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Nazan Aydın [a], Hasan Mervan Aytaç [b], Esra Yazıcı [c], Doğan Yılmaz [d], Pınar Çetinay Aydın [b], Gökşen Yüksel Yalçın [e], Yücel Kadıoğlu [f], Cana Canbay [d], Merve Terzioğlu [b], Onur Şenol [f], Cavide Çakmak [b] and Aysel Özer [b]

aDepartment of Psychology, Humanities and Social Sciences Faculty, Üsküdar University, İstanbul, Turkey; bBakirkoy Prof. Dr. Mazhar Osman Mental Health and Neurological Disease Education and Research Hospital, Istanbul, Turkey; cDepartment of Psychiatry, Faculty of Medicine, Sakarya University, Sakarya, Turkey; dVan Training and Research Hospital, Department of Psychiatry, Bakirkoy Research & Training Hospital for Psychiatry, Neurology and Neurosurgery, Alcohol and Drug Research Treatment and Training Center (AMATEM), İstanbul, Turkey; ePsychiatryDepartment, Acıbadem Health Group Bakırköy Hospital, Istanbul, Turkey; fDepartment of Analytical Chemistry, Faculty of Pharmacy, Atatürk University, Erzurum, Turkey

ABSTRACT

BACKGROUND: Haloperidol has been used as an effective antipsychotic for many years and continues to be one of the first options in difficult patients who require parenteral therapy in the acute phase. However, the depot form is less preferred in the treatment of patients with non-adherence among these patients whose clinical stabilization has been achieved by using parenteral haloperidol in the acute phase. Therefore, updating the information about the side effects of the depot form of haloperidol, which is still an effective treatment option, will be useful in reconsidering the position of this medicine among new and different options.

METHODS: A total of 54 schizophrenic patients with severe symptoms and poor adherence to treatment who were hospitalized and treated with depot haloperidol following an acute stabilization period were included in this study. First, the Structured Clinical Interview for DSM-IV Axis I disorders (SCID-CV) was used to confirm the diagnosis, the Brief Psychiatric Rating Scale (BPRS), Scale for the Assessment of Positive Symptoms (SAPS) and Scale for the Assessment of Negative Symptoms (SANS) to assess the clinical severity and Global Assessment of Functioning (GAF) to assess the functionality. The Simpson-Angus Scale (SAS) was used to assess extrapyramidal side effects. With the exception of Visit 0, plasma haloperidol levels were measured at all visits. Also, measurements of waist circumference and weight, plasma fasting blood glucose, triglyceride, HDL, iron, haemoglobin (Hgb), prolactin (PRL) and HbA1c were also used for evaluation of the metabolic effects.

RESULTS: Significant improvements were observed in the BPRS, SANS, SAPS scores in the long-term follow-up with the depot haloperidol treatment. While the dosage decreased over time, the plasma levels remained changed, and symptom improvement was maintained. No signs such as neuroleptic malignant syndrome or acute dystonia were observed and SAS scores were within acceptable limits during the treatment ($\mu = 1.40 \pm 2.55$). There is no statistically significant difference between measurements of the weight even there was a significant difference between three of the waist circumference values ($p = 0.987$). The first measurement of the waist circumference is statistically significantly higher than both the mid-measurement and the final measurement, interestingly ($p = 0.002$). When fasting blood glucose, triglyceride, HDL, iron, Hgb, PRL and HbA1c were measured at different times throughout the study, only prolactin levels increased significantly over time with the use of haloperidol ($p < 0.001$). At the end of a year, 50% of the patients participating in the study still continued to use the haloperidol decanoate. This means also that half of the patients had stopped to use haloperidol decanoate. However, only 18.5% of them ($n = 5$) discontinued use of this drug because of extrapyramidal side effects.

CONCLUSION: Depot haloperidol remains an effective treatment option that improves treatment compliance in challenging schizophrenia patients with severe symptoms. The long-term metabolic and extrapyramidal side effect profile of the patients were generally within the safe limits with the use of haloperidol depot. According to the obtained data, the depot haloperidol continues to be a reliable treatment option in terms of adverse effects in the maintenance treatment of schizophrenia patients with severe symptoms and poor adherence to treatment.

Introduction

Schizophrenia is a disabling and chronic illness which can cause severe difficulties in personal, social and occupational functioning with a burden on patients, their families, and community. Psychotic episodes, partial or full remissions, relapses take part in the long-term nature of schizophrenia. The symptoms of disease begin at early puberty and show chronicity and there may be a long duration of hospitalizations and high costs due to the chronic relapses [1]. In

addition, since the increased risk of violence, suicide attempts and substance abuse during the period of relapsewere observed, long-acting injectable antipsychotics (LAIs) were produced in the 1960s to make better the long-term treatment of schizophrenia. In a recent cohort-study involving 29.823 individuals, LAIs have been found to superior to oral antipsychotics in terms of relapse prevention [2]. In another study, LAIs have not only been found to be more effective than oral antipsychotics for the prevention of relapses, but also for the management of other problems such as substance abuse and reduced quality of life [3]. San et al. published that 1646 patients with schizophrenia/schizoaffective disorder who are admitted to acute care and the main reason for 58.6% of these patients for hospital admission was non-adherence [4]. In the other study non-adherence with antipsychotic treatment is higher, with up to 75% of patients had been non-adherent with antipsychotic medication at 2 years of post-hospital discharge. Although non-adherence rates are between 50% and 75%, use of LAI is still below the desired level in most of the countries. Especially fear of serious adverse events are the reason for this low level usage of LAI's. There are many fears related usage of LAIs like containing higher doses than oral forms, possibility of combination with oral antipsychotics, loading dose procedures at beginning of treatment and irreversible side effects after injection [5]. Currently, there are two types of antipsychotics which is named as the first-generation and second-generation LAIs in use. According to our classical knowledge, some disadvantages and side effects exist for both types of drug groups. While the first-generation LAIs accused of extrapyramidal symptoms (EPSs) and tardive dyskinesia, second-generation LAI's hold responsible with weight gain and metabolic syndrome so contributing to the risk of type 2 diabetes and cardiovascular disease [6]. However, there are still conflicting and missing information on the comparative tolerability and cost-effectiveness of atypical and typicaldepot formulations of antipsychotics, especially in a real-world practice. The recent large trials and meta-analyses have also published that there is no effectiveness or tolerability advantage between first-generation and second-generation LAI's [7,8]. In this article, we present a one-year naturalistic follow-up study of patients diagnosed with schizophrenia who were using haloperidol deconoate after the acute psychotic symptoms controlled with parenteral and oral haloperidol.

Methods

Ethics approval

Approval for this observational follow-up study was obtained from the Institutional Review Boards of Bakırköy Sadi Konuk Research and Training Hospital, Istanbul (Prot. No. 2013/92) and the Head of Department, Clinical Drug Research, Agency for the Medicines and Medical Devices, the Turkish Ministry of Health.

Selection and management of the patients

The study population consisted of schizophrenic patients who were admitted to a major mental health care facility (the Prof. Dr. Mazhar Osman Mental Health and Neurological Disorders Hospital). Male and female patients undergoing inpatient treatment in segregated male and female (one male and one female) patient wards for acute psychiatric disorders were included. Patients with mental retardation, alcohol substance use for the last 3 months, relevant organic pathology were excluded. The departments in which the patients were hospitalized function as psychiatric intensive care units (PICU), which are specialized, high-security wards with high staffing levels. The patients in PICUs are acute and severely symptomatically challenging with low treatment adherence and poor responsiveness to therapy. Rapid tranquilization is required for most patients during the acute management phase.

A total of 54 consecutive patients responded well to acute treatment with the first injection of haloperidol were included in the study. The patients had the anamnesis of noncompliance to treatment and inadequate response to atypical antipsychotics and refusal of oral treatment and expression of aggression and/or excitation needs to chemical stabilization, so haloperidol were preferred for their acute treatment. Depot haloperidol treatment was planned after acute treatment with parenteral (i.m.) haloperidol because of the anamnesis of low compliance to the treatment. All patients or their legal representatives provided informed consent to participate in the study. Despite individual differences, the switch from parenteral to oral therapy was accomplished within one week following the improvement of symptoms and achievement of treatment compliance. The patients also continued to receive oral treatment for a week after parenteral treatment. In this way, they were stabilized with haloperidol treatment for a total of 14 days. When the clinical stabilization was judged by the clinician, the treatment with haloperidol decanoate was initiated with the gradual tapering off the oral treatment. Additional treatment with biperiden or lorazepam was allowed in cases of side effects or psychomotor excitation.

Assessment parameters

(1) Assessment of clinical efficacy and functionality for haloperidol decanoate
(2) Haloperidol plasma levels
(3) Extrapyramidal symptoms and metabolic side effect profile

(4) Long-term treatment adherence

Assessment of clinical efficacy and functionality for haloperidol decanoate

The diagnoses were confirmed using the structured clinical interview for DSM-IV axis I disorders (SCID-CV) [9]. The treatment response was evaluated using the Brief Psychiatric Rating Scale (BPRS) [10], the Scale for the Assessment of Positive Symptoms (SAPS) [11], and the Scale for the Assessment of Negative Symptoms (SANS) [12]. Functions were assessed using the Global Assessment of Functioning (GAF) [13]. These assessments were performed at the time of admission, on the first day of haloperidol decanoate administration, weekly for the following one-month period, every two weeks in the second month, and monthly thereafter. The assessment at the time of admission was designated as Visit 0, and the day of first haloperidol decanoate administration was designated as Visit 1. The following four visits (Visits 2 to 5) were performed on a weekly basis. Then two visits every two weeks (Visits 6 and 7) were conducted followed by monthly visits (Visits 8 to 18). All patients were followed-up for one year.

Haloperidol plasma levels

With the exception of Visit 0, plasma haloperidol levels were measured at all visits. The plasma assays were performed using a C_{18} chromatographic colon with a mass-spectrometry reverse phase HPLC device (LC/MS; Agilent 1200 Series).

Extrapyramidal and metabolic side effect profile:

The Simpson-Angus Scale (SAS) [14] was used for each interview to assess extrapyramidal side effects. Waist circumference and weight measurements were taken at each visit; fasting blood glucose, triglyceride, HDL, iron, haemoglobin (Hgb), prolactin (PRL) and HbA1c measurements were performed at initial, 2, 5, 8 and 12 months to assess metabolic and haematologic side effects.

Long-term compliance with therapy:

The interviews were conducted on the first day when decanoate was made during hospitalization and then once a week for the first month, once every 15 days for the second month, then once a month. The assessment made during the hospitalization was noted as Interview 0 and the first interview when haloperidol decanoate was administered was noted as Interview 1. The next 4 interviews (interview 2–5) were conducted as a weekly follow-up. The interviews were conducted every two weeks (interview 6–7) in next month and then subsequent interviews were conducted monthly [8–18]. In this way, one-year follow-up was completed with the follow-up patients over time. Since the study is a naturalistic observation study, some of the patients continued on the last follow-up interview at the 12th month of treatment, but some of them left the treatment or removed from the follow-up due to the change in the treatment protocol. Some of them did not leave treatment but did not come to the controls. It was learned that these patients continued treatment at other centers by examining pharmacy information system and hospital records. These patients were evaluated as patients who continued haloperidol decanoate in terms of treatment compliance. However, since the data of these patients were incomplete because they were removed from the follow-up, the efficacy monitoring parameters of the patients who were remained in 12 months of follow-up and who came to regular controls were evaluated.

Statistical analyses

The SPSS 24 for Mac software program was used to analyse the study data. Descriptive statistics (i.e. mean, standard deviation, frequency) were used to assess the study results. The MANOVA was used with repeated measures of more than two time-points in which the parametric assumptions were met for the quantitative data. The post-hoc Bonferroni test was used to identify the causes of differences in the results. Friedman's test was used in repeated measures with more than two repetitions in which parametric assumptions were not met. The cause of the difference was identified using the Wilcoxon sign test. Spearman's Rho correlation test was used to evaluate the associations between variables in which parametric assumptions could not be met. The levels of significance were set at $p < 0.016$ and $p < 0.007$ with the Bonferroni correction.

To determine the changes in BPRS, SANS, SAPS and GAF over time, the non-parametric Friedman's test was used instead of a one-way ANOVA for the parametric repeated measures because the assumptions of normal and global distribution were not met. The Bonferroni correction was applied because multiple scales were utilized. A p value of less than 0.01 was considered significant.

In our study, the difference between baseline, mid-study, and one-year assessment time-points was examined, mainly for two reasons. Firstly, when a statistically significant difference is identified in time-dependent variables, a total of 153 post-hoc comparisons were required to determine the parameter responsible for the difference. Therefore, the Bonferroni correction performed in this case would be too conservative, significantly elevating the type 2 error risk. Secondly, the interpretation of the differences detected between multiple-measurements would be too complicated and confound the significance assessments.

A third measurement, that is, the mid-study measurement, was used not only because it coincided with the middle portion of the study but also because

Table 1. Distribution of clinical characteristics and scale scores of the patients participating in the study.

N:54	Min–Max	Mean + SD (Median)
Age	25–75	42.30 ± 10.22(41)
Education time	0–15	5.93 ± 3.17(5)
Disease Duration (years)	0–33	14.15 ± 8.51(13)
Hospitalization numbers	0–50	6.24 ± 9.78(3)
BPRS Baseline Score	6–62	34.54 ± 13.57 (36)
SANS Total Baseline Score	0–56	10.74 ± 7.66(10)
SAPS Total Baseline Score	1–18	7.33 ± 3.99(7)
SAS Baseline Score	0–13	1.40 ± 2.55(0)
GAF Baseline Score	15–75	33.07 ± 11.35(35)

a relative plateau was reached after a strong trend toward that point.

Results

A total of 41 female and 13 male schizophrenic patients between 25 and 75 years of age (mean 42.30 ± 10.22 years) were included. The patient characteristics are shown in Table 1.

Baseline (Visit 0): the score recorded on the day of first haloperidol dose.

Efficacy

Table 2 presents the comparison of the BPRS, SANS, SAPS, SAS, and GAF scores during one year in the patients who participated in the study.

The baseline BPRS scores were significantly higher compared to those in the mid-study ($Z = -4.346$, $p < 0.001$) and at the end of the study ($Z = -3.409$, $p = 0.001$) scores. The mid-study BPRS scores were significantly higher compared to the scores at the end of the study ($Z = -2.805$, $p = 0.005$) (Figure 1).

The baseline SANS scores were significantly higher compared to those in the mid-study ($Z = -3.603$, $p < 0.001$) and at the end of the study ($Z = -3.411$, $p = 0.001$). There were no significant differences between the mid-study and the end-study measurements ($p > 0.016$) (Figure 2).

The baseline SAPS were significantly higher compared those in the mid-study ($Z = -3.867$, $p < 0.001$) and at the endof the study ($Z = -3.301$, $p = 0.001$). There were no significant differences between the mid-study and the end-study measurements ($p > 0.016$) (Figure 3).

The baseline GAF scores were significantly lower compared to those in the mid-study ($Z = -4.083$, $p < 0.001$) and at the end of the study ($Z = -3.438$, $p = 0.001$). There were no significant differences between the mid-study and the end-study measurements ($p > 0.016$) (Figure 4).

Haloperidol dose and plasma levels

The changes in the haloperidol dose and plasma levels from the study baseline, at mid-study, and at one-year in the subjects who completed the follow-up period were examined (Figure 5). Because the assumptions of normal and global distributions were not met, non-parametric Friedman's test was used instead of the one-way ANOVA for the parametric repeated measures test. The results showed that the mean haloperidol dose at the end of the study was statistically significantly lower than both the first dose ($Z = -2.982$, $p = 0.003$) and the mid-study dose ($Z = -2.591$, $p = 0.010$). Similarly, the mean haloperidol dose received at mid-study was significantly lower than the baseline dose ($Z = -2.640$, $p = 0.008$). However, the alterations in plasma levels were not statistically significant. Table 3 shows the haloperidol doses received by the patients and their plasma levels.

Table 2. Comparison of baseline and final scores in patients completing the study.

| N:17	First score Mean ± SD (Median)	Mid-study score Mean ± SD (Median)	Final score Mean ± SD (Median)	$\chi^{2(2)}$	p
BPRS	36.47 ± 12.61 (38)	6.13 ± 7.49 (4)	0.73 ± 1.71 (0)	28.182	<0.001
SANS	12.80 ± 12.73 (11)	5.20 ± 11.48 (0)	0.53 ± 1.13 (0)	26.941	<0.001
SAPS	8.40 ± 3.96 (8)	0.93 ± 1.53 (0)	0.60 ± 2.06 (0)	26.000	<0.001
GAF	32.33 ± 12.66 (30)	60.73 ± 15.12 (60)	68.67 ± 10.60 (70)	25.107	<0.001
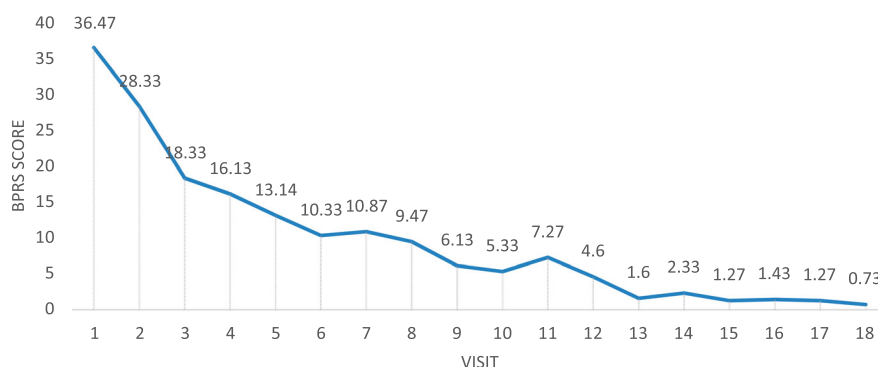
Figure 1. Change in BPRS scores over time.
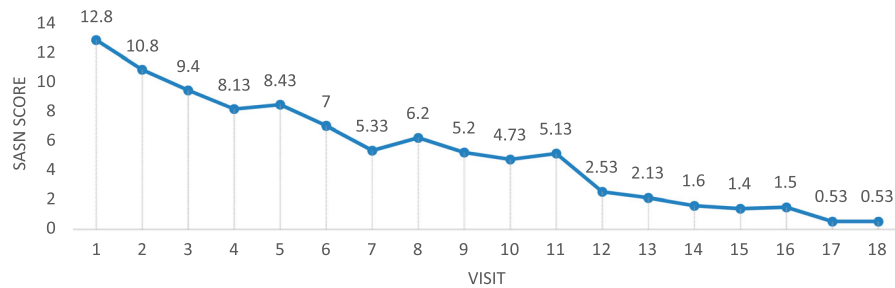
Figure 2. Change in SANS scores over time.

## Extrapyramidal symptoms and metabolic side effect profile

To investigate extrapyramidal side effects, the relationship between SAS scores and haloperidol doses was first investigated. According to this; there was a statistically significant correlation between the initialdose of haloperidol and SAS scores in the positive direction ($p < 0.05$), but there was no statistically significant correlation between the dose of haloperidole decanoate and SAS scores in the middle and final assessments ($p > 0.05$). The relationship between haloperidol dose and SAS side effect scale scores of the patients who completed the study is given in Table 3 and the change in SAS scale scores over time is given in Figure 6.

The changes in metabolic measurements (fasting blood glucose, triglyceride, HDL, iron, Hgb, PRL and HbA1c) of patients who completed the study over time were compared. As the metabolic properties were examined with more than one variable, Bonferroni correction was used to determine whether there was any difference between the measurements. Therefore, univariate analysis results were evaluated at $p = 0.007$ level. Non-parametric Friedman Test analysis was used because parametric assumptions such as normal distribution and sphericity were not met in the variable groups. According to this; there is a statistically significant difference between measurements of PRL variable over time ($p < 0.007$) (Figure 7).
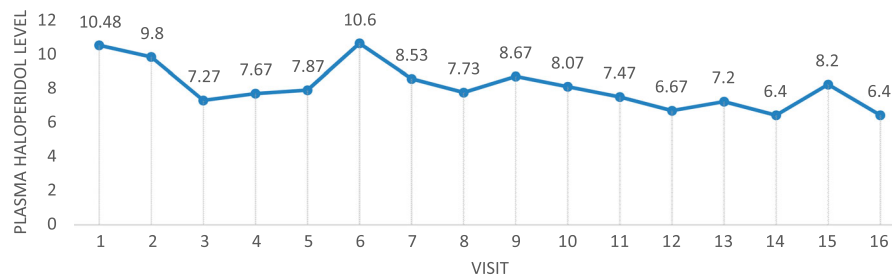
The Wilcoxon Sign Rank Test was used to determine the source of the difference, the results of the binary
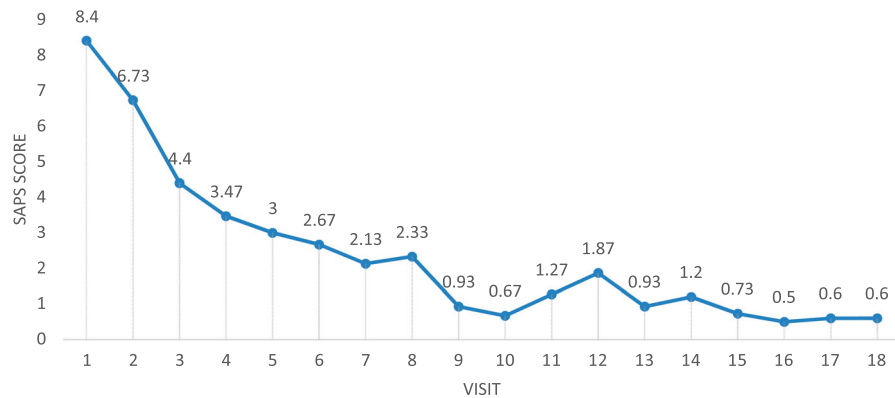
Figure 3. Change in SAPS scores over time.
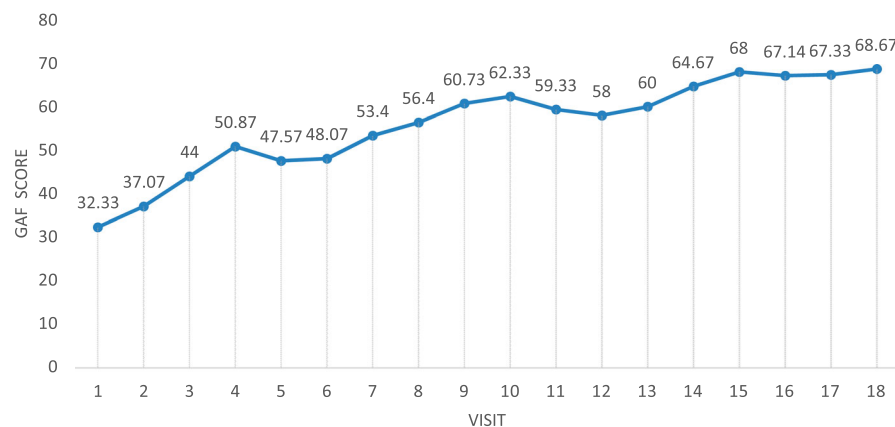
Figure 4. Change in GAF scores over time.

Figure 5. Change in plasma haloperidol levels over time.

Table 3. The Relationship between haloperidol dose and SAS side effect scale scores of patients completing the study.

**	SAS initial	SAS middle	SAS final
Haloperidol Initial dose ($n = 53$)	−0.339*		
Haloperidol Middle dose ($n = 25$)		−0.061	
Haloperidol Final dose ($n = 17$)			0.060

comparisons were assessed by Bonferroni correction and the level of significance was determined as $p < 0.005$. According to the binary comparison results, the first PRL measurement was statistically significantly lower than the third ($Z = –3.411$, $p = 0.001$, effect size $d_{cohen} = 2.95$, large effect size), fourth ($Z = –2.831$, $p = 0.0046$, effect size $d_{cohen} = 1.89$, large effect size) and fifth ($Z = –2.985$, $p = 0.003$, effect size $d_{cohen} = 2.09$, large effect size). There was no statistically significant difference between the other measures ($p > 0.005$) (Table 4).

Measurements of weight and waist circumference were also used to evaluate the metabolic side effects of haloperidol. Weight and waist circumference measurements of the follow-up patients were evaluated with MANOVA for repeated measurements. Both weight and waist circumference measurements seem to meet the assumptions of the normal distribution (Shapiro–Wilk $p > 0.05$) and sphericity (For weight; χ^2 (2) = 2.901, $p = 0.234$, for waist circumference $\chi^2(2) = 5.398$, $p = 0.067$).

The MANOVA multivariate test results for recurrent measurements were statistically significant (Wilk's $\lambda = 0.618$, $F(4, 54) = 3.679$, $p = 0.010$, Partial $\eta^2 = 0.21$) and univariate results were examined to determine if there is a significant difference between the measurements for which variable(s). According to this, there was no statistically significant difference between measurements in weight variable, but there was a significant difference in waist circumference ($p < 0.01$, Partial $\eta^2 = 0.35$, large effect size). For the determination of the source of the difference, Bonferroni corrected binary comparison results have been examined.

Accordingly, the first measurement of waist circumference was statistically significant high ($p < 0.016$) than both the mid- and final measurements. There was no statistically significant difference between the middle measurement and final measurement for waist circumference ($p > 0.016$) (Table 5).

Compliance with treatment

In the study, the proportion of patients to continue treatment for 1 year were evaluated and 50% of the patients (n:27) continued to use haloperidol decanoate when the whole group was evaluated, 14.8% (n:8) switched to ansecond-generation antipsychotics (SGAs), 7.4% (n:4) used a mood stabilizer with another SGA, 7.4% (n:4) switched to another depot antipsychotic. 20.4% of the patients (n:11) had completely left the treatment. As a result, 50% of the patients were still on haloperidol treatment and 79.6% of the patients were still on treatment at the end of 1 year. When the causes of treatment discontinuation were evaluated, it was determined that treatment
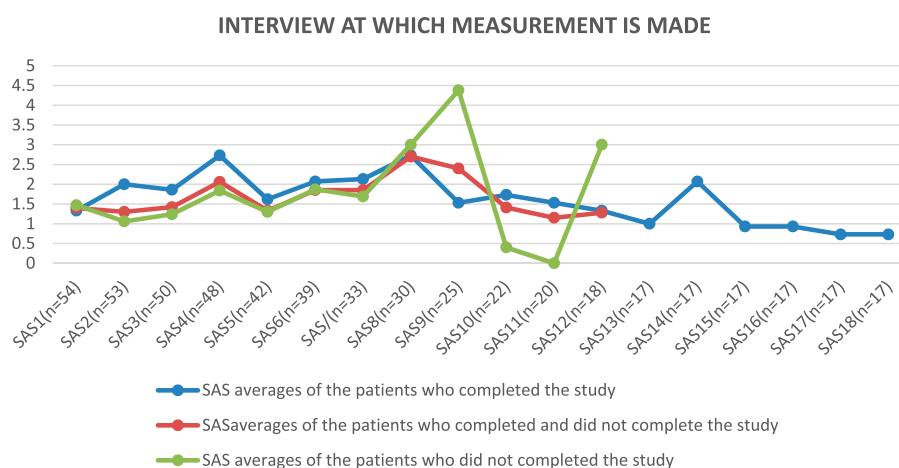
Figure 6. Changes in SAS scale scores over time.
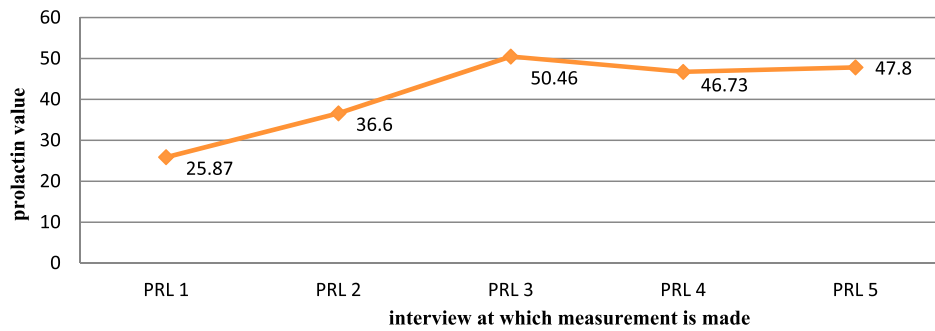
Figure 7. Changes in prolactin levels over time.

was changed with the recommendation of the following doctor due to a change in the initial diagnosis or due to side effects in 37% of patients, 33.3% of the patients had no social support to provide access to treatment, 29.6% of patients discontinued treatment with their request. The side effects were reported only 5 of the patientsas a cause by their doctor (Figure 8).

Discussion

With regard to efficacy, haloperidol decanoate showed a treatment effect as early as the first week of treatment. Of particular note in terms of efficacy was the continued improvement in BPRS, SANS, and SAPS scores in the patients who initially responded to oral haloperidol and who were considered suitable for the depot formulation. The results showed that the reduction in BPRS scores continued to decline until the end of the one-year period.

An important aspect of this study is that it was based on a one-year follow-up in a real-life treatment setting. The dosages were adjusted according to the clinical needs of the patients, who were followed-up during the natural course of their real-life conditions. Thus, the reduction in SAPS, SANS, and BPRS scores and the improvement in functions are clinically significant. The improvement in patient function is an indication that not only were the patients tranquilized but also they regained some functionality in their daily living activities.

We believe that the inclusion of hard-to-treat schizophrenic patients is an important feature of the current study. Rapid tranquilization was required because of the agitation and excitation in this challenging group of patients with severe symptomatology. The treatment of these patients with haloperidol resulted in the presented findings. In a previous meta-analysis comparing the efficacy of antipsychotics in patients with inadequate response to treatment or with treatment resistance, second-generation antipsychotic agents, such as olanzapine and risperidone, were found to be effective in addition to clozapine [15].

Although clozapine is an effective therapeutic option in treatment-resistant schizophrenia, only 40% of patients benefit from this agent. The search for a novel drug continues because clozapine is associated with several undesirable effects, including agranulocytosis, myocarditis, thromboembolism, ileus, and pneumonia [16,17]. Furthermore, the presence of intramuscular formulations of haloperidol, which is suitable for patients resistant to treatment during acute episodes, represents an important advantage over clozapine and other oral antipsychotics because it provides rapid tranquilization. Regarding maintenance therapy, although other second-generation antipsychotics are a therapeutic option, the results of the present study indicate that haloperidol decanoate may also be considered a viable treatment in hard-to-treat patients.

In our patients, the plasma haloperidol decanoate levels remained above 4 μg/L at both 6- and 12-month assessments. This level is considered to represent a threshold for both clinical efficacy and reduced relapse risk [18,19]. It has been reported that significantly lower doses of haloperidol decanoate may be administered in the third or fourth month of treatment compared to the initial oral doses. Similarly, the haloperidol doses given to the patients in the present study declined over time, and clinical stability was maintained at these lower dose levels. Steady-state plasma haloperidol levels were reported to occur after the second month of treatment with haloperidol decanoate [20], and clinical stability was maintained even after plasma concentrations were reduced in the remaining course of the treatment [21]. The results of our analysis showed that the reduced doses of depot haloperidol administered to the patients were not accompanied by similar levels of decline in plasma haloperidol levels, which suggests that the same plasma levels could be achieved using gradually reduced doses. The "flip-flop" phenomenon has been reported in the pharmacokinetics of haloperidol, showing an absorption half-life longer than an elimination half-life [18]. This finding implies that lower doses may be needed over longer terms. Compared with oral haloperidol, lower haloperidol plasma levels have been detected during treatment with haloperidol decaonate. This effect may be related to the pharmacokinetic differences between the two formulations as well as the

Table 4. Comparison of changes in metabolic measurements of patients completing the study over time.

N:17 ***	Measurement 1 Mean ± SD (Median)	Measurement 2 Mean ± SD (Median)	Measurement 3 Mean ± SD (Median)	Measurement 4 Mean ± SD (Median)	Measurement 5 Mean ± SD (Median)	$\chi^2(4)$	p
FBG	101.35 ± 28.14 (96)	101.38 ± 42.25 (91)	112.41 ± 50.60 (100)	102.35 ± 29.79 (93)	111.53 ± 42.65 (103)	6.503	0.165
Tg	118.06 ± 62.61 (99)	122.13 ± 55.22 (105)	148.35 ± 73.99 (142)	137.94 ± 71.07 (120)	137.29 ± 63.08 (132)	10.724	0.030
HDL	55.13 ± 20.81 (51.5)	-	55.71 ± 23.41 (49)	53.82 ± 17.00 (54)	55.71 (22.92 (56)	2.162	0.539
Iron	68.06 ± 26.76 (67.5)	66.75 ± 27.94 (63)	64.47 ± 29.14 (63)	63.53 ± 24.33 (60)	61.81 ± 23.35 (65)	6.331	0.176
HgB	13.06 ± 1.75 (13)	12.60 ± 1.84 (13)	12.73 ± 2.05 (13)	12.80 ± 1.52 (13)	13.33 ± 1.54 (13)	4.808	0.319
PRL	25.87 ± 17.39 (25)	36.60 ± 24.71 (35)	50.46 ± 32.06 (43)	46.73 ± 30.59 (40)	47.80 ± 29.13 (45)	26.111	<0.001*
HbA1c	5.64 ± 1.63 (5)	5.42 ± 1.65 (5)	5.43 ± 1.34 (5)	5.43 ± 1.60 (5)	5.50 ± 1.69 (5)	1.367	0.850

*** RepeatedMeasures Friedman Test.

absence of several parameters in parenteral drug administration, including gastrointestinal absorption and hepatic first-pass metabolism [20]. In this regard, our results are consistent with previous reports [19].

The results of our study showed that a loading dose of haloperidol decanoate may be safely and effectively administered to acutely ill patients, which is in line with the findings of previous studies in which loading doses of this agent were used [19–23]. Among the previous studies that also examined plasma haloperidol decanoate levels, the current study is distinguished by the long duration of the follow-up.

Extrapyramidal symptoms (EPS) which contains acute dystonia, akathisia, parkinsonism and tardive dyskinesia can be observed in two phases. While early-onset EPS like acute dystonia and akathisia develops at the beginning of treatment with antipsychotics or when the dose is increased, the late-onset EPS like tardive dyskinesia (TD) usually occurs on future stage of treatment. Acute EPS usually resolve with dose reduction of the antipsychotic or require anticholinergic treatment [24]. It has been reported that neurologic side effects are related to the dose of antipsychotic drugs [25]. In previous studies, it was also published that when the haloperidol dose have been increased in the treatment, the extrapyramidal side effects of antipsychotic also increase [26]. In addition, it has been reported that haloperidol reaches steady-state plasma level after second application of haloperidol decanoate [20] and that patients remain clinically stable even if plasma concentrations decrease in the later stages [21]. In the light of this information, we also decreased the initiating dose of haloperidol in order to avoid side effects. In this way, while there was a statistically significant correlation between the beginning initial dose of haloperidol and EPS scores in the positive direction, no statistically significant relationship was found between the middle and final dose of the haloperidol treatment and EPS scores.

When our patients were examined for side effects also, it wasn't any sign such as neuroleptic malignant syndrome or acute dystonia and SAS scores were at acceptable limits during the treatment although five of patients dropped out from the study because of side effect. While acute dystonia is common with haloperidol, it was also published that 7.2% of the patients who had used long-acting risperidone had an acute dystonia [27]. Also, after initiation of aripiprazole or ziprasidone treatment, acute dystonia could be observed as a side effect [28,29]. In the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, which compared the first-generation antipsychotic (FGA) (perphenazine) with atypical antipsychotics (olanzapine, quetiapine, risperidone, ziprasidone) in schizophrenia groups, no significant differences across the groups in the incidence of EPS, although significantly more perphenazine patients

Table 5. Comparison of weight and waist circumference measurements of follow-up patients *RepeatedMeasures MANOVA.*

| N:17	Initial measurement Mean ± SD (Median)	Middle measurement Mean ± SD (Median)	Final measurement Mean ± SD (Median)	$F_{(2, 28)}$	p	Partial η^2
Weight	69.20 ± 15.29 (65)	69.20 ± 14.60 (67)	69.53 ± 12.90 (67)	0.013	0.987	0.001
Waist circumference	94.13 ± 16.42 (99)	86.07 ± 11.99 (83)	84.53 ± 14.72 (82)	7.588	0.002	0.352

discontinued treatment due to extrapyramidal adverse effects [30]. It wasalso reported that akathisia rates similar between FGAs and second-generation antipsychotics (SGAs) [31]. The Cost Utility of the Latest Antipsychotics in Schizophrenia Study Band 1 (CUtLASS-1) is a randomized controlled trial (RCT) that tested the differences of the clinical and cost-effectiveness between FGAs and SGAs. In this study, FGAs have a trend towards better outcomes and lower costs. There were no significant differences in rates of objectively assessed extrapyramidal side effects between the SGA and FGA patients [7]. There are also some studies that show the opposite results in the literature. Lammers et al. published that although there was no apparent difference in treatment discontinuation or hospitalization between second-generation antipsychotic long-acting injectable (SGA-LAI) and first-generation depot antipsychotics treated patients. EPS which were more common in first-generation depot antipsychotics treated patients [32]. In the previous study, paliperidone palmitat and haloperidol deconate were compared and haloperidol deconate was shown to have a higher risk of akathisia, although the long-term effects of paliperidone were not superior [33]. Zhao et al. found that fluphenazine decanoate, haloperidol, haloperidol decanoate and trifluoperazine produced more extrapyramidal adverse effects than olanzapine or quetiapine. Again when the patient used paliperidone palmitate and risperidone microspheres, co-medication against extrapyramidal symptoms was less frequently used compared to with haloperidol decanoate [34].

Although many controversial studies have been published about efficacy and side effects, SGAs have been increasingly used in the treatment of schizophrenia in preference to FGAs recently [35]. It was thought that SGAs are promoted as offering several therapeutic advantages when compared with the FGAs like enhanced efficacy for negative symptoms,

low extrapyramidal side effects etc. [36]. However, it is now believed that all SGAs, except clozapine, have capacity lead to EPS and the last studies have also shown that there is no advantage of SGAs regarding tolerability and effectiveness compared with FGAs. There are also a lot of disadvantages to use of SGA's compared with FGAs for metabolic syndrome [6] include weight gain, obesity, glucose intolerance, insulin resistance, dyslipidemia and hypertension. In our study there is also no statistically significant difference between measurements of the weight in our natural follow-up study throughout 12 months, however, there was a significant difference between three of the waist circumference values. The first measurement of the waist circumference is statistically significantly higher than both the mid-measurement and the final measurement interestingly. Since the treatment of schizophrenic patients with atypical antipsychotics is very common nowadays, these patients may be treated with atypical antipsychotics before haloperidol decanoate treatment. 62 schizophrenic patients who were treated with typical (haloperidol) and atypical (clozapine, risperidone, olanzapine, quetiapine, aripiprazole) antipsychotics were observed over 20 years by Francesco &Cervone. They point out that at the endpoint of the period of observation [20 years] the patients with haloperidol reported satisfactory and a better glycemic and lipidic profiles than SGA's [37]. It was reported also no change in prevalance of metabolic syndrome (MetS) in FGA group (perphenazine) in CATIE study at follow-up for three months, however, an increase in prevalance of MetS was seen in SGA group (olanzapine) [38]. In Meteor study also which was consist of 2270 adults with schizophrenia, significantly higher frequencies of dysglycaemia, low HDL cholesterol and metabolic syndrome were observed in patients taking SGAs considered to carry high metabolic risk [39]. De Hert et al. had reported that the odds of developing MetS were 3-fold in patients started on SGAs compared to FGAs in MetS naive first-episode patients with schizophrenia. Approximately 1 out of 3 first-episode patients met criteria of MetS after three years of begining of SGAs [40]. It was explained by Lindenmayer et al. that a higher weight gain, elevated postload glucose and cholesterol level in SGA group (clozapine and olanzapine), compared with FGA (haloperidol) group, also had been recognized that higher prevalence of diabetes in clozapine-treated patients [41]. Although it is not appropriate to compare second-generation antipsychotics with haloperidol all together, these studies are also important to give an idea about differences between

Causes of Treatment Discontinuation

■ Lack of support   ■ Doctor-based   ■ Patient-based
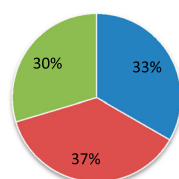
Figure 8. Percentage of reasons why patients discontinued haloperidol decanoate treatment.

SGAs and FGAs. When we search if there is any study where SGA antipsychotics compare with haloperidole separately, the current meta-analysis is consist of fifteen antipsychotics (only haloperidol was used as a member of FGA medication) and mutual comparisons between antipsychotics showed that haloperidol had the least effect over weight gain [42]. Fasting blood glucose, triglyceride, HDL, iron, Hb, PRL and HbA1c were measured at baseline 2, 5, 8 and 12th month in our study. Among all these measures, only prolactin levels increased significantly over time with the use of haloperidol. There was no significant statistical change in other metabolic parameters. Currently, it is a generally accepted approach to categorize antipsychotics according to their effects on prolactin levels as prolactin-raising and -sparing antipsychotics. Among SGA's, risperidone, paliperidone, amisulpride, and sulpiride are the ones that lead to an increase in the prolactin level with the highest rate. FGA and zotepine lead to a marked increase in prolactin levels, whereas clozapine, olanzapine, quetiapine, ziprasidone, sertindol, and asenapine lead to slight or transient increases [43]. In the literature, there are studies that investigate the relation between haloperidol use and prolactin level and obtain different results. David et al. examined the comparative effects on PRL of olanzapine, risperidone, and haloperidol in multicenter, double-blind, randomized clinical trials. They published that PRL is elevated moderately by olanzapine, intermediately by haloperidol and strongly by risperidone [44]. In contrast another study where prolactin levels had been measured in 110 patients with medication-naive and first-episode psychosis, olanzapine and haloperidol treatments didn't significantly affect serum prolactin levels at long term although elevated prolactin levels persisted in most patients were treated with risperidone after a year [45]. Although the results of these comparisons are expected to come against risperidone, these results are important to see position of haloperidol among the other antipsychotics. We know that risperidon consta can be administered every two weeks so we should compare the antipsychotics that must be applied every month like haloperidol. When we look at the studies, Mc Evoy et al. reported that serum prolactin concentrations were significantly higher with once monthly formulations of paliperidone palmitate than with haloperidol decanoate in both men and women ($p < 0.001$); however, there were no significant differences in sexual dysfunction or galactorrhea [33].

Although duration of the study was relatively short to assess some side effects like tardive dyskinesia none of the patients had left from our study because of tardive dyskinesia. Again when paliperidone palmitat and haloperidol deconate were compared by McEvoy et al., it was found that treatment discontinuations due to tardive dyskinesia according to clinician judgment were as follows 2.7% on haloperidol deconate compared to 0.7% on paliperidone palmitat [33]. In the study of Novick et al., the patients treated with typical antipsychotic agents (oral and depot) and risperidone had a higher risk of developing EPS and TD than the patients treated with olanzapine [46]. In our study patients were followed with haloperidol decanoate and since low dosage procedures were applied, we may not have observed tardive dyskinesia-related separation from our study.

Marcus et al published that both first-generation antipsychotic long-acting injectable (FGA-LAI) and second-generation antipsychotic long-acting injectable (SGA-LAI) have benefits in terms of adherence and re-hospitalizations among currently hospitalized, nonadherent patients with schizophrenia [47]. Some studies have shown that a higher rate of adherence among patients receiving SGA's compared with those receiving FGA's [48]. In contrast, some studies published that there was no apparent difference in treatment discontinuation between SGA's and FGA's treated patients. Again Nielsen et al. published that SGA-LAIs not superior to FGA-LAIs regarding time to psychiatric hospitalization, all-cause discontinuation, and duration of hospitalization [49]. In our study when adherence to treatment was observed throughout a year, it was seen that half of the patients continued to use the depot haloperidol, the rate of continuity of the depot haloperidol was 50% and the rate of continuity any treatment was 79.6%. This is a high continuity rate for patients with schizophrenia since the CATIE study showed that 74% of patients had discontinued medication within 18 months due to insufficient efficacy, intolerable side effects etc. [30]. All of these results may suggest that haloperidol deconoate choice is positively associated with adherence to treatment with appropriate followup and treatment planning. It was also suggested that antipsychotic side effects are associated with lower levels of adherence. Hudson et al. found that approximately 35% of patients, Loffler et al. also published that 50% of patients had side effects as a reason for non-adherence [50,51]. Although EPS/agitation-related side effects were the most strongly associated with nonadherence in previous studies, only 5 of the patients (18.5%) terminated the treatment due to the cause of extrapyramidal side effects in our study.

When the causes of non-adherence were evaluated in our study, it was learned that 37% of the patients had changed the treatment with his/her doctor's effect; 33.3% of the patients discontinued treatment because of inadequate social support to provide access to treatment; and 29.6% of the patients left treatment with their desire. In one study consist of 100 patients starting long acting risperidone, 51% discontinued during the first 6 months. The reasons for discontinuation were that the ineffective medication (47%), refused (35%), or not tolerated by the patient (18%) [52]. Although this study has been done with the patients who were

treated with long acting atypical antipsychotic, the results were similar to our haloperidol decanoate study.

The weaknesses of this study were lack of control group, including the sample consisted of a small number of treatment-resistant patients who is likely to have an adherence problem and since the study does not consist of first-episode psychotic patients, the possibility of earlier use of a wide variety of oral form antipsychotics. In addition, strengths of this study are the one-year naturalistic observation study, inclusion of patients in consecutive way, questioning whether or not they are currently using treatment by reaching the patient who is leaving the follow-up and also checking whether or not patients receive drugs from pharmacies via the computer system if satisfactory information cannot be obtained, standardization of visits and treatments to be the same for each patient.

Conclusion

It is important that this study is a natural follow-up study which demonstrated that the haloperidol deconoate is still unique as an effective and tolerable treatment option in schizophrenia patients with severe and non-adherence to pharmaceutical treatment. The availability of effective treatment options for patients with clinical severity and non-adherence to drugs is facilitating the treatment process for both the patients and physicians in real life.

Disclosure statement

No potential conflict of interest was reported by the authors.

ORCID

Nazan Aydın http://orcid.org/0000-0003-3232-7713
Hasan Mervan Aytaç http://orcid.org/0000-0002-1053-6808
Esra Yazıcı http://orcid.org/0000-0002-2575-7398
Doğan Yılmaz http://orcid.org/0000-0003-4575-9478
Pınar Çetinay Aydın http://orcid.org/0000-0002-1605-2724
Gökşen Yüksel Yalçın http://orcid.org/0000-0001-9961-4464
Yücel Kadıoğlu http://orcid.org/0000-0001-6590-7306
Cana Canbay http://orcid.org/0000-0002-3836-3718
Merve Terzioğlu http://orcid.org/0000-0002-0668-1105
Onur Şenol http://orcid.org/0000-0002-0252-396X
Cavide Çakmak http://orcid.org/0000-0002-2549-1219
Aysel Özer http://orcid.org/0000-0001-8354-6890

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