Adverse Effects of Medication and Quality of Life in Patients Receiving Second Generation Antipsychotics: A Comparison of Long Acting Injectable and Oral Therapies

Demet SAĞLAM AYKUT[1], Filiz CİVİL ARSLAN[2], Evrim ÖZKORUMAK[3], Ahmet TİRYAKİ[4], Serdar KARAKULLUKÇU[5]

SUMMARY

Objective: Maintenance treatment with antipsychotic drugs for patients with schizophrenia is highly effective in decreasing the recurrence rate of the disease. In the current study, we aimed to compare long-acting second generation antipsychotic drug injections and oral forms of second generation antipsychotic drugs in terms of their adverse effects and quality of life.

Method: Forty-one patients receiving second generation antipsychotic drugs and 139 patients diagnosed with schizophrenia or schizoaffective disorder were treated with oral second generation antipsychotic drugs and enrolled in the study. All patients were evaluated with Positive and Negative Symptoms Scale (PANNS), extrapyramidal symptom rating scale (ESRS) and UKU, and Quality of Life Enjoyment and Satisfaction questionnaire (Q-LES-Q).

Results: The impact of adverse effects of oral second generation antipsychotic drugs on the daily performance of patients with schizophrenia or schizoaffective disorder was found to be significantly higher than that of the long acting injection antipsychotic drugs. The quality of life of patients receiving long acting second generation antipsychotic drug injection was significantly higher when compared with that of the patients treated with oral second generation antipsychotic drugs.

Conclusion: The results of this study showed that the long-acting second generation antipsychotic injection treatment was superior to second generation oral forms of antipsychotic drugs in terms of adverse effects and measures of quality of life. Further studies with specific a design and the supplementation of larger samples are needed.

Keywords: Schizophrenia, antipsychotic drugs, adverse effect, quality of life

INTRODUCTION

Schizophrenia is a chronic disease where positive and negative symptoms, cognitive ability deficiency, disorganized symptoms, mood symptoms and mood symptoms may be observed throughout the course of the disease (Heckers et al. 2010, Tandon and Carpenter 2012, Bruijnzeel et al. 2014). If left untreated, schizophrenia leads to increased mortality rates, impairing social and occupational functioning, and quality of life (Wunderink et al. 2013).

Studies have shown that in addition to reducing recurrence rates, treatment of schizophrenia with antipsychotic drugs is also effective in improving symptoms of the disease (Leucht et al. 2012). However, the effect of antipsychotic drug therapies on improving cognitive and functional states observed in schizophrenia is limited (Owens 2008). In addition, it is unclear to what extent these therapies improve life expectancy and psychosocial functioning in patients with schizophrenia (Wunderink et al. 2013). Psychotropic drugs may also have anticholinergic, extrapyramidal, hormonal, cardiovascular,

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[1, 2]Assist. Prof., [3, 4]Assoc. Prof., Karadeniz Technical University, School of Medicine, Department of Psychiatry, Trabzon, [5]Research Assistant, Karadeniz Technical University, School of Medicine, Department of Public Health, Trabzon, Turkey.

e-mail: *demetsaglam@hotmail.com*

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and hematological side-effects (Usher 2001). Studies have reported that 80% of patients using antipsychotics experience at least one side-effect (Gray 2001). The lack of compliance with treatment and drug rejection frequently observed in patients with schizophrenia has also been reported to frequently derive from these side-effects (Kanea et al. 1998).

Various degrees of impairment in the quality of life due to the side-effects of drug therapies may be seen in schizophrenia patients. Although the improvement in psychopathology is targeted in the treatment of schizophrenia, an increasing number of clinical studies have emphasized that improvement must also be assessed in terms of changes in quality of life criteria in addition to clinical outcome parameters (Collins et al. 1991, Kanea et al. 1998).

Pharmacological studies have also focused on the effects on quality of life in addition to effects on recurrence of disease and rehospitalization rates of different treatment strategies in the oral or long-acting injection form (Pikney et al. 1991, Kanea et al. 1998). In addition, interventions aimed at improving treatment compliance of patients with psychotic disorders include dose reduction (Diaz et al. 2004, Marinis et al. 2007) and also the use of novel, better-tolerated antipsychotics and long-acting injection forms (Girardi et al. 2010, Kane 2006).

Although the advantages of long-acting antipsychotic injections in patients with chronic psychotic disorder are well known, the percentage of psychotic patients treated with such therapies is only 15.0% worldwide, and there are wide national, regional, and local variations (Rothbard 2003).

The purpose of this study is to investigate whether long-acting antipsychotic drugs used in the treatment of patients with schizophrenia have better results in terms of side-effects and quality of life compared to second generation oral antipsychotic drugs. The role of these drugs in terms of side-effects and patient quality of life will be investigated and discussed.

METHOD

Sampling

Four hundred ninety-two patients diagnosed with schizophrenia and 96 diagnosed with schizoaffective disorder presented to the Ataköy Psychiatric and Nervous Diseases Hospital, Turkey, between May 2013 and May 2014. A total of 197 patients diagnosed with schizophrenia and 32 diagnosed with schizoaffective disorder were identified as using long-acting antipsychotic injections or second generation antipsychotics from psychiatrist and record checks. They were determined not to be in the active phase of the disease through clinician decision and had a PANSS score of less than 70. In addition, they had to attend at least three consecutive appointments and were identified as using their medications on a regular on the basis before they were included and evaluated for the study. Additional psychiatric diseases other than schizophrenia or schizoaffective disorder according to DSM-IV by the application of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I), treatment for any physical disease, previous diagnosis of dementia, a history of physical disease affecting the central nervous system, or head trauma causing loss of consciousness, mental retardation and informed consent, which could not be obtained, constituted the exclusion criteria.

One hundred eighty patients diagnosed with schizophrenia or schizoaffective disorder (bipolar/depression type) on the basis of DSM-IV through the application the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-1) and followed-up with long-acting antipsychotics or second-generation oral antipsychotics were enrolled in the study. Forty-one of these were using long-acting injection second-generation antipsychotics and 139 were using orally administered second-generation antipsychotics. The patients included in the study were not using any psychotropic medications other than antipsychotics. Treatments were initiated and maintained by other physicians. Patients were assessed by the same researcher in terms of data collection for the study.

Patients' sociodemographic characteristics were recorded after their written informed consents were obtained. Positive and Negative Syndrome Scale (PANSS) in order to determine severity of symptoms, the Extrapyramidal Symptoms Rating Scale (ESRS), and the Ugvalg for Kliniske Undersgelser (UKU) rating scale to determine side-effect severity, and the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) were applied respectively to all patients. Clinical interviews and SCID-I, PANSS, ESRS, UKU, and Q-LES-Q applications were performed by the physician in charge of the study.

The study was performed following receipt of official approval from the Clinical Research Ethical Committee of Kanuni Education and Research Hospital, Trabzon.

Evaluation Tools

Sociodemographic Data Form: This was designed by the authors and used to collect the participants' sociodemographic characteristics (age, sex, marital status, employment etc.) and clinical features (including age at onset of disease, total duration of disease, and total number of admissions).

Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-1): SCID-I was developed in 1987 for the purpose of diagnosing DSM-III-R Axis I disorders with a structured assessment tool (First et al. 1997). It was subsequently updated for DSM-IV.

Positive and Negative Syndrome Scale (PANSS): PANSS was developed by Kay et al (1987). It is a semi-structured interview scale consisting of 30 items and a 7-point severity evaluation. Seven of the 30 psychiatric parameters comprised the positive symptoms subscale, seven comprised the negative symptoms subscale, and the remaining 16 belong to the general psychopathology subscale. The reliability and validity of the Turkish-language version were confirmed by Kostakoğlu et al. (1999).

Extrapyramidal Symptoms Rating Scale (ESRS): The scale was developed by Chouinard et al. (1984) in order to assess extrapyramidal system side-effects of drugs in patients using antipsychotics and consisted of four sections and 22 items. A scale of 0-3 was used for scale evaluation. In preliminary studies, a reliability correlation coefficient of 0.96 ($p<0.001$) was determined among assessors for the Turkish-language version of the ESRS.

Ugvalg for Kliniske Undersgelser (UKU) Side-Effect Rating Scale: This consisted of 3 sections containing 48 items that evaluated psychological, neurological, autonomous system and general side-effects. Four scoring options are available for each item from "0" (no side-effect) to "3" (severe) (Lingjaerde et al. 1987). In preliminary studies, a reliability correlation coefficient of 0.76 ($p<0.001$) was determined among assessors for the Turkish-language version of the UKU.

Quality of Life Enjoyment and Satisfaction Questionnaire; (Q-LES-Q): This self-report questionnaire was developed by Endicott et al. (1993) in order to measure quality of life. High scores indicate a high level of contentment and satisfaction. The validity and reliability of the Turkish-language version of the questionnaire was confirmed by Özer et al. (2001), although psychometric data were not reported. The general evaluation section has been used in some studies from Turkey, and also in the present study.

Statistical Analysis

Normal distribution of variables was tested using the Kolmogorov-Smirnov test. Descriptive analyses were performed using mean plus standard deviation for normally distributed variables and median plus minimum and maximum for non-normally distributed variables. The chi square test was used in the comparison of qualitative data such as sex, marital status, occupational status, and UKU values. A student's t test was used to compare age, years in education, and Q-LES-Q parameters, which were normally distributed. The Mann-Whitney U test was used to compare non-normally distributed total duration of most recent treatment, total duration of disease, total number of hospitalizations and PANNS and ESRS parameters. A p-value of less than 0.05 was considered statistically significant.

RESULTS

The 41 patients treated with long-acting second generation antipsychotic injections were not using any other antipsychotic medication. The long-acting second generation antipsychotics and doses used were risperidone (Consta) 37.5-50 mg once every 15 days and paliperidone palmitate 100-150 mg (once monthly). One hundred eight of the 139 patients treated with oral second generation antipsychotics received a single second generation antipsychotic and 31 received two antipsychotics. The oral second generation antipsychotics and doses used were quetiapine 600-1200 mg/day, olanzapine 15-30 mg/day, paliperidone 6-9 mg/day, aripiprazole 15-30 mg/day, risperidone 4-8 mg/day, amisulpride 400-1200 mg/day, and clozapine 300-600 mg/day.

The mean age of the 139 patients receiving oral antipsychotics was 38.63±10.98 years (min:19-max:67) and that of the 41 patients using long-term injection antipsychotics was 37.49±8.98 years (min:22-max:58). No statistically significant difference was determined between the two groups in terms of age, sex, years of education, and occupational status ($p>0.05$). A statistically significant difference was determined between the groups in terms of marital status, with significantly more single patients using long-acting second generation antipsychotics compared to single patients using oral second generation antipsychotics ($p=0.006$, $x^2=10.192$). In terms of clinical characteristics between the two groups, a total number of hospitalizations was significantly higher in patients using long-acting second generation antipsychotics ($p= 0.001$, $U=1916$). Participants' sociodemographic and clinical characteristics are summarized in Table 1.

No statistically significant difference was observed between the patients using second generation antipsychotics and those using long-acting antipsychotics in terms of PANSS positive subscale (P) and PANSS negative subscale (N) scores ($p>0.05$). However, the PANSS general subscale (G) scores of the patients receiving oral second generation antipsychotics were significantly higher than those of the patients using long-acting second generation antipsychotics ($p=0.005$). No significant difference was observed in terms of ESRS median values.

In terms of the UKU subgroup values (psychic, neurological, autonomic, side-effect and intervention), the UKU side-effect (general evaluation of the effect of existing side-effects on the patient's day-to-day performance) subgroup values were significantly higher in the patients receiving long-acting second generation antipsychotics ($p=0.034$, $x^2=4,486$). No significant difference was found between the two groups in terms of the other subgroups (psychic, neurological, autonomic and intervention) ($p>0.05$).

Table 1. Sociodemographic Data and Clinical Characteristics of the Patient Groups

	Oral AP (n=139)	Long-acting AP (n=41)	p value
Age (years) [Mean±SD]	38.63±10.98	37.49±8.98	0,545**
Gender [n (%)]			0.258*
Men	79 (56.8)	28 (68.3)	
Women	60 (43.2)	13 (31.7)	
Marital status [n (%)]			0.006*
Single	66 (47.5)	26 (63.4)	
Married	63 (45.3)	8 (19.5)	
Widow	10 (7.2)	7 (17.1)	
Duration of education (years) [Mean±SD]	9.47±3.68	9.44±3.45	0.970**
Employment status [n (%)] (n %)			0.986*
Positive	62 (44.6)	19 (46.3)	
Negative	77 (55.4)	22 (53.7)	
Total usage time of the last treatment (months) [Median (min-max)]	12 (1–96)	7 (1-96)	0.124***
Total duration of disease (years) [Median (min-max)] (yıl)	10 (1-35)	12 (2-40)	0.411***
The total number of hospitalizations [Median (min-max)]	2 (0–12)	4 (1-15)	0.001***

Mean±SD: Mean ± Standard Deviation, AP: Antipsychotic
* Chi-square test ** Student's t test *** Mann Whitney U test.

Table 2. PANNS, ESRS, UKU and Q-LES-Q Scores of Patient Groups

	Oral AP (n=139)	Long-acting AP (n=41)	p value
PANSS P [Median (min-max)]	7 (7-20)	7(7-20)	0.345*
PANSS N[Median (min-max)]	7 (7-27)	7 (7-16)	0.410*
PANSS G [Median (min-max)	17 (16-38)	16 (16–26)	0.005*
ESRS [Median (min-max)]	0 (0-9)	0 (0-1)	0.621*
UKU [n (%)]			
Psychic	72 (51.8%)	16 (39.0%)	0.391**
Neurological	5 (3.6%)	5 (12.2%)	0.050***
Autonomic	23 (16.5%)	7 (17.1%)	1.000**
Other	36 (25.9%)	7 (17.1%)	0.339**
Side effect	58 (41.7%)	9 (22.0%)	0.034**
Intervention	26 (18.7%)	3 (7.3%)	0.133**
Q-LES-Q [Mean±SD]	55.97±7.96	64.63±8.61	<0.001***

PANSS: Positive and Negative Syndrome Scale; ESRS: Extrapyramidal Symptoms Rating Scale; UKU: (Ugvalg for Kliniske Undersgelser) Side-Effect Rating Scale. Q-LES-Q: Quality of Life Enjoyment and Satisfaction Questionnaire. Mean±SD: Mean ± standard deviation, AP: Antipsychotic
* Mann Whitney U test ** Chi-square test *** Student's t test.

The mean Q-LES-Q was significantly higher in the patients using long-acting second generation antipsychotics compared to those receiving oral second generation antipsychotics (p<0.001, t: 6.040) (Table 2).

When the patients using two oral antipsychotics were excluded from the analysis and patients using a single oral antipsychotic were compared with those using depot antipsychotics, PANSS G was significantly higher in patients using a single second generation antipsychotic compared to those using a long-acting second generation antipsychotic (p=0.002). No statistically significant difference was determined among other PANNS values (p>0.05). Also, there was no difference between the two groups in terms of ESRS scores (p=0.570). Comparison of the patients using a single oral antipsychotic with those using depot antipsychotics in terms of UKU subgroups revealed a significantly higher UKU side-effect subgroup value in the patients using a single oral second generation antipsychotic compared to those using long-acting second generation antipsychotics (p=0.026). No significant difference was determined in terms of the other subgroups (p>0.05). The mean Q-LES-Q was significantly higher in patients using long-acting second generation antipsychotics compared to those using a single oral second generation antipsychotic (p<0.001).

DISCUSSION

The purpose of this study was to compare patients diagnosed with schizophrenia or schizoaffective disorder and receiving oral second generation antipsychotics or long-acting second generation antipsychotic injections in terms of quality of life and drug side-effects.

In terms of sociodemographic characteristics, there was no statistically significant difference between the two groups in respect of age, sex, education level, or occupational status. In terms of marital status, the level of single individuals in the patient group receiving long-acting second generation antipsychotics was significantly higher than in the group using oral second generation antipsychotics. Although most single patients with schizophrenia in Turkey live with their families, features of poor prognosis that may impact their marrying may also affect drug selection. In addition, wider use long-acting second generation antipsychotics by these patients may be regarded as a more appropriate choice in terms of drug monitoring and compliance.

Total number of hospitalizations previous to the initiation of most recent treatment was significantly higher in patients receiving long-acting second generation antipsychotics compared to those on oral second generation antipsychotics. The

preference of long-acting antipsychotic agents to oral medications may be regarded as an appropriate choice in patients with frequently recurring disease characteristics. Studies have suggested that long-acting antipsychotics are more advantageous than oral treatments in reducing recurrence rates in terms of non-compliance with medication than that frequently observed in schizophrenia (Nasrallah 2007).

PANNS-P, PANSS-N, and PANSS-G scale scores in the two treatment groups were evaluated as below the mild level, and compatible with the period of remission when patients were assessed. This suggests that the oral and long-acting second generation antipsychotic therapies were in appropriate doses and effective. Antipsychotics have been reported to be more effective than the placebo in lowering the risk of recurrence and in reducing positive and disorganized symptoms (Leucht et al. 2012). However, they have very little effect on negative and cognitive symptoms that are significantly associated with loss in schizophrenia. No consistent variation among antipsychotics has been shown from that perspective (Tandon and Carpenter 2012). In addition, PANNS-G scores in this study were below the mild level in both treatment groups but, also significantly higher in patients using oral second generation antipsychotics compared to those using long-acting antipsychotics. Although a period of remission was observed in both treatment groups, this may suggest that long-acting second generation antipsychotics are more effective than oral second generation antipsychotics regarding the improvement of symptoms.

UKU side-effect levels (general evaluation of the effect of existing side-effects on the patient's day-to-day performance) were statistically significantly higher in the group receiving long-acting second generation antipsychotic injections. The side-effects of antipsychotic medications (such as akathisia, impairment of sexual function and weight loss), frequently lead to non-compliance with and rejection of medication in patients with schizophrenia (Kanea et al. 1998). Studies have reported lower levels of treatment compliance with available oral forms of several second generation antipsychotics compared to injection therapies (Marinis at al. 2007). The lower level of side-effects observed with injectable forms may also contribute to the higher compliance observed with these drugs.

In addition to the nature and severe psychopathology of the disease, the drugs used in the treatment of schizophrenia also affect patients' quality of life. Another finding of this study is that the quality of life of patients using oral second generation antipsychotics was statistically significantly lower than that of subjects using long-acting second generation antipsychotics. In support of these findings, 50 hospitalized schizophrenia patients receiving risperidone therapy for at least 3 months either continued treatment in the form of oral risperidone or with the long-acting form in one 12-week study in the literature. The two groups were largely similar in terms of effectiveness, although significantly fewer side effects, lower prolactin levels, and better social functioning were observed in patients shifting to the long-acting form (Bai et al. 2006). In agreement with the findings of the present study, another large scale (N = 1,876), 6-week open-ended European study reported that long-acting second generation antipsychotics were generally well tolerated. In addition, there was a discontinuation level of only 6% due to side-effects, and significant improvement in clinical symptoms and functioning was described with long-acting second generation antipsychotics (Möller et al. 2005).

The fact that the patients in both groups enrolled in this study were monitored with the same treatment for at least 1 year may be considered astrength of this study. However, one limitation is that the pharmacological molecules of the long-acting and oral antipsychotics are not exactly equivalent. Although the oral forms of long-acting antipsychotics were included in the oral antipsychotics group, it was impossible to establish a sufficiently large group to compare oral and long-acting forms. Another limitation of this study is the difficulty of establishing dose equivalence when the different drugs were compared. However, the fact that patients in both groups were monitored with the same treatment for at least 1 year suggests that the drugs were used in effective doses.

Another limitation of this study may be that patients were evaluated in a sectional manner by the same researcher.

This study shows that long-acting antipsychotic forms are associated with better outcomes compared the oral forms in terms of side-effects and quality of life. The original aspect of this study is that it reports the results of natural observation from a regional psychiatric hospital. Further large-scale methodological studies that indicate social, cultural, and economic factors and their impact on treatment are needed.

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