number of

Table 1: Comparison of sociodemographical factors between patients with and without use of long acting antipsychotics. LAI: Long acting injection

	LAI group (n=96)	Patients without LAI use (n=156)	Statistic	p
Age (years)	36.44 ± 10.66	35.87 ± 10.21	t=-0.427	0.66
Gender				
Female	41 (42.7%)	77 (49.4%)	χ^2=1.56	0.185
Male	55 (52.3%)	79 (50.6%)	df=2	
Family status				
Single	51 (53.1%)	76(48.7%)	χ^2=2.7	0.44
Married	26(27.1%)	25(35.3%)	df=3	
Seperated	19(19.8%)	55(16%)		
Employment status				
Works Regulary	47 (49%)	64(41%)	χ^2=6.06	0.195
Unemployed	49 (51%)	92 (59%)	df=4	
Length of education (years)	9.72 ± 2.2	9.16±1.66	t=-0.974	0.78
Living Place				
Rural	41 (42.7%)	60 (38.5%)	χ^2=0.45	0.296
Urban	55 (57.3%)	96 (61.5%)	df=1	
Economic Status				
Low	54(56.2%)	79 (50.6%)	χ^2=4.82	0.19
Medium	32(33.5%)	63(40.4%)	df=3	
High	10(10.4%)	14(9%)		

Table 2: Comparison of clinical characteristics between patients with and without use of long acting antipsychotics. LAI: Long acting injection. Significant P values predicted in bold character

	LAI group n=96	Patients without LAI use n=156	Statistic	p
SANS	32.55 ± 16.9	28.75 ± 14.35	Z=-1.54	0.122
SAPS	25.56 ± 17.1	23.03 ± 18.1	Z=-1.67	0.095
BPRS	24.52 ± 12.17	22.91 ± 11.28	Z=-1.009	0.313
Types of OA				
Conventional	20 (44.4%)	50(33.3%)	χ^2=2.18	0.31
Atypical	40(48.9%)	80(60%)	df=1	
Combined	36(6,7%)	22(6,7%)		
Numbers of relapses				
1	20 (20.8%)	24(15.4%)	χ^2=4.9	0.082
2	18 (18.8%)	39 (25%)	df=2	
3 or more	69(71.9%)	93(59.6%)		
Numbers of hospitilization				
0	7 (7.3%)	41(26.3%)	χ^2=2.01	0.36
1	20 (20.8%)	35 (22.4%)	df=2	
2 or more	58(60.4%)	80(51.3%)		
Duration of treatment	12.33 ± 9.67	9.89 ± 7.68	Z=-2.25	**0.024**
Age at illness onset	24.14 ± 7.39	26.67 ± 8.46	Z=-2.43	**0.015**
History of suicide				
Yes	60 (62.5%)	49 (31.4%)	χ^2=23.4	**<0.001**
No	36 (37.5%)	107 (68.6%)	df=1	
History of violence				
Yes	82(85.4%)	55(35.3%)	χ^2=60.26	**<0.001**
No	14(14.6%)	101(64.7%)	df=1	
Family history of schizophrenia				
Yes	50	50	χ^2=7.78	**0.001**
No	46	102		
Substance abuse				
Yes	9(9.4%)	11(7.1%)	χ^2=2.08	0.32
No	87(90.6%)	145(99.4%)	df=1	
Alcohol abuse				
Yes	4(2.1%)	2(1.3%)	χ^2=0.27	0.87
No	92(97.9%)	154(98.7%)	df=2	
Smoking				
Yes	55(57.3%)	76(48.7%)	χ^2=2.5	0.28
No	41(42.7%)	80(51.3%)	df=2	

Table 3: Logistic regression analysis of variables associated with long acting injection antipsychotic use. Sch: Schizophrenia. Significant P values predicted in bold character

Variable	OR	P	CI
Age	1.006	0.650	0.990- 1.037
Gender	0.763	0.30	0.457-1.273
SANS	1.013	0.278	0.990- 1.037
SAPS	1.010	0.332	0.990-1.030
BPRS	0.996	0.804	0.965-1.028
Duration of illness	1.009	0.632	0.974-1.045
Age at onset	0.958	**0.043**	0.919-0.999
Violence	10.442	**<0.001**	5.212-20.919
Suicide	1.266	**<0.001**	1.895-6.641
Family history of Sch	0.543	**0.042**	0.286-1.032

hospitalizations, type of OA, use of long acting antipsychotics, scores on the SAPS (Median, minimum -maximum scores of SAPS were 18.5 and 0-87, respectively; Z=-1.67, P=0.095) and the BPRS (Median and minimum -maximum scores of BPRS were 22 and 3-72, respectively; Z=-1.009, P=0.313), status of substance, alcohol and tobacco abuse and family history of suicide attempt (P 0.05). The score on the SANS tended to be higher in the LAI antipsychotic group; however, it was not statistically significant (Median, minimum -maximum scores of SANS were 26, 0-83, respectively; Z=-1.54, P=0.122). The onset of illness was earlier (Median, minimum -maximum values of age at illness onset were 24 years and 17-57 years, respectively; Z=-2.436, P=0.015) and duration of schizophrenia was longer in the LAI antipsychotic group compared with patients who did not use LAI antipsychotics (Median, minimum -maximum values of age at illness onset were 2 years and 2-31 years, respectively; Z=-2.263, P=0.024). The percentage of history of violent behavior and suicide attempts were significantly higher in the LAI antipsychotic group (χ^2=60.26, P<0.001; χ^2=23.4, P<0.001, respectively). The family history of schizophrenia was considerably higher in the LAI antipsychotic group (χ^2=7.78, P=0.001) (Table 2).

The scores on the SANS, SAPS and BPRS, age at illness onset, duration of illness as continuous predictors; sex, history of violence and suicide attempts and family history of schizophrenia as categorical predictors were included into a logistic regression. The logistic regression equation was capable of correctly classifying 75% of the cases. The equation was generally more exact on predicting patients without use of LAI antipsychotics (81.4%) than patients who were using LAI antipsychotics (63.5%). The age at illness onset (OR=0.958, P=0.043, Cl=0.919-0.999), history of suicide attempts (OR=1.266, P<0.001; Cl=1.895-6.641), history of violent behaviour (OR=10.442, P<0.001; Cl=5.212-20.919) and family history of schizophrenia (OR=0.543, P=0.042; Cl=0.286-1.032) were found to be significant predictors for use of LAI antipsychotics (Table 3).

DISCUSSION

In this retrospective cohort study, we aimed to demonstrate the predictors for use of LAI antipsychotics in patients with schizophrenia in terms of sociodemographic and clinical characteristics. Taking medication several times a day might be disturbing to patients who suffer from a chronic mental illness such as schizophrenia (14). Long-acting antipsychotics can address all-cause discontinuation and poor adherence, (33) and treatment guidelines (e.g., from the American Psychiatric Association, the Schizophrenia Patient Outcomes Research Team and the Texas Medication Algorithm Project) strongly recommend using long acting formulations for patients, who are nonadherent with oral agents, but clinicians seem reluctant to modify their practice, even for patients who are overtly nonadherent in daily clinical practice (13). It has been reported that psychiatrists considered long acting antipsychotic injections to manage fewer than 1 out of 5 patients with schizophrenia having episodes of medication nonadherence. Historically, long-acting agents (particularly depot formulations of

typical antipsychotic agents) have been considered to be reserved for more chronically ill patients with a clear history of nonadherence, but some authors have suggested a role for such agents earlier in the course of illness, including for first-episode patients (13,34). The feasibility of this approach has been demonstrated by the finding that 73% of first-episode patients, who were stable after treatment with an oral atypical antipsychotic, accepted a recommendation to switch to a long-acting atypical agent when it was discussed as part of an integrated treatment plan (35).

There are limited numbers of studies, which have investigated the possible predictors of use of LAI antipsychotics in the literature. Valenstien et al. (36) firstly described the characteristics of patients, who had been treated with depot antipsychotics and they reported that patients on depot and oral agents had similar levels of psychiatric symptoms, but patients on depot antipsychotics were more likely to receive high doses and complain of side effects. West et al. (37) have reported that initiation of LAI antipsychotics was significantly and positively associated with public insurance, prior inpatient admission, proportion of time with lack of adherence, average or above average intellectual functioning, and living in a mental health residence. Use of LAI antipsychotics was inversely associated with using second-generation antipsychotics and other oral psychotropic medications prior to medication nonadherence. Vehof et al. (38) reported that predictors for switching to depot versus oral antipsychotics were male sex, previous use of depot antipsychotics, recent use of an anticholinergic drug, and a gap in the dispensing history of the antipsychotic. The methodological approaches of previous studies and our study have significant discrepancies. Firstly, the parameters that were investigated by West et al. and Vehof et al. are not exactly similar to those in our study. Secondly, they also investigated the properties and attitudes of prescribers. Our results are in line with previous studies in terms of similar levels of psychiatric symptoms in both groups. However, sex distribution, median age and number of previous psychiatric inpatient admissions were to the opposite of previous studies. The disparities of our results may due to the smaller sample size of our study compared with previous studies.

The duration of illness in patients who used LAI antipsychotics was longer in our study. We suggest that this result was unsurprising. As previous studies have reported, LAI antipsychotics were generally considered for patients who were more chronic and more nonadherent to oral medication (13). The age at illness onset was significantly earlier in patients who used LAI antipsychotics. It was also found to be a significant predictor of usage of LAI antipsychotics in regression analysis. It has been conceptualized that age at onset may act as a surrogate measure of severity of the disease process by DeLisi (39). An earlier age at onset has been associated with more severe clinical and behavioural symptoms (40, 41), more social disability (42), narrower posterior brain segments (43) and larger ventricles (44). Cognitive deficits in schizophrenia are also associated with earlier onset (45). To our knowledge, there is no data which describes the association between earlier onset of schizophrenia and the use of LAI antipsychotics. Altough we did not have data about the cognitive assessments in our study, we may suggest that schizophrenic patients being treated with LAI antipsychotics may have worse cognitive symptoms. We also suggest that patients with earlier onset might be given LAI antipsychotics to reduce relapses and promote better adherence.

The percentage of history of suicide attempts was significantly higher in patients who were given LAI antipsychotics. Moreover, suicide attempts were found to be a significant predictor for usage of LAI antipsychotics in regression analysis. A number of risk factors for suicide attempts in schizophrenia has been suggested to be similar to the general population such as mood disorders, grief for a recent loss, drug misuse and previous suicide attempts (46). However, risk factors including fear of mental disintegration, agitation or restlessness, and poor adherence with treatment (46,47). To our knowledge, there are no data in previous studies that support an association between use of LAI antipsychotics and suicidality. We suggest that getting started with LAI antipsychotics for patients who are considered to be

more suicidal might lead to a reduction in mortality rates due to suicide attempts in specific patients with poor adherence to oral administration.

Violent behaviour among schizophrenic patients is more common than in the general population. In our study, the percentage of history of violent behaviour was higher in the LAI antipsychotic group compared with schizophrenic patients who were treated only with OA. The presence of violent behaviour also found to be a predictor for using LAI antipsychotics. The occurrence of violence in schizophrenia is not explained by a single variable, but is the result of interaction among different factors related to the individual and the society. Epidemiological studies conducted in the general population have shown that violent behaviour was associated with younger males from low socioeconomic fgroups, substance abuse problems and a history of violence (48). The population of patients with schizophrenia has the same risk factors as the general population, plus the presence of positive symptoms, poor awareness of the disease and poor treatment compliance (49-51). It has been postulated that patients with schizophrenia who took their medication were no more violent than the general population (49). Thus, it might be accepted that violence is an indirect predictor for nonadherence in patients with schizophrenia. We suggest that LAI antipsychotics might be considered for schizophrenic patients with repetitive violent behaviour even if they are in the early stage of their illness.

The worldwide lifetime expectancy for developing schizophrenia in the general population is around 1% but is much higher in the relatives of people with schizophrenia (3). In our study, the percentage of family history of schizophrenia is higher in patients with use of LAI antipsychotics and was also found to be a significant predictor of usage of LAI antipsychotics. We cannot completely explain this result. One possible explanation is that having a first degree relative with schizophrenia may cause poor adherence. Thus, we suggest that this finding is quite interesting and schizophrenic patients with a family history might be considered as candidates for initiating LAI antipsychotics for nonadherence.

Our study has several limitations. Because our study design is retrospective and the scales for adherence were not administered routinely in daily clinical practice, we could not present any numerical data for adherence; we think that this was the major limitation of our study. The sample size of our study is small for a retrospective study; that is another major limitation. We could not give data about the subtypes of schizophrenia and dosages and classes of oral antipsychotics; these were our other limitations. The attitude of prescribers might have a great impact on the initiation of LAI antipsychotics in schizophrenic patients. We did not investigate the prescribers' attitudes for initiating LAI antipsychotics because it was not an aim of the present study. However, it might be also considered as a limitation.

CONCLUSION

We suggest that LAI antipsychotics are an important part of the treatment of patients with schizophrenia. Relapses due to nonadherence can be overcome by LAI antipsychotics. We conclude that earlier onset of illness, history of violent and suicidal behavior and family history of schizophrenia are predictors for the use of LAI antipsychotics. In addition to the familiar causes of nonadherence, the specific predictors of use of LAI antipsychotics should be determined carefully and patients should be initiated on treatment with LAI antipsychotics even if they are in an early phase of the illness.

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