# The Effectiveness of Risperidone Long-acting Injection in Oral Antipsychotic Non-Adherent Patients with Schizophrenia: A Retrospective Study

Cengiz Akkaya[1], Aslı Sarandol[1], Vahap Ozan Kotan[2], Şengül Cangür[3], Ayşegül Aydın[2], Selçuk Kırlı[1]

**ÖZET:**

## Oral antipsikotik ilaç kullanımına uyumsuz şizofreni hastalarında uzun-etkili risperidon enjeksiyon tedavisinin etkinliğinin retrospektif olarak incelenmesi

**Amaç:** Bu çalışmada, oral antipsikotik ilaç kullanımına uyum göstermeyen şizofreni hastalarında uzun-etkili risperidon enjeksiyon tedavisine uyum ve tedavi etkinliğinin belirlenmesi amaçlanmıştır.
**Yöntem:** Mevcut oral antipsikotik tedavisine tam veya kısmi uyumsuzluğa bağlı relaps nedeniyle kliniğe yatırılmış olan 30 şizofreni hastası (12 erkek, ortalama yaş=36.1±9.5 yıl) retrospektif olarak incelenmiştir. Kısa Psikiyatrik Değerlendirme Ölçeği (BPRS), Pozitif Semptomları Değerlendirme Ölçeği (SAPS), Negatif Semptomları Değerlendirme Ölçeği (SANS) ve Simpson-Angus Ölçeği (SAS) değerlendirme amacıyla kullanılmış ölçeklerdir. Ortalama izlem süresi 236.1±121.0 (28–336) gündü. On bir hastada (%36.7) uzun etkili risperidon enjeksiyon tedavisiyle birlikte başlanan ek oral antipsikotik tedavi üçüncü risperidon enjeksiyonunu takiben kesilebilmişken (No-OAT grubu), 19 hastada (%63.3) ek oral antipsikotik tedaviye devam edildi (OAT grubu).
**Bulgular:** Tüm hastalarda tedaviyi bırakma oranı %46.7 iken, bu oran OAT grubunda %45.5 ve No-OAT grubunda %47.4 (P=0.781) idi. Ortalama BPRS, SAPS, SANS ve SAS skorları izlem sürecinde belirgin olarak azaldı. Başlangıca göre BPRS skorlarındaki yüzdelik değişim açısından No-OAT grubunda 3, 6, 9, 10, 11, 12, 13, 15 ve 17. vizitlerde OAT grubuna göre daha fazla azalma olurken, SANS skorlarında No-OAT grubunda OAT grubuna göre 6 ve 10. vizitlerde daha fazla azalma oldu (Her ikisi için P<0.05). Tüm grup için ortalama uzun etkili risperidon dozu 46.9±6.7 mg idi, OAT ve No-OAT grupları ortalama doz açısından farklılık göstermedi (sırasıyla 49±9.8 ve 44±9.8, P = 0.292).
**Tartışma:** Şizofreni hastalarının tedavisinde uzun etkili risperidon enjeksiyon tedavisi günlük klinik pratikte etkindir, ancak ağır ve kronik olgularda sıklıkla oral antipsikotik tedavi ile kombinasyona gerek duyulmaktadır. Ağır ve kronik şizofreni hastalarında uzun etkili risperidon tedavisinin tek başına etkinlik veya tedavi uyumu açısından herhangi bir üstünlüğü mevcut değildir.

**Anahtar sözcükler:** Uzun-etkili risperidon, şizofreni, ilaç uyumsuzluğu

**Klinik Psikofarmakoloji Bülteni 2009;19:255-262**

**ABSTRACT:**

## The effectiveness of risperidone long-acting injection in oral antipsychotic non-adherent patients with schizophrenia: A retrospective study

**Objective:** To determine effectiveness and adherence to risperidone long-acting injection (RLAI) in schizophrenic patients who were non-adherent to oral antipsychotic treatment.
**Method:** We retrospectively checked over 30 schizophrenic patients (12 males, mean age=36.1±9.5 years) who were hospitalized for relapse of their disorder due to non-adherence to oral antipsychotic drugs. Assessment tools were Brief Psychiatric Rating Scale (BPRS), Scale for Assessment of Positive Symptoms (SAPS), Scale for Assessment of Negative Symptoms (SANS) and Simpson-Angus Scale (SAS). Mean follow-up was 236.1±121.0 (28–336) days. For 11 patients (36.7%), oral add-on antipsychotic treatment (OAT) was discontinued after the 3rd injection of risperidone (No-OAT group); for 19 (63.3%), it was continued (OAT group).
**Results:** The proportion who discontinued medications was 46.7% overall; it was 45.5% for OAT and 47.4% for No-OAT groups (P=0.781). Mean BPRS, SAPS, SANS, and SAS scores decreased significantly from baseline during follow-up. The No-OAT group had a greater decrease (percent change in BPRS from baseline) than the OAT group at the 3rd, 6th, 9th, 10th, 11th, 12th, 13th, 15th and 17th visits; for SANS, it was greater at the 6th and 10th visits (P<0.05 for both). The mean dose of RLAI was 46.9±6.7 mg, and this was similar for OAT and No-OAT groups (49±9.8 and 44±9.8, respectively, P = 0.292).
**Conclusions:** In daily clinical practice, long-acting injectable risperidone is effective in schizophrenic patients, but oral antipsychotic drugs are frequently needed to be used together with RLAI in severe and chronic cases. RLAI had no additional effectiveness or adherence advantage in this study for patients with severe forms of schizophrenia.

**Key words:** Long-acting risperidone, schizophrenia, non-compliance

**Bulletin of Clinical Psychopharmacology 2009;19:255-262**

Uludag University, Medical Faculty, MD, Assistant Professor[1], MD[2], Department of Psychiatry and MSc[2], Department of Biostatistics, Bursa-Türkiye

Yazışma Adresi / *Address reprint requests to:* Dr. Cengiz Akkaya, Uludağ Universitesi Tıp Fakültesi, Psikiyatri Anabilim Dalı 16059 Gorukle, Bursa-Türkiye

Telefon / *Phone*: +90-224-295-1821

Faks / *Fax*: +90-224-442-8597

Elektronik posta adresi / *E-mail address:* cakkaya@uludag.edu.tr

Kabul tarihi / *Date of acceptance:* 26 Haziran 2009 / June 26, 2008

**Bağıntı beyanı:**
C.A., A.S., V.O.K., S.C., A.A.: yok.
S.K.: Çok sayıda ilaç firmasından bilimsel aktiviteleri karşılığı honorarium kabul etmiştir.

***Declaration of interest:***
C.A., A.S., V.O.K., S.C., A.A.: none.
S.K.: Received honoraria for scientific activities from various pharmaceutical companies.

## INTRODUCTION

Antipsychotic drugs are the mainstay of treatment in schizophrenia, which is a heterogeneous disorder characterized by the presence of positive and negative symptoms and functional impairment (1,2). Since schizophrenia typically requires long-term antipsychotic treatment, discontinuation of treatment is a major problem in the clinical management of the disorder (3). Non-adherence or partial adherence with drug treatment is a common problem which leads to devastating consequences. Poor adherence to treatment often limits the effectiveness of treatment for both typical and atypical antipsychotic drugs (4,5).

It has been suggested that the use of injectable depot antipsychotics decreases the need for daily drug usage and improves patients' adherence to treatment in schizophrenia (6-8). Depot antipsychotics are usually found to be well-tolerated and more efficacious than their oral equivalents (6,9).

Risperidone is the only atypical antipsychotic available as a long-acting injectable preparation (Risperdal® Consta®, Janssen). It combines the advantages of long-acting formulations with those of an atypical agent and provides a new mode of treatment that can improve effectiveness and patient adherence (10). Pharmacokinetic studies have shown that fluctuations in plasma drug levels and peak plasma drug levels are lower with long-acting risperidone than with the oral form, indicating that the new formulation may provide more consistent and predictable plasma drug levels with superior tolerability (11). Clinical trials have shown that long-acting injectable risperidone (RLAI) is well-tolerated and effective for patients with schizophrenia who have been receiving oral antipsychotics (12,13).

In addition to poor adherence to treatment, another important problem encountered during the management of schizophrenia is high dose and multiple drug usage in severe cases (14-19). The frequency of this problem may increase, when clinicians underestimate the level of non-adherence to existing treatment. In clinical practice, clinicians rely on patients' reports of medication compliance and patients usually tend to overestimate their level of compliance (20). As a result, clinicians increase the dose of medication or add new drugs to existing treatment to overcome the ineffectiveness, which is actually a consequence of adherence problems. Therefore, by increasing patient adherence and effectiveness of treatment, RLAI may prevent high dose drug usage and polypharmacy. Accordingly, we hypothesized that RLAI monotherapy has high effectiveness and increased adherence in the treatment of schizophrenia.

In this study, we sought to define the effectiveness as tolerability in terms of neuroleptic-induced parkinsonism, and patient compliance of risperidone long-acting injection as a monotherapy in the treatment of schizophrenia. To verify previous data suggesting long-acting risperidone improves patient adherence, we examined the files of RLAI using schizophrenic patients who were hospitalized due to relapse as a consequence of non-adherence to their existing antipsychotic treatments.

# METHODS

## Study design and patients

This was a naturalistic and retrospective study in which patients' hospital records were analyzed. Schizophrenic patients, whose psychotic symptoms relapsed due to non-adherence or partial adherence to oral antipsychotic treatment were included in the study. Patient adherence was evaluated based on the statements of patients and their care givers. The cause of relapse was accepted as a compliance problem, if patient's psychotic symptoms emerged or increased after non-adherence or partial adherence to the existing antipsychotic treatment. Study patients had been hospitalized in Psychiatry Clinic of Uludag University Medical Faculty between 02.06.2004 and 25.11.2005, and included in RLAI treatment programme during hospitalization. Thirty non-adherent or partially adherent patients hospitalized during this period were enrolled in this study. After discharge, they were followed up at 2 week intervals at psychosis out-patient clinic specialized in the management of psychotic patients. Long-acting risperidone was administered by a nurse under the supervision of a doctor every 2 weeks during hospitalization and follow-up period after discharge. Diagnoses of schizophrenia were made according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) (21) after a semi-structured interview by a psychiatrist, and confirmed by at least another psychiatrist. Since the effective blood level of RLAI is reached only after 4–6 weeks of treatment (11), an oral antipsychotic drug was added during the first 4 weeks of treatment. Risperidone was used in 22 (73.3%) of our study patients as the add-on oral antipsychotic. The other 8 patients received, an antipsychotic that had been reported to be effective in the patient's previous medical history as the add-on oral antipsychotic. For all patients, add-on oral antipsychotic treatment was continued until the third long-acting risperidone injection. Depending on the clinical status of the patient, oral antipsychotic treatment was stopped after the third risperidone injection or continued as a part of the treatment. It was continued for the disturbed patients who had positive symptoms of schizophrenia. Patients were not given mood stabilizers or anxiolytic drugs. According to the use of oral antipsychotic

treatment, study patients were divided into two analysis groups: no oral antipsychotic treatment after third long-acting risperidone injection (No-OAT) group and continuous oral antipsychotic treatment (OAT) group. The day of each long-acting risperidone injection was recorded as a study visit. A total of 25 injections were administered to every patient during the follow-up period of 336 days. Adherence, effectiveness and tolerability of the treatment were evaluated.

This project was approved by the Local Ethics Committee of Uludag University Medical Faculty and conforms to the provisions of the last version of the Declaration of Helsinki. Due to the retrospective and naturalistic design of the study, and the data were extracted from medical records informed consents were not needed. This practice was approved by the Local Ethics Committee.

### Evaluation of effectiveness, tolerability, and adherence

Scales used routinely in our clinic to evaluate patients with schizophrenia were used in this study. These were the Scale for Assessment of Negative Symptoms (SANS) (22,23), the Scale for Assessment of Positive Symptoms (SAPS) (24,25), the Brief Psychiatric Rating Scale (BPRS) (26) for the assessment of effectiveness, and the Simpson-Angus Scale (SAS) (27) for the assessment of extrapyramidal side effects of antipsychotic treatments. All scales were completed by one psychiatrist for all patients. Patients who had all 25 injections and were followed for 336 days in average were considered as treatment adherent patients; patients who dropped-out before completion of the 25$^{th}$ injection were considered as treatment non-adherent patients. The rate of non-adherent patients (rate of discontinuation) was evaluated to assess the effectiveness of the treatment.

### Data Analysis

Statistical analysis was done using SPSS version 13. The study data were summarized with descriptive statistics (e.g. frequency, mean, standard deviation). Kolmogorov-Smirnov and Shapiro-Wilk tests were used to determine whether the data were normally distributed. The homogeneity of study variables (BPRS, SAPS, SANS, and SAS) was evaluated for pre-treatment data. Percent change with time was calculated for study variables. Study groups were compared using a t-test for independent variables for normally distributed data, or using a Mann-Whitney U test for not normally distributed data. The change in study variables with time was analyzed using a Wilcoxon test. For discrete variables, Pearson chi-square and Fisher's exact chi-square tests were used to analyze differences between groups.

## RESULTS

### Basic characteristics of patients

A total of 30 patients (12 males; mean age 36.1±9.5 years) were included in the study. For 11 patients (36.7%), add-on oral antipsychotics were discontinued after the third injection (No-OAT group); for 19 patients (63.6%) it was continued as part of the treatment (OAT group). Oral antipsychotics administered at the time of the first RLAI were quetiapine (n=12), olanzapine (n=6), risperidone

**Table 1: The number of patients for whom RLAI and study scales were administered at each study visit.**

| Injection/study visit | OAT (n=19) | No-OAT (n=11) | Total (n=30) |
|---|---|---|---|
| 1. | 19 | 11 | 30 |
| 2. | 19 | 11 | 30 |
| 3. | 19 | 11 | 30 |
| 4. | 19 | 10 | 29 |
| 5. | 18 | 10 | 28 |
| 6. | 15 | 9 | 24 |
| 7. | 15 | 9 | 24 |
| 8. | 15 | 9 | 24 |
| 9. | 15 | 9 | 24 |
| 10. | 13 | 9 | 22 |
| 11. | 13 | 8 | 21 |
| 12. | 13 | 8 | 21 |
| 13. | 12 | 8 | 20 |
| 14. | 12 | 8 | 20 |
| 15. | 11 | 8 | 19 |
| 16. | 11 | 8 | 19 |
| 17. | 11 | 7 | 18 |
| 18. | 11 | 7 | 18 |
| 19. | 11 | 7 | 18 |
| 20. | 10 | 7 | 17 |
| 21. | 10 | 6 | 16 |
| 22. | 10 | 6 | 16 |
| 23. | 10 | 6 | 16 |
| 24. | 10 | 6 | 16 |
| 25. | 10 | 6 | 16 |

OAT: continuous oral antipsychotic treatment. No-OAT: no oral antipsychotic treatment after third long-acting risperidone injection

**Table 2: Sociodemographics and disease characteristics of patients. Data are presented as mean±standard deviation, median (min–max) or n (%)**

| | OAT (n=19) | No-OAT (n=11) | Total (n=30) | P value |
|---|---|---|---|---|
| Age (years) | 37.7±10.6<br>38 (21–54) | 33.3±6.8<br>32 (23–48) | 36.1±9.5<br>35 (21–54) | 0.225* |
| Sex | | | | |
| Male | 8 (42.1%) | 4 (36.4%) | 12 (40%) | 1.00** |
| Female | 11 (57.9%) | 7 (63.6%) | 18 (60%) | |
| Working status | | | | |
| Working | 2 (10.5%) | 6 (54.5%) | 8 (26.7%) | 0.028** |
| Not working | 17 (89.5%) | 5 (45.5%) | 22 (73.3%) | |
| Marital status | | | | |
| Married | 8 (42.1%) | 2 (18.2%) | 10 (33.3%) | 0.246** |
| Single | 11 (57.9%) | 9 (81.8%) | 20 (66.7%) | |
| Disease duration (years) | 11.1±5.9<br>12 (1–20) | 9.4±5.7<br>7 (4–22) | 10.5±5.8<br>10.5 (1–22) | 0.444* |
| Duration of hospitalization (days) | 53.0±29.1<br>47 (28–158) | 45.5±17.2<br>36 (28–75) | 50.2±25.4<br>44 (28–158) | 0.442* |
| Schizophrenia type | | | | |
| Paranoid (1) | 13 (68.4%) | 8 (72.7%) | 21 (70%) | 0.269 (1-2) ** |
| Disorganized (2) | 4 (21.1%) | 0 | 4 (13.3%) | 0.620 (1-3) ** |
| Undifferentiated (3) | 2 (10.5%) | 3 (27.3%) | 5 (16.7%) | 0.167 (2-3) ** |
| Number of psychiatric hospitalizations | 3.4±2.3<br>3 (1–10) | 3.3±2.0<br>2 (1–6) | 3.3±2.1<br>3 (1–10) | 0.908* |
| Number of relapses | 5.6±4.4<br>4 (1–20) | 3.5±2.1<br>4 (1–7) | 4.9±3.8<br>4 (1–20) | 0.268*** |
| Hospital application | | | | |
| With patients' will | 0 | 3 (27.3%) | 3 (10%) | 0.041** |
| By force | 19 (100%) | 8 (72.7%) | 27 (90%) | |

OAT: continuous oral antipsychotic treatment. No-OAT: no oral antipsychotic treatment after third long-acting risperidone injection

* Independent-samples t test; ** Fisher' exact test; ***Mann-Whitney U test

(n=5), ziprasidone (n=2), haloperidol (n=1), flupenthixol (n=1), zuclopenthixol (n=1) and pimozide (n=1). The following oral antipsychotics were given in addition to risperidone injections: risperidone (n=22), quetiapine (n=3), haloperidol (n=3), olanzapine (n=1) and clozapine (n=1). In the OAT group, oral antipsychotic treatment was continued after the third risperidone injection with risperidone (n=13), quetiapine (n=3), olanzapine (n=1), clozapine (n=1) and haloperidol (n=1). The mean dose of oral risperidone in 13 of the 19 patients in the OAT group was 3.7±1.5 (1–6) mg. The mean dose of RLAI was 46.9±6.7 mg, and this was similar for OAT and No-OAT groups (49±9.8 and 44±9.8, respectively, P = 0.292). The number of patients for whom RLAI was administered at each study visit is shown in Table 1.

Sociodemographic and disease characteristics of patients in No-OAT and OAT groups are summarized in Table 2. Duration of hospitalization was 50.2±25.4 days (53.0±29.1 and 45.5±17.2 for OAT and No-OAT groups, respectively, P = 0.442). All of the (100%) continuous oral antipsychotic treatment (OAT) group patients, but 72.7% of No-OAT group patients had been admitted to the hospital involuntarily. This difference was significant (P= 0.041). The rate of unemployment was higher in the OAT group than in the No-OAT group (P= 0.028).

## Effectiveness and tolerability

Baseline mean SANS score for the OAT group was significantly higher than for the No-OAT group (P= 0.007). Mean BPRS, SAPS, and SANS scores for all patients significantly decreased during follow-up beginning at the 2nd visit (P < 0.01). The decrease in mean SAS score from baseline became significant starting with

the 8th visit (P < 0.05). Mean BPRS scores (Fig. 1) and SAPS scores (Fig. 2) decreased significantly beginning from the 2nd visit for both OAT and No-OAT groups. The decrease from baseline was significant for both variables (P < 0.05). The decrease in mean SANS scores reached statistical significance beginning with the 3rd visit for the OAT group (P < 0.01). For the No-OAT group, it reached statistical significance beginning with the 2nd visit (P < 0.05) (Fig. 3). While the decrease in mean SAS scores was

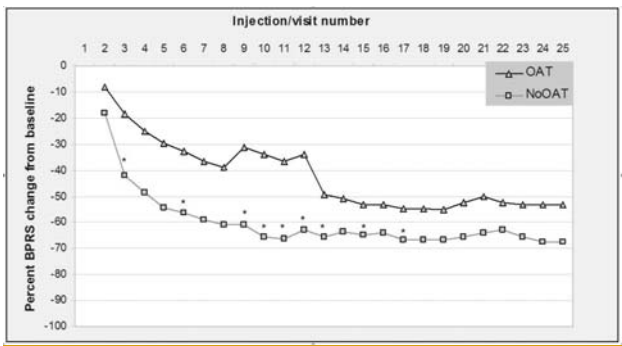


**Figure 1: Percent changes from baseline of BPRS scores.**

* Indicates a statistically significant difference (P < 0.05).

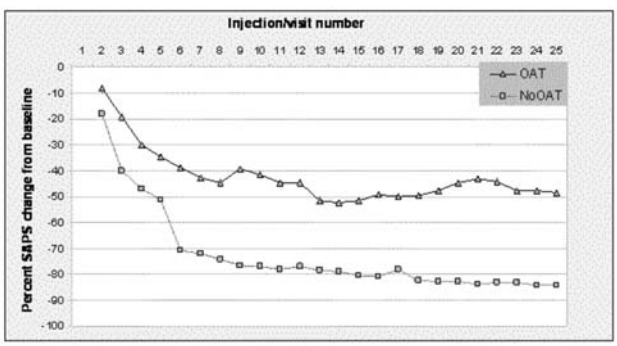


**Figure 2: Percent change from baseline for SAPS scores.**

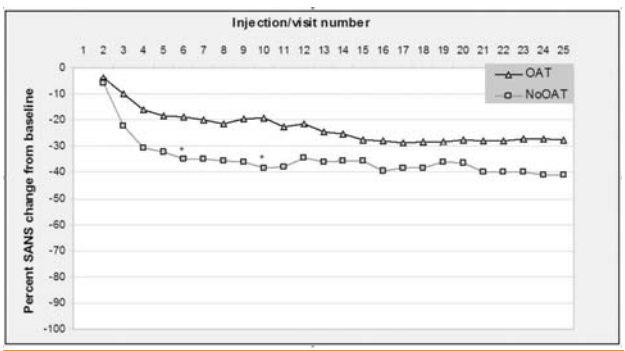


**Figure 3: Percent change from baseline for SANS scores.**

* Indicates a statistically significant difference (P < 0.05).

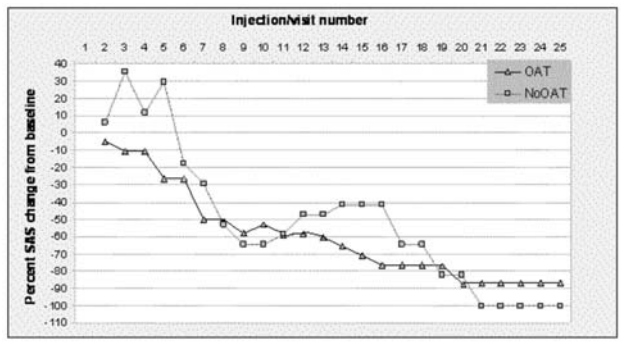


**Figure 4: Percent change from baseline for SAS scores.**

significant beginning with the 7th visit for the OAT group (P < 0.05), it was not significant during follow-up for the No-OAT group (Fig. 4). The comparison of OAT and No-OAT groups in terms of percent changes from baseline of scale scores revealed that the mean percent change from baseline was significantly higher in the No-OAT group than the OAT group at the 3rd, 6th, 9th, 10th, 11th, 12th, 13th, 15th and 17th visits for BPRS scores (P < 0.05) (Fig. 1); it was significantly higher at the 6th and 10th visits for SANS scores (P < 0.05) (Fig. 3).

## Patient adherence

The mean number of risperidone injections was 17.9±8.6 (3–25) for all study patients. It was similar (P = 0.832) for OAT patients (17.5±8.8 (4–25)) and No-OAT patients (18.5±8.7 (3–25))

All 25 injections were administered only to 16 patients (53.3%). The number of patients who did not receive all 25 injections was 5 (45%) in the No-OAT group and 9 (47%) in the OAT group. Of the latter, 10 were lost to follow-up, 1 had injection site pain, 1 had amenorrhea due to hyperprolactinemia, and 2 experienced a lack of efficacy. The mean duration of follow-up (time to all-cause medication discontinuation) was 236.1±121.0 (28–336) days for all patients, 230.6±123.6 (42-336) days for the OAT group, and 245.6±121.8 (28–336) days for the No-OAT group (P= 0.832). For the total group, the rate of discontinuation of medications was 46.7%; it was 45.5% for the OAT group and 47.4% for the No-OAT group (P= 0.781). There was no significant difference between the sociodemographic and clinical characteristics of the 16 patients who had continued the treatment, (n=16) and the drop-outs (n=14).

## DISCUSSION

In this retrospective study, we found that RLAI was effective in daily clinical practice for schizophrenic patients who were hospitalized for relapse of their disorder due to non-adherence or partial adherence to oral antipsychotic drug treatment. But injectable risperidone is frequently used in combination with oral antipsychotics (OAT group), and we found that, as a monotherapy, it has no additional effectiveness or compliance advantages (OAT vs. No-OAT group) for severe cases.

The intramuscular injectable form of risperidone is the first atypical antipsychotic that is long-acting (10). It was suggested that RLAI could extend the benefits of assured medication delivery and improved long-term outcomes for patients with schizophrenia (28). To the best of our knowledge, this is the first study to evaluate the effects of long-acting risperidone on non-adherent or partially adherent patients.

In this study, the OAT group patients had a relatively more severe and chronic form of schizophrenia than No-OAT patients. Baseline mean SANS score for the OAT group was significantly higher than the mean score for the No-OAT group, but the differences between OAT and No-OAT groups in terms of baseline mean BPRS, SAPS, and SAS scores appear to be small and insignificant. The rates of unemployment and admission to the hospital involuntarily were significantly higher for patients in the OAT group. For these patients, their disorder could not be controlled with RLAI monotherapy and add-on antipsychotics were needed. Our findings are similar to an earlier report of the use of antipsychotic co-medication during risperidone injections in which usage as combination was higher among patients with a more severe form of disorder (29).

Although patients in the OAT group received concomitant oral antipsychotics, the number of risperidone injections, all-cause medication discontinuation and injectable risperidone dose were not significantly different between OAT and No-OAT groups. Furthermore, the use of RLAI did not effect either the oral risperidone dose, which can be considered as high (3.7±1.5 mg (range: 1–6 mg) or polypharmacy in patients with severe and chronic forms of the disorder. These findings show that RLAI does not have any additional advantage; it does not increase adherence, not prevent polypharmacy or high dose drug usage in patients with more severe and chronic forms of schizophrenia (OAT group) compared to the No-OAT group.

BPRS, SAPS, SANS and SAS scores decreased after week 2, indicating that the overall antipsychotic treatment applied was effective and safe. Considering that all of the patients treated with injectable risperidone received concomitant oral antipsychotics during the first two weeks, the decrease in scores can not be solely attributed to the effect of injectable risperidone. There was no difference between OAT and No-OAT groups for percent changes of scores except for BPRS and SANS scores where score changes were greater for the No-OAT group than for the OAT group. A patient population with milder forms of schizophrenia in the No-OAT group can explain the greater percent change (decrease from baseline) of BPRS and SANS scores in the No-OAT group compared to the OAT group. Although patients in the OAT group received additional antipsychotics, the change in scores was either similar between the groups or greater in the No-OAT group. Therefore, the treatment of patients with severe and chronic forms of schizophrenia seems problematic even with injectable risperidone in combination with oral antipsychotics.

Studies with long-acting risperidone have usually focused on the effect of drug on stable patients (13,30-32). Our findings suggest that injectable risperidone may not be effective in severe and chronic schizophrenia patients who are non-adherent with oral antipsychotic drug treatment, as much as it is in stable patients.

Our study has the advantage of being conducted under conditions of daily clinical practice. In randomized clinical trials, injectable risperidone has been reported to be well-tolerated and effective for schizophrenic patients who have been receiving oral antipsychotics (12,13,33,34). Although randomized clinical trials are the "gold standard" for establishing efficacy and safety of drugs due to strong internal validity, they are usually conducted under strict protocol and regulatory guidelines. Therefore, they do not reflect the effect of medications under field conditions. This implies that the results obtained from randomized clinical trials often can not be generalized to effects seen when the drug is used in a general clinical practice (35,36). A limited number of studies have been done under conditions of daily clinical practice with long-acting risperidone (37,38).

The major limitations of this study were retrospective

study design, limited sample size, and short duration of treatment and follow-up. As the design of the study was retrospective, the subjective applications of the clinicians, according to their clinical judgement and experience, were inevitable. Although the retrospective study design has low internal validity, it has important advantages, ones that reflect the real-life conditions of daily clinical practices. In addition to the findings of randomized clinical studies, our study demonstrated that RLAI may result in different levels of effectiveness and patient adherence for different levels of severity of schizophrenia in clinical practice. There are limited data in the literature on the use of oral antipsychotics in combination with injectable risperidone (29). Therefore, our study provides important data on the use of injectable risperidone in daily practice. Sample size of this study was small due to difficulty in finding a sufficient number of patients from one center. Failure to find significant differences in group comparison appears largely attributable to the small number of each subgroup, which increases beta (type 2) error. A larger sample size would increase the power of the study and longer treatment and follow-up duration would give additional information on the effect of injectable risperidone, but in daily clinical practice, there may be difficulty in following a large number of patients for long periods. Although the sample size was small, this preliminary study is important for providing a basis for further studies.

We conclude according to findings of this study, although RLAI is effective, and does not induce parkinsonism in patients with schizophrenia, there was no difference between patients with severe and milder form of schizophrenia regarding the drug's effectiveness and patient adherence in daily clinical practice. Furthermore, it is difficult to apply RLAI as monotherapy in clinical practice, particularly in treatment-resistant and severe cases. Although patient adherence is high with RLAI treatment, it does not seem to prevent combination treatment and high-dose drug treatment for severe forms of schizophrenia. Further multi-center studies on large populations are needed to determine the advantages and disadvantages of RLAI monotherapy, especially for severe forms of schizophrenia in real-life clinical settings.

## References:


1. Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, Keefe RS, Davis SM, Davis CE, Lebowitz BD, Severe J, Hsiao JK. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med 2005; 353:1209-1223.
2. Swartz MS, Perkins DO, Stroup TS, McEvoy JP, Nieri JM, Haak DC. Assessing clinical and functional outcomes in the clinical antipsychotic trials of intervention effectiveness (CATIE) schizophrenia trial. Schizophr Bull 2003; 29:33-43.
3. Wahlbeck K, Tuunainen A, Ahokas A, Leucht S. Dropout rates in randomised antipsychotic drug trials. Psychopharmacology (Berl) 2001; 155:230-233.
4. Awad AG, Hogan TP. Subjective response to neuroleptics and the quality of life: Implications for treatment outcome. Acta Psychiatr Scand Suppl 1994; 380:27-32.
5. Dilbaz N, Karamustafalıoğlu O, Oral T, Önder E, Çetin M. Psikiyatri polikliniğine başvuran şizofreni hastalarında tedaviye uyumun ve uyumu etkileyen faktörlerin değerlendirilmesi. Klinik Psikofarmakoloji Bülteni -Bulletin of Clinical Psychopharmacology 2006; 4: 223- 231.
6. Davis JM, Matalon L, Watanabe MD, Blake L, Metalon L. Depot antipsychotic drugs. Place in therapy. Drugs 1994; 47:741-773.
7. Kane JM. Strategies for improving compliance in treatment of schizophrenia by using a long-acting formulation of an antipsychotic: Clinical studies. J Clin Psychiatry 2003; 64 Suppl 16:34-40.
8. Yıldız M, Yüksel AG. Psikotik bozuklukların tedavisinde depo antipsikotik ilaç (flufenazin dekanoat) kullanımı neden hala önemlidir? Klinik sonuç açısından bir inceleme. Klinik Psikofarmakoloji Bülteni - Bulletin of Clinical Psychopharmacology 2006; 16: 98-103.
9. Adams CE, Fenton MK, Quraishi S, David AS. Systematic meta-review of depot antipsychotic drugs for people with schizophrenia. Br J Psychiatry 2001; 179:290-299.
10. Fleischhacker WW, Eerdekens M, Karcher K, Remington G, Llorca PM, Chrzanowski W, Martin S, Gefvert O. Treatment of schizophrenia with long-acting injectable risperidone: a 12-month open-label trial of the first long-acting second-generation antipsychotic. J Clin Psychiatry 2003; 64:1250-1257.
11. Eerdekens M, Van Hove I, Remmerie B, Mannaert E. Pharmacokinetics and tolerability of long-acting risperidone in schizophrenia. Schizophr Res 2004; 70:91-100.
12. Kane JM, Eerdekens M, Lindenmayer JP, Keith SJ, Lesem M, Karcher K. Long-acting injectable risperidone: efficacy and safety of the first long-acting atypical antipsychotic. Am J Psychiatry 2003; 160:1125-1132.
13. van Os J, Bossie CA, Lasser RA. Improvements in stable patients with psychotic disorders switched from oral conventional antipsychotics therapy to long-acting risperidone. Int Clin Psychopharmacol 2004; 19:229-232.
14. Akkaya C, Sarandol A, Cangur S, Kirli S. Retrospective database analysis on the effectiveness of typical and atypical antipsychotic drugs in an outpatient clinic setting. Hum Psychopharmacol 2007; 22:515-528.
15. Paton C, Lelliott P, Harrington M, Okocha C, Sensky T, Duffett R. Patterns of antipsychotic and anticholinergic prescribing for hospital inpatients. J Psychopharmacol 2003; 17:223-229.
16. Schumacher JE, Makela EH, Griffin HR. Multiple antipsychotic medication prescribing patterns. Ann Pharmacother 2003; 37:951-955.

17. Tapp A, Wood AE, Secrest L, Erdmann J, Cubberley L, Kilzieh N. Combination antipsychotic therapy in clinical practice. Psychiatr Serv 2003; 54:55-59.

18. Sarandöl A, Akkaya C, Cangür Ş, Mercan Ş, Pirinççi E, Kırlı S. Ayaktan takip edilen şizofreni hastalarının takip sürelerini etkileyen sosyodemografik, hastalık ve tedaviye ait özellikler. Klinik Psikofarmakoloji Bulteni- Bulletin of Clinical Psychopharmacology 2007; 17: 15-23.

19. Kahiloğulları AK, Örsel S, Sargın AE, Hatıloğlu U, Berber MS, Özbay MH. Changes in Drug Prescription Patterns in Schizophrenia in Five Years. Klinik Psikofarmakoloji Bulteni -Bulletin of Clinical Psychopharmacology 2008; 18: 162-166.

20. Keith SJ, Kane JM. Partial compliance and patient consequences in schizophrenia: Our patients can do better. J Clin Psychiatry 2003; 64:1308-1315.

21. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 4th ed. Washington, DC: American Psychiatric Association; 1994.

22. Andreasen NC. Negative symptoms in schizophrenia. Definition and reliability. Arch Gen Psychiatry 1982; 39:784-788.

23. Erkoc S, Arkonac O, Atakli C. Validity and reliability of Scale for the Assessment of Negative Symptoms (SANS). Dusunen Adam 1991; 4:14-19.

24. Andreasen NC. Scale for the assessment of positive symptoms (SAPS). Iowa City, IA: University of Iowa; 1984.

25. Erkoc S, Arkonac O, Atakli C. Validity and reliability of Scale for the Assessment of Positive Symptoms (SAPS). Dusunen Adam 1991; 4:20-24.

26. Overall J, Gorham D. The brief psychiatric rating scale. Psychol Rep 1962; 10:799-812.

27. Simpson GM, Angus JW. A rating scale for extrapyramidal side effects. Acta Psychiatr Scand Suppl 1970; 212:11-19.

28. Love RC, Conley RJ. Long-acting risperidone injection. Am J Health Syst Pharm 2004; 61:1792-1800.

29. Lasser RA, Bossie CA, Gharabawi GM, Kane JM. Remission in schizophrenia: Results from a 1-year study of long-acting risperidone injection. Schizophr Res 2005; 77:215-227.

30. Chue P, Eerdekens M, Augustyns I, Lachaux B, Molcan P, Eriksson L, Pretorius H, David AS. Comparative efficacy and safety of long-acting risperidone and risperidone oral tablets. Eur Neuropsychopharmacol 2005; 15:111-117.

31. Fleischhacker WW, Rabinowitz J, Kemmler G, Eerdekens M, Mehnert A. Perceived functioning, well-being and psychiatric symptoms in patients with stable schizophrenia treated with long-acting risperidone for 1 year. Br J Psychiatry 2005; 187:131-136.

32. Lasser RA, Bossie CA, Gharabawi GM, Baldessarini RJ. Clinical improvement in 336 stable chronically psychotic patients changed from oral to long-acting risperidone: A 12-month open trial. Int J Neuropsychopharmacol 2005; 8:427-438.

33. Lasser R, Bossie CA, Gharabawi G, Eerdekens M, Nasrallah HA. Efficacy and safety of long-acting risperidone in stable patients with schizoaffective disorder. J Affect Disord 2004; 83:263-275.

34. Simpson GM, Mahmoud RA, Lasser RA, Kujawa M, Bossie CA, Turkoz I, Rodriguez S, Gharabawi GM. A 1-year double-blind study of 2 doses of long-acting risperidone in stable patients with schizophrenia or schizoaffective disorder. J Clin Psychiatry 2006; 67:1194-1203.

35. Lagomasino IT, Dwight-Johnson M, Simpson GM. Psychopharmacology: the need for effectiveness trials to inform evidence-based psychiatric practice. Psychiatr Serv 2005; 56:649-651.

36. McKee M, Britton A, Black N, McPherson K, Sanderson C, Bain C. Methods in health services research. Interpreting the evidence: Choosing between randomised and non-randomised studies. BMJ 1999; 319:312-315.

37. Deslandes P, Thomas A, Faulconbridge G, Davies W. Experience with risperidone long-acting injection: results of a naturalistic observation study. Int J Psychiatr Clin Pract 2007; 11:1-5.

38. Yumru M, Savaş HA, Kokaçya MH, Vırıt O. Şizofreni Tedavisinde Uzun Etkili Risperidon: Geriye Dönük Bir Çalışma. Klinik Psikofarmakoloji Bulteni-Bulletin of Clinical Psychopharmacology 2007; 17: 119-123.