Long-Acting Typical and Atypical Antipsychotics in Treatment of Schizophrenia: A Retrospective Comparison

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ÖZET:

Şizofreni tedavisinde uzun etkili tipik ve atipik antipsikotikler: Geriye dönük bir karşılaştırma

Amaç: Uzun etkili antipsikotik ilaçlar şizofreninin uzun süreli tedavisinde, tedavi uyumsuzluğu nedeniyle kötü gidişi düzeltmek için geliştirilmişlerdir. Şizofreni hastalarının yaklaşık %15'i tedavilerini bu depo ilaçlarla devam ettirmektedirler. Tipik ve atipik uzun etkili ilaçların çeşitli özelliklerini araştıran birçok çalışma yapılmıştır. Bununla beraber, bu iki tür ilacın ileriye veya geriye dönük birebir karşılaştırmasıyla ilgili yeterli çalışma yoktur. Biz bu çalışmada şizofrenide tipik ve atipik uzun etkili antipsikotikleri kullanan hastaları sosyodemografik, klinik ve tedavi özellikleri açısından geriye dönük olarak karşılaştırmayı amaçladık.

Yöntem: Çalışma Gaziantep Üniversitesi Tıp Fakültesi Psikiyatri Anabilim Dalı Psikotik Bozukluklar Birimi'nde takip edilen DSM-IV'e göre 207 şizofreni ve 13 şizoaffektif bozukluk hastası içinden uzun etkili antipsikotik kullanmış veya halen kullanmakta olan toplam 68 hasta ile yapılmıştır. Bunlardan 46 hasta tipik depo (TD) (flupentiksol dekanoat: 28, zuklopentiksol dekanoat: 15, flufenazin dekanoat: 3) ve 22 hasta ise uzun etkili risperidon (UER) kullanmış veya halen kullanıyor idi. Bu iki grup ilacı kullanan hastaların tıbbi dosyaları geriye dönük olarak incelenmiş ve karşılaştırılmıştır.

Bulgular: Bu uzun etkili ilaçların başlanma nedeni hemen tüm hastalar için oral tedaviye uyumsuzluk idi. Tedavide kalma süresi TD ve UER için sırasıyla 20.43±29.85 ve 15.19±8.12 ay idi (t=2.25, df=66, p=0.02). Bununla beraber, TD kullananların %58.7'si ve UER kullananların ise %90.9'u halen mevcut tedavilerine devam etmekteydiler (χ2=5.206, df=1, p=0.02). Birlikte diğer psikotrop ilaçlarının kullanımı yaygındı ve en sık birlikte kullanılan ilaçlar her iki grup için de özellikle atipikler olarak oral antipsikotiklerdi. TD grubundaki PANNS negatif alt ölçek puanı hariç, her iki grupta da PANNS ve KGİ-belirti şiddeti puanlarında belirgin düşme olduğu görüldü. TD grubundaki PANNS negatif alt ölçek puanındaki düşme istatistiksel olarak anlamlı değildi. Bununla beraber TDs ve UER grupları karşılaştırıldıklarında PANNS negatif alt ölçek puanı da dahil iki grup arasında istatistiksel olarak fark bulunamadı. UER grubunda daha az yan etki vardı.

Tartışma: Şizofrenide oral antipsikotiklere uyumsuzluk ve dolayısı ile kötü seyir uzun etkili ilaçların kullanılması ile önlenebilir gibi görünmektedir. Bu çalışma, her iki grup arasında hastalık belirtilerini iyileştirme açısından anlamlı bir fark olmadığını göstermiştir. Tedavide kalma açısından TD ilaçlar, buna karşın halen aynı tedaviye devam ediyor olma ve yan etki açısından UER üstündür.

Anahtar sözcükler: Şizofreni, depo antipsikotik, uzun etkili risperidon

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ABSTRACT:

Long-acting typical and atypical antipsychotics in treatment of schizophrenia: A retrospective comparison

Objective: Long-acting antipsychotics were introduced to improve therapeutic outcomes in patients with schizophrenia experiencing sub-optimal improvement due to lack of or partial adherence to long-term treatment. Approximately 15% of schizophrenia patients in maintenance antipsychotic treatment receive depot preparations. Many studies investigated characteristics of long-acting typical and atypical antipsychotics. However, so far there has been a dearth of prospective and retrospective comparison studies of typical and atypical depots. Therefore we retrospectively compared typical and atypical long-acting injectable antipsychotics regarding socio-demographic, clinical, and treatment characteristics of patients with schizophrenia in the present study.

Method: This study was conducted at the Psychotic Disorders Unit of Gaziantep University, School of Medicine, Department of Psychiatry. We reviewed the charts of all 220 outpatients diagnosed with schizophrenia (n=207) or schizoaffective disorder (n=13) according to DSM-IV. Sixty-eight patients from this population, had used or were still using long-acting antipsychotics. Forty-six of 68 patients had used or were using typical depots (TD) (flupenthixol decanoate; 28, zuclopenthixol decanoate; 15, fluphenazine decanoate; 3) and 22 of them had used or were still using long-acting risperidone (LAR). The medical charts for these two groups were reviewed and the findings were compared.

Results: The reason for initiating long acting antipsychotics was non-adherence to oral antipsychotics in almost all patients. The average duration of staying on treatment was 20.43±29.85 and 15.19±8.12 months for TD and LAR groups, respectively (t=2.25, df=66, p=0.02). 58.7% of TD and 90.9% of LAR patients were still using these drugs (χ2=5.206, df=1, p=0.02). Concomitant use of other psychotropic drugs was very common. The most co-prescribed drugs were oral antipsychotics especially atypicals in both groups. Significant decreases were found in both TD and LAR groups with respect to PANNS and CGI-symptom severity scores, except in PANNS negative subscale score in TD group, in which decrease wasn't statistically significant. Nevertheless no statistically significant difference was detected when CGI-S and PANNS scores including PANNS negative subscale scores of TD and LAR groups were compared. The LAR patients had fewer adverse effects than TD patients as a group.

Discussion: Poor therapeutic outcome because of non-adherence to oral antipsychotics could be improved with use of long-acting antipsychotics in schizophrenia. In our study there was no significant difference between TD and LAR treatments in symptom improvement based on PANNS and CGI. TDs were superior to LAR regarding duration of treatment, but LAR was superior in terms of duration of staying in the same treatment and causing fewer adverse effects.

Key words: Schizophrenia, depot antipsychotic, long-acting risperidone

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INTRODUCTION

Non-adherence to antipsychotic medications is a leading source of preventable morbidity in the treatment of schizophrenia (1). Approximately one-third of patients with schizophrenia are non-compliant with their prescribed medications (2). These patients are at increased risk of symptom exacerbation (3) and inpatient readmission (4).

Conventional/typical depot (TD) antipsychotics were introduced in 1960s to improve therapeutic outcomes in patients with schizophrenia experiencing sub-optimal outcomes due to lack of or partial compliance with long-term treatment (5). Long-acting risperidone (LAR) was introduced in 2003 and it has a different pharmacokinetic characteristic from TDs (6). The advantages of long-acting formulations are not limited to guaranteed medication delivery and simplified administration, but also include increased stability and predictability of plasma levels, reduced likelihood of rapid symptom recurrence following missed doses, and improved treatment team contact to support psychosocial interventions, all enhancing the potential to maintain clinical remission in long-term schizophrenia treatment (7-9). Approximately 15% of schizophrenia patients in maintenance antipsychotic treatment receive depot preparations (10,11). With respect to relapse and time-in-hospital, studies have shown a significant benefit of long-acting antipsychotics compared to short-acting oral medications (12,13). Clinical research (14,15) and expert opinion (16) support use of long-acting antipsychotic medications as maintenance treatment for patients with a history of medication non-adherence. However, in one recent study, only 29.9% of schizophrenia patients with a recent history of antipsychotic non-adherence were prescribed a long-acting injection antipsychotic medication (2). Psychiatrists tend to prefer long-acting injection medications in addition to poor compliance, for patients with persistent psychotic symptoms (17,18) and substance abuse problems (19). Many patients prefer depot injections to oral antipsychotic agents because of their convenience (20).

Four antipsychotic medications are currently available in Turkey as long-acting injections. The typicals, flupenthixol decanoate, zuclopenthixol decanoate, fluphenazine decanoate, have been used for long time and atypical long-acting risperidone (LAR) has been available since 2004. All these drugs are included in government sponsored health insurance and reimbursement formulary. Hence most schizophrenia patients could get them if prescribed by their physicians.

Oral atypical antipsychotics are associated with better efficacy (21,22), lower rates of relapse (23), and fewer movement disorders (24,25) than typical oral or depot antipsychotics. Patients who were switched from a TD antipsychotic to oral risperidone have experienced significant reductions in psychotic symptoms and improved ratings for movement disorders (26,27).

Many studies investigated characteristics of long-acting typical or atypical antipsychotics, but we were able to find only one prospective study comparing typical and atypical depot antipsychotics. Rubio et al. compared the efficacy of LAR and zuclopenthixol decanoate in a prospective design but they included only schizophrenia patients with substance abuse co-morbidity (28). Several studies reported switching to LAR from TDs (29-31). Olfson et al. compared typical and atypical long-acting antipsychotics retrospectively by analyzing administrative data from California Medicaid (Medi-Cal) beneficiaries with schizophrenia who were initiated fluphenazine decanoate (FD), haloperidol decanoate (HD), or LAR treatment. The included patients were required to be continuously enrolled in Medi-Cal for 180 days before and 180 days after the start of the new episode of long-acting antipsychotic therapy. Authors reported several limitations of the study including lack of data regarding clinical efficacy, medication tolerability, and adverse effects. Also LAR was approved by the Food and Drug Administration (FDA) during the study period, as a result, their data provided information on LAR early in its market cycle and there were reimbursement problems. Their results might have underestimated the duration of treatment episodes that were initiated during an inpatient stay. The post treatment follow-up involved a small number of patients over a short time period and the results might not be extended to the patients who were not covered by the Medicaid program (32).

The goal of our study was to compare TDs and LAR regarding effectiveness, adverse effects, period of staying on treatment, and other clinical features retrospectively in schizophrenia and schizoaffective patients.

METHOD

Patients

The medical records of all schizophrenia and schizoaffective disorder patients, who were treated and followed between June 1, 2000 and June 1, 2008 at The Gaziantep University Hospital, Department of Psychiatry, Psychotic Disorders Unit, were retrospectively reviewed. A total of 207 schizophrenia (men;58.4%, n=121 and women; 41.6%, n=86) and 13 schizoaffective (men; 76.9%, n=10, women;13.1%, n=3) patients were diagnosed and treated in the mentioned period. Out of 220 records, 68 showed depot antipsychotic use. The data were ascertained from these 68 medical charts. Forty six patients were treated with TD (flupenthixol decanoate; 28, zuclopenthixol decanoate; 15, fluphenazine decanoate; 3) and 22 were prescribed LAR.

Inclusion and Exclusion Criteria

All schizophrenia and schizoaffective disorder patients, who were prescribed long-acting antipsychotics included in the study. There were no age limits on the study population and all patients were 18 or older. Presence of co-morbid psychiatric and medical conditions was not in exclusion criteria either.

Distribution of schizophrenia subtypes for TDs using patients (n=46) were as follows: 10 paranoid, 2 disorganized, 1 catatonic, 2 residual, 26 undifferentiated. Five patients in TD group had schizoaffective disorder. Among 22 LAR using patients, there were 8 paranoid, 2 disorganized, 1 residual, 9 undifferentiated schizophrenia subtypes and 2 schizoaffective disorder patients. The study was in accordance with the Declaration of Helsinki and was approved by the institutional ethic committee. TDs and LAR using patients were compared based on sociodemographic, clinical, and treatment characteristics.

Psychotic Disorders Unit

At the Psychotic Disorders Unit at Gaziantep University Department of Psychiatry the patients with schizophrenia and other psychotic disorders have been evaluated and treated since year 2000. A research assistant trained in psychiatric rating scales evaluates patients and completes Psychotic Disorders Monitoring Form, which include socio-demographic data, height, weight, laboratory tests, PANNS, CGI, and other scales under supervision of an academic faculty member. The data have been charted regularly and kept in the medical records.

Psychiatric Assessment Scales

The severity of symptoms were assessed by the Positive and Negative Syndrome Scale (PANSS) (33), and Clinical Global Impression-Severity Scale (CGI-severity) (34).

PANSS: It measures positive symptoms (7 items), negative symptoms (7 items), and general psychopathology (14 items). In total it consists of 30 items and the symptom severity is scored from 1 to 7 points in each item.

CGI: It assesses a general evaluation of illness severity and the response to the treatment. Clinicians base their rating on how sick a patient is and how much the patient improves compared to all other patients they have seen and baseline, respectively. We used only CGI symptom severity (CGI-S) in this study.

Criteria in Choosing Data from Medical Records

For the patients, who were on depot antipsychotics sometime during the study period, but were not using at the time of review, we used the values just before initiation of depot antipsychotics and the last values prior to stopping depot antipsychotics. For the patients, who have been started and still continuing on depot antipsychotics we recorded the values just before initiation of depot medications and most recent values at the time of the review.

Statistical Analysis

The Statistical Package for Social Sciences (SPSS 13.0, SPSS Inc, Chicago, IL) was used for all statistical analyses. Differences between TD and LAR groups were tested by t-test and Mann–Whitney U-test for normally and non-normally distributed quantitative variables, respectively, and by chi-square test for categorical variables. Normality of quantitative data was checked by

Table 1: Sociodemographic and clinical characteristics of patients

	TDs	LAR	
Male	60.88% (n=28)	81.8% (n=18)	$\chi2$=1.95, df=1, p=0.16
Female	39.2% (n=18)	18.2% (n=4)	
Age	34.11±10.24	34.50±9.08	t=-0.15, df=66, p=0.87
Age of onset of illness	22.76±7.44	26.32±7.78	t=-1.79, df=66, p=0.07
Duration of illness (years)	10.87±7.54	8.27±7.56	t=1.32, df=66, p=0.18
Number of hospitalization	1.69±1.93	1.14±1.13	t=1.16, df=66, p=0.24
Co-morbide psychiatric disorders	19.6% (n=9)	40.9% (n=9)	$\chi2$=3.483, df=1, p=0.062
Co-morbide medical illness	6.6% (n=3)	4.6% (n=1)	$\chi2$=0.118, df=1, p=0.731
ECT history	32.6% (n=15)	31.8% (n=7)	$\chi2$=0.015, df=1, p=0.901
Alcohol-substance use			
No	58.7% (n=27)	63.6% (n=14)	$\chi2$=0.986, df=3, p=0.805
Smoking	37.0% (n=17)	36.4% (n=8)	
Alcohol	4.3% (n=2)	0.0% (n=0)	
Other	0.0% (n=0)	0.0% (n=0)	

TD: Typical Depot, LAR: Long Acting Risperidone

Table 2: Clinical characteristics of patients

	TDs	LAR	
Duration of remaining on treatment (month)	20.43±29.85	15.19±8.12	t=2.25, df=66, p=0.02
Weight gain	15.2% (n=7)	31.9% (n=7)	$\chi2$=2.509, df=1, p=0.113
Reason the discontinuation of oral medication			
No response	6.6% (n=3)	13.6% (n=3)	$\chi2$=1.008, df=2, p=0.604
Refuse treatment	47.8% (n=22)	40.9% (n=9)	
No compliance	45.6% (n=21)	45.5% (n=10)	
Adverse effect	65.2% (n=30)	36.4% (n=8)	$\chi2$=5.44, df=1, p=0.02
Previously depot drug use			
No	80.4% (n=37)	63.6% (n=14)	$\chi2$=3.315, df=2, p=0.191
Typical	17.4% (n=9)	36.4% (n=8)	
LAR	2.2 % (n=1)	0.0% (n=0)	
Drug used with	93.4% (n=43)	95.5% (n=21)	$\chi2$=0.105, df=1, p=0.746
Oral antipsychotic with			
Typical	21.7% (n=10)	9.1% (n=2)	$\chi2$=2.320, df=1, p=0.128
Atypical	54.3% (n=25)	77.2% (n=17)	
Anticholinergic	36.6% n=17)	18.2% (n=4)	$\chi2$=2.458, df=1 p=0.117
Anxiolitic	19.6% (n=9)	13.6% (n=3)	$\chi2$=0.360, df=1, p=0.549
Antidepressants	4.3% (n=2)	22.7% (n=5	$\chi2$=5.444, df=1, p=0.020
Mood stabilizator	10.9% (n=5)	0.0% (0)	$\chi2$=2.581, df=1, p=0.108
Treatment condition			
Continuing	58.7% (n=27)	90.9% (n=20)	$\chi2$=5.206, df=1, p=0.023
Discontinued	41.3% (n=19)	9.1% (n=2)	
Reason of discontinuation			
Adverse effect	23.9% (n=11)	4.5% (n=1)	$\chi2$=10.831, df=2, p=0.004
No response	17.4% (n=8)	0.0% (n=0)	
Other	0.0% (n=0)	4.5% (n=1)	

TD: Typical Depot, LAR: Long Acting Risperidone

using the Kolmogorov–Smirnov one-sample test. According to the results of this test, appropriate parametric tests were used for analysis of quantitative variables. The 2-tailed significance level was set at $p<0.05$.

RESULTS

Age, gender, age of onset of the disorder, number of hospitalizations, and duration of illness of patients were displayed in Table 1.

Mean duration of treatment was 20.43±29.85 months for TDs and 15.19±8.12 months for LAR (t=2.25, df=66, p=0.02). However, 58.7% of initial TD patients have remained on TDs and 90.9% of initial LAR patients have stayed on LAR ($\chi2$=5.206, df=1, p=0.02) (Table 2).

Usage of long-acting medications in men was more

Table 3: Decreased scores of PANNS and CGI-severity for typical depots and long acting risperidone

	TDs	LAR
	Mean score±SD	Mean score±SD
PANSS -Total-First	70.21±19.53	78.35±20.18
PANNS-Total-Last	48.34±17.25	45.75±15.95
Decrease ratio	31.14%	41.60%
Statistic	Z= -3.56, p<0.001	t=8.50, df=88, p<0.001
PANSS-Positive-First	22.43±11.96	22.04±9.49
PANSS-Positive-Last	10.86±6.48	12.33±6.77
Decrease ratio	51.58%	44.05%
Statistic	Z= -4.15, p<0.001	t=5.59, df=88, p<0.001
PANSS-Negative-First	17.39±10.04	20.28±9.77
PANSS-Negative-Last	13.43±6.57	12.02±6.47
Decrease ratio	22.77%	40.73%
Statistic	Z= -1.57, p=0.116	t=4.73, df=88, p<0.001
PANSS-GP-First	30.82±8.58	35.46±12.78
PANSS-GP-Last	24.04±8.13	21.40±7.11
Decrease ratio	21.99%	39.65%
Statistic	Z= -2.89, p=0.004	t=6.45, df=88, p<0.001
CGI-Severity-First	5.13±1.17	5.46±1.03
CGI-Severity-Last	2.91±1.64	2.71±1.39
Decrease ratio	43.27%	50.36%
Statistic	Z= -4.24, p<0.001	t=10.65, df=88, ,p<0.001

PANSS: Positive and Negative Syndrome Scale, CGI: Clinical Global Impression, SD: Standart Deviation, GP:General psychopathology, TD: Typical Depot, LAR: Long Acting Risperidone

common than that of women; 67.64% (n=46) for men and 32.36% (n=22) for women ($\chi 2$=15.54, df=1, p=0.001). However, the percentage of men admitted Psychotic Disorder Clinic (59.5%, n=121) was higher than that of women (40.5%, n=86) ($\chi 2$=11.02, df=1, p=0.001). Gender distribution for TDs and LAR was given in Table 1.

The main reason for prescription of the long-acting drugs was non-adherence to oral antipsychotics for almost all patients. Co-prescribing other psychotropic drugs was very common and the most co-prescribed drugs were oral antipsychotics, especially atypicals for both groups (Table 2). The antidepressant usage was more common in LAR group than TD group ($\chi 2$=5.444, df=1, p=0.02). Fewer adverse effects were observed in LAR than TD group ($\chi 2$=5.44, df=1, p=0.02) (Table 2).

Eighteen of 68 patients had a history of another treatment episode with long-acting medications in the past. Nine of 46 TD patients reported that they had used another TD and only one of the 9 had used LAR previously. In LAR group (n=22); 8 patients had a history of using TD antipsychotics in the past.

The reasons for discontinuation of long-acting treatment with TDs were adverse effects (23.9%) and inadequate response (17.4%). In LAR group one patient discontinued the LAR treatment due to adverse effect and another patient discontinued for an unidentified reason. No patient discontinued LAR treatment because of inadequate response ($\chi 2$=10.831, df=2, p=0.004). The above mentioned findings were summarized in Table 2.

Changes in PANNS and CGI-severity scores for TD and LAR groups were shown in Table 3. There were statistically significant decrease in PANNS total and subscale scores in TD and LAR groups, except in PANNS negative subscale scores of TD group. In other words, the decrease in PANNS negative subscale scores of TD patients was not statistically significant. When compared two groups; there were no statistically significant difference among all scores, including PANNS negative subscale scores (p>0.05).

DISCUSSION

Long acting antipsychotics were initiated because of non-adherence to oral antipsychotics and refusal of treatment with oral antipsychotics in both TD and LAR group patients in this study. Previous research had linked medication non-adherence to initiation of depots (35,36). In addition to medication non-adherence, presence of

substance abuse disorder was reported as a reason for initiation of treatment with depots (1,37). Alcohol and substance abuse were not common in our sample.

Adherence to antipsychotic medications is an important factor in successful treatment of schizophrenia. It has been suggested that long acting medications increased adherence and continuation of treatment (13-15,38,39). In randomized controlled trials with TDs, discontinuation rates have ranged from as low as 12.5% over 36 weeks (40) and 19% over 24 weeks (41) to 50.5% at 52 weeks (42). One should keep in mind that randomized-controlled trials involve carefully selected subjects who consent to extended assessments and care under controlled conditions. Therefore in randomized controlled trials significantly lower discontinuation rates are to be anticipated compared to usual practice conditions. Taylor et al. reported that in one prospective study of 100 patients who started LAR, 51% discontinued during the first 6 months. The most common reasons for discontinuation were that the medication was considered ineffective by the prescribing physician (47%), refused by the patient (35%), or not tolerated by the patient (18%) (43). Olfson et al. compared initiating fluphenazine decanoate (FD), haloperidol decanoate (HD), or LAR due to poor compliance with oral treatment. In their study, the mean duration of depot treatment episodes was 58.3 days for FD, 71.7 days for HD, and 60.6 days for LAR. Authors reported the study had several important limitations (32). The duration of staying on the medication and treatment period were higher in our sample compared to previous studies. Surprisingly, in our sample patients who used TDs had stayed on treatment longer than patients who had been on LAR. This was not an expected finding. One possible explanation for this would be the availability of TDs for many more years compared to that of LAR, which became available in 2004. In fact if our study had been conducted later this difference would disappear, and eventually LAR duration would become longer. Because, 90.9% of LAR patients and only 58.7% of TD patients had been continuing their medications. Significantly greater proportion of initial LAR prescribed patients were still on LAR, which might have been related to the fewer adverse effects in LAR using group.

In our study population men used long acting drugs more frequently than women. However, more male patients were admitted to the Psychotic Disorders Unit than females, which might explain higher number of males using long acting antipsychotics. Some previous studies reported more men than women getting depots (44,45), yet some others found no gender difference in the use of depots (17,46).

In our sample, the PANNS total and subscale and CGI-severity scores decreased significantly with TD or LAR treatment, except the decrease in PANSS negative subscale scores in patients treated with TD failed to reach statistical significance. Rubio et al. enrolled 115 schizophrenia subjects with co-morbid substance abuse disorder to an open-label, randomized, and controlled, 6-month follow-up study to compare the efficacy of LAR and zuclopenthixol depot. They found LAR was more effective in improving substance abuse and schizophrenia symptoms, especially negative symptoms (28). Lasser et al. reported that in a multi-center, open-label study of 725 stable schizophrenics on TDs with mild or residual symptoms, there was a significant improvement in psychiatric and movement disorder symptomatology following 1-year treatment with LAR. The greatest improvement occurred in negative symptoms (29). Also, Turner et al. studied schizophrenia patients who were symptomatically stable on TDs and were switched to LAR in an open-label, multicentre, 12-week trial. The severity of movement disorders decreased, the PANSS total and subscale scores and CGI severity scale scores were significantly reduced during LAR treatment. Moreover 48% of the patients showed 20% decrease in PANSS scores at the endpoint (30). Marinis et al. found similar results in schizophrenia patients unsatisfactorily treated with oral or depot conventional antipsychotics after switching to LAR. The patients showed improvement in symptom control, medication tolerability, and patient satisfaction after switching to LAR (31).

In our study significant decrease in negative symptom subscale of PANNS in LAR but not in TD group could be explained by co-prescription of more antidepressants in LAR using patients. It has been speculated in the literature that antidepressants might possess some beneficial impact on negative symptoms (47). However Rubio et al. and Lasser et al. found a decrease in the negative symptoms after the switch from TDs to LAR despite there was no change in antidepressants. Additionally LAR itself as an atypical antipsychotic depot drug might have caused the decrease in negative symptoms. It's generally accepted

that atypicals are more effective for treating negative symptoms than typicals (21,22).

Fewer adverse effects in LAR group would be an expected result, as it's well known that the atypical drugs cause milder or less frequent adverse effects than typicals (24,25). The studies of Lasser et al. and Turner et al. have shown that switching from TDs to LAR resulted in a decrease in extrapyramidal and movement disorders (28,29).

Concomitant use of other psychotropic drugs with depot antipsychotics was common in the present study. The most commonly prescribed drugs were oral antipsychotics especially atypicals in both groups. Previous studies have determined that prescriptions of oral antipsychotics and other psychotropic medications, especially mood stabilizers and antidepressants, were also common with depots (32). In a large observational study of outpatients with schizophrenia, a substantial proportion of patients received anxiolytics/hypnotics (29.8%) at the time of starting TDs, but relatively few received antidepressants (9.5%) or mood stabilizers (6.8%) (47). A literature review found no convincing evidence to support or disprove the efficacy of antidepressant treatment for depressive symptoms in adults with schizophrenia (48). Evidence for an augmenting effect of mood stabilizers in the antipsychotic treatment of schizophrenia was similarly mixed (49,50). Given that concurrent medication administration increases the risk of adverse drug reactions (51) efforts to reduce psychotropic co-prescribing might help improve tolerability and adherence to medications (52). In Olfson et al.'s study, treatment with mood stabilizers was significantly less common among patients during treatment with LAR than during treatment with TDs (32). They wrote that this difference might reflect inherent mood stabilizing properties of risperidone (53,54) or less mood instability in patients selected for LAR therapy.

We should emphasize that the patients in this study were put on depot antipsychotics primarily because of non-adherence to oral medications and they were mostly treatment resistant patients with poor insight. In addition to high rate of adherence to treatment with long acting agents, oral medication use improved even in patients with inadequate response to depot antipsychotics. This was an important factor and impacted the outcome positively.

The limitations of the study include retrospective design, lack of randomization, mining the data from medical records, and relatively few cases. Another limitation was use of other psychotropic drugs together with depots, which might have interfered with the results.

In conclusion, by using both TDs and LAR a significant improvement in symptoms of schizophrenia and schizoaffective disorder was achieved. There was not a significant difference between TDs and LAR groups. TDs were superior regarding the duration of the treatment, but LAR was superior based on fewer adverse effects and staying on the initial long acting antipsychotic. Non-adherence to oral medications could be significantly improved by using depot antipsychotics.

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