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Common Side Effects and Metabolic Syndrome due to Clozapine: Relationship with the Clinical Variables and Disability

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SUMMARY

Objective: Common side effects due to clozapine may affect the treatment process negatively. In this study, we aimed to assess the common side effects and the prevalence of metabolic syndrome in schizophrenia patients treated with clozapine, and to study their relationship with clinical variables and disability.

Method: One hundred and twenty two patients who met DSM-IV criteria for schizophrenia, and were on clozapine treatment were included in the study. Clinical status was evaluated through a clinical interview and review of the medical records, and physical measures and laboratory tests were recorded. Patients were assessed with the Structured Clinical Interview for DSM-IV Axis I Disorders, UKU (Udvalg for Kliniske Undersogelser) Side Effect Rating Scale, World Health Organization (WHO)-Disability Assessment Schedule II, Positive and Negative Syndrome Scale, Global Assessment Scale, Clinical Global Impression Scale.

Results: Common side effects of clozapine were found to be hypersalivation, fatigue, sedation and constipation, and the relationship between constipation and clozapine dose, and dizziness and norclozapine plasma levels were significant. The prevalence of metabolic syndrome was calculated as 50%, and patients with metabolic syndrome had higher means of age and lifetime cigarette consumption. Disability was positively correlated with the severity of psychopathology and the number of side effects, and negatively correlated with the age at onset of illness. Severity of the psychopathology and the number of side effects predicted the severity of the disability.

Conclusion: Clozapine has a wide side effect profile and half of the patients have metabolic syndrome. Assessment of common side effects due to clozapine is important for reducing disability.

Keywords: clozapine, schizophrenia, side effect, metabolic syndrome

INTRODUCTION

Clozapine, despite its proven therapeutic effect on treatment resistant schizophrenia, is not the first choice agent among the current antipsychotic treatments on grounds of serious side effects such as agranulocytosis (Solmi et al. 2017). It has a wide profile of adverse effects (Remington et al. 2016), with hypersalivation, sedation and weight gain, generally lowered and rarely elevated blood pressure, tachycardia, dizziness, fatigue, constipation, fever, nocturnal enuresis being among the most frequently observed side effects (Taylor et al. 2015).

Patients need to be clinically evaluated with respect to physical measurements and laboratory tests at specific stages of clozapine treatment for purposes of protection against the side effects (Taylor et al. 2015, Bleakley and Taylor 2013). Following up plasma clozapine concentration is a useful approach for reducing side effects, maintenance of treatment compliance and the effectiveness of the therapy (De Berardis

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et al. 2018). Clozapine is converted to N-desmethylclozapine (norclozapine) by the mitochondrial *Cytochrome P450 enzyme system,* mainly via the CYP450 1A2 and to a less degree by the CYP 3A4, 2D6, 2C9 and 2C19 (de Leon et al. 2005). There are conflicting reports on the relationship between the side effects of clozapine treatment and the clozapine dose used, plasma clozapine and norclozapine levels and the clozapine/norclozapine ratio (Bleakley and Taylor 2013, Remington et al. 2013).

Hypersalivation, reported to have 30-80% prevalence (Praharaj et al. 2006, Syed et al. 2008) generally presents at early stages, continuing throughout clozapine treatment with increased complaints at night time. In a 98-patient series, 91.8% had experienced hypersalivation, with nocturnal sialorrhea prevalences determined to vary as absent (15.3%), mild (53.1%), moderate (15.3%) and severe (16.3%) in comparison to daytime sialorrhea prevalences varying as absent (52%), mild (16.3%), moderate (13.3%) and severe (18.4%) (Maher et al.2016). Sialorrhea results in social isolation, skin irritations and infection, parotid gland inflammation and sleep disorders which can necessitate termination of clozapine treatment (Sockalingam et al. 2007).

Sedation is a common side effect of antipsychotic agents, clozapine being the most frequently reported second generation antipsychotic agent causing this side effect (Asenjo et al. 2010, Leucht et al. 2013). Increased sleep duration and sedation has been observed in 45% of patients under clozapine treatment (McEvoy et al. 2006). Sedation presents mostly in the first weeks of the treatment with development of tolerance in 2-3 months (Miller 2000) and has been associated with clozapine dose (Lameh et al. 2007). In a 133-patient series, 64.7% were reported to sleep over 9 hours per day, the sleep duration being correlated with the plasma norclozapine concentration and attributed to the differences of clozapine and norclozapine receptor binding (Ramos Perdigues et al. 2016).

Fatigue has been defined as a lasting burnout and weakness comprising reports by patients on musculoskeletal symptoms, attention and concentration problems, headaches and sleep disorders (Fukuda et al.1994). Patients receiving clozapine treatment frequently complain of fatigue (Taylor et al. 2015); in a 38-patient series (Kishi et al. 2013) 79% of patients reported this particular side effect. Most studies have evaluated fatigue in combination with sedation and sleepiness (Citrome 2017). It is believed that differentiation of the drug effects and the adverse effects of schizophrenia per se should be useful in handling fatigue (Waters et al. 2013).

Prevalences of clozapine associated constipation vary in the 14-60% range (Palmer et al. 2008). Severe constipation resulting in intestinal obstruction, toxic megacolon, necrotizing colitis, colon perforation and intestinal infarction and also aspiration of vomit secondarily to these problems which may lead to mortality have been reported. Clinicians have been warned to be aware of these complications (De Hert et al. 2011, WHO 2011). Although constipation may be observed at any stage of clozapine treatment, prevalences of constipation related complications are more frequent in the first 4 months of the treatment. (Palmer et al. 2008). A metaanalysis reported a prevalence of 31.2% for clozapine related constipation, and that factors of age, gender, diagnosis, dose and plasma level of clozapine and the treatment duration were not predictive for constipation (Shirazi et al. 2016). There are, however, studies proposing the observed constipation effect to be caused by clozapine dosage (De Hert et al. 2011), by the plasma levels of clozapine and norclozapine rather than the treatment dose (De Leon et al. 2003) or by the norclozapine levels alone, due to the differences in receptor binding by the drug and its metabolite (Olianas et al. 2009).

Urinary incontinence due to clozapine use is a common side effect frequently experienced nocturnally. Prevalences of 44.3%, with 25% chronicity (Lin et al. 1999), and of 20.7%, with significant increase in comparison to cases treated with olanzapine, quetiapine and risperidone have been reported (Harrison-Woolrych et al. 2011). Clozapine action on the cholinergic system is believed to inhibit the detrusor muscle of the bladder causing urinary retention and overflow (Harrison-Woolrych et al. 2011).

Orthostatic hypotension is a frequently observed side effect of clozapine (De Berardis et al. 2018) caused by α1-adrenergic receptor blockage (Gugger and Ehret 2016). The third phase of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study reported 24% prevalence of faintness due to orthostatic hypotension among 270 clozapine using patients (Stroup et al. 2009). Whereas patients with mild orthostatic hypotension complain of dizziness, severe orthostatic hypotension can cause stupor, impaired cognition and syncope. U.S. *Food and Drug Administration* (FDA) data indicate a 6% prevalence of syncope in clozapine using patients. After receiving 25 mg clozapine, 2/3 of healthy individuals have presented with orthostatic hypotension (Mackin 2008).

Tachycardia of over 100 beats per minute is believed to result from the anticholinergic action of clozapine (Rostagno et al. 2011) and is seen more frequently in clozapine treatment as compared to other atypical antipsychotic agents (Mackin 2008, Raedler 2010). It has been reported to be a dose

dependent side effect (Mackin 2008, Anıl Yağcıoğlu and Ertuğrul 2011). Myocarditis and cardiomyopathy are the rarely observed cardiovascular side effects of clozapine that can be fatal (Raedler 2010).

During antipsychotic treatment, the mean weight gain is highest in clozapine use (Leucht et al. 2013). Generally weight gain during antipsychotic treatment is fastest during the first 3-4 months of use, reaching a plateau after long term use (Rummel-Kluge et al. 2010, Wetterling 2001). Differences are observed between the antipsychotics in reaching the plateau level, with possible continuation of weight gain for 4 years and further during clozapine use (Rummel-Kluge et al. 2010, Henderson et al. 2000). There are not adequate data to support the attribution of this side effect to dosage and plasma levels of clozapine (Citrome et al. 2016, Simon et al. 2009).

Metabolic syndrome is a complex disorder with combination of factors increasing the risk of cardiovascular disease and DM-type II (Cornier et al. 2008). There are different diagnostic criteria for metabolic syndrome, the most frequently used being those stipulated by the US National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III - Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults 2001), by the ATP III adapted (Grundy et al. 2004) and by the International Diabetes Federation (IDF) (2005), which propose equal threshold values for blood pressure, fasting blood triglyceride and HDL levels but different values for fasting blood glucose level and the waistline circumference measurement. The ATP III and ATP IIIA base diagnosis on minimally 3 of the 5 clinical criteria, while IDF recommends minimally 2 criteria and the measurement of the waist line circumference to be included for diagnosis.

Metabolic syndrome is diagnosed more frequently in patients on treatment with the second generation antipsychotic agents especially with olanzapine and clozapine (Papanastasiou 2013). Metabolic effects of clozapine create a risk for cardiovascular disease and DM-type II (Hirsch et al. 2017). Diagnostic criteria for metabolic syndrome were reported to be met by 53.8% of the clozapine using patients (Lamberti et al. 2006). Metabolic syndrome prevalence determined on the basis of the ATP III, ATP IIIA and the IDF diagnostic criteria varied, respectively, as 34.2%, 37% and 41.7%, in 319 schizophrenia patients treated in our clinic with 32.6% of the patients being on clozapine treatment (Yazıcı et al. 2011). This study was continued after a mean interval of 8 years with reevaluation of 149 patients maintained on different antipsychotic agents with 106 (73.1%) only using clozapine or olanzapine. Metabolic syndrome prevalence was found to have increased from 35.6% to 44.3%, from 38.9% to %53 and from 43.6% to 55.7% on the basis of, respectively, the ATP-III, ATP-IIIA and IDF criteria; and presence of metabolic syndrome was found not to correlate with factors of age, gender, disease duration and cigarette smoking (Yoca et al. 2019).

Schizophrenia which is a disorder with symptoms involving the thought content, affect, perception and cognitive functions and causes disturbance in daily functioning, is one of the main causes of disability (WHO 2011). Patients with schizophrenia have deficits in many domains of daily functioning which may cause permanent disability in 80% of the patients (Zipursky et al. 2013). Investigations on the effects of the second generation antipsychotic agents on quality of life are predominated by studies on clozapine in treatment resistant schizophrenia. Clozapine has been observed to increase the psychometric scores on quality of life (Naber et al. 2001). Next to the improvements in the psychopathology, different outcomes are observed on the disabilities in relation to the adverse side effects of the drug. Although the treatment is terminated with development of serious and life threatening side effects such as agranulocytosis or myocarditis, the impact of the frequently observed side effects on the treatment and disability may be overlooked. Therefore, there is need for studies on the relationship of the side effects and the clinical markers in order to determine side effects that can result in disability.

The several aims of this study on the use of clozapine in schizophrenia include evaluating together the prevalence and the severity of the side effects, investigating the relationship of the side effects with clinical variables, determining the side effects the patients subjectively complain most about, conducting physical and laboratory tests to assess the prevalence of metabolic syndrome , determining the effects of clinical variables on the development of metabolic syndrome and evaluating the impact of the side effects on disability.

Patients complaining of clozapine caused side effects have been evaluated after separation into groups on the basis of the side effect severity. There are limited number of studies in the literature on investigation on the relationship between side effects and their severity on clinical variables with inclusion of data on the dosage and plasma levels of clozapine.

METHOD

Participants

This study is a cross sectional evaluation of clozapine using schizophrenia patients presenting to the outpatient clinic of Hacettepe University Medical Faculty Department of

Psychiatry. The participants consisted of patients of 18-65 years of age, meeting the schizophrenia diagnosis criteria of the DSM-IV (American Psychiatric Association –APA-1994), accepting to give written informed consent when invited to join the study. The design and the aim of the study was given the approval coded "E.K. No: GO15-4801" by the Hacettepe University Non-Interventional Clinical Research Ethics Committee.

Out of the total of 147 patients reached, 13 refused to participate, 11 were diagnosed with schizoaffective disorder after the SCID I interview and 1 patient was excluded on grounds of Parkinson's Disease comorbidity, leaving 122 patients to be included as the participants of the study.

Assessment Tools for Clinical Evaluation

Sociodemographic and clinical information was acquired on the Sociodemographic and Clinical Questionnaire on the basis of the history taken from the participants and their relatives during clinical interviews and by reviewing hospital charts. The participants were assessed by the Structured Clinical Interview for DSM-IV (SCID I), the UKU – Side Effect Rating Scale, the WHO Disability Assessment Schedule-II (WHO-DAS II), the Positive and Negative Syndrome Scale (the positive, negative and general psychopathology sub scores), The Global Assessment Scale (GAS), the Clinical Global Impression Scale (CGI) (disease severity and side effect severity) to evaluate the clinical situation and the level of functioning.

Sociodemographic and Clinical Information Questionnaire : The sociodemographic and clinical data of the participants, including the clinical variables queried as "before" and "after" clozapine use, and the subjective complaints of the participants on clozapine side effects, apart from the evaluations on the UKU, were recorded in this form.

The Structured Clinical Interview for DSM-IV Axis I Disorders- SCID-: The SCID is the structured clinical interview chart investigating the existence of Axis I diagnoses according to the DSM-IV by taking into consideration "the current situation" and "the life time" characteristics in healthy and sick people. The presence of the diagnostic criteria depend on symptoms exceeding the threshold severity. The SCID was developed by First et al (1997) and translated to the Turkish language and standardized for reliability by Özkürkçügil et al. (1999).

The Positive and Negative Syndrome Scale- PANSS: The PANSS was originally developed by Kay et al. (1987) primarily for evaluating the positive and negative symptoms in schizophrenia. It is a semistructured interview, consisting of 30 items each evaluating symptom severity over 7 points. Translation to the Turkish language and the study for validity and reliability was carried out by Kostakoğlu (1999).

The Clinical Global Impression Scale-CGI: The CGI was developed by Guy et al. (1976) for evaluating all psychiatric disorders at each age and observing the changes during follow up. The CGI has 3 dimensions to assess disease severity, the improvement relative to the previous evaluation, and the severity of side effects.

The Global Assessment Scale-GAS: The GAS assesses the general wellbeing and functioning of an individual by using variables related to disease symptoms, the overall social and professional functioning and the ability to cope with problems (Endicott et al. 1976). Evaluations of health-disease level of psychiatric patients are based on history taking and the information acquired from the relatives of the patients. These are graded by giving scores between 1 and 100, corresponding to the least and the most healthy individual. In our study score intervals have been used for evaluating the participants by grouping them on the basis of 20- score intervals as shown in Table 2. Correlation analyses were used to evaluate wellbeing on the basis of 10-score intervals.

The UKU Side Effect Rating Scale-UKU: The UKU Sacle (Udvalg for Kliniske Undersogelser-The Committee on Clinical Investigations) was developed to evaluate users of psychotropic agents and to scan the side effects of antipsychotic agents used (Lingjaerde et al. 1987). It comprises 48 items evaluating psychological, neurological, autonomic and other side effect symptoms of the last 72 hours and the severity is scored between 0 and 3. In our study, the scores are grouped on the basis of 0 score for none, 1 for mild, 2 for moderate and 3 for high severity.

The World Health Organization Disability Assessment Schedule-II - WHO-DAS-II: The WHO-DAS-II is a 36-item semistructured interview (WHO 1999) developed to assess the limitations in the activity level and social relationships of individuals independently of medical diagnoses. It comprises 6 different domains common to and considered important by many cultures, including (1) understanding and communicating with the world, (2) moving and getting around, (3) self-care, (4) getting along with people, (5) life activities, (6) participation in society., and includes questions on the difficulty experienced in activities related to each domain, and the answers are scored between 1 and 5. The total score on the WHO-DAS-II is calculated using a special formula, by weighing the scores on the basis of the number of the questions, the maximum score being 100. The validity and reliability of WHO-DAS-II in the Turkish language was carried out by Uluğ et al. (2001).

Physical Measurements and Laboratory Investigations

Physical measurements of the participants were recorded concurrently with the clinical evaluations by the same responsible nurse. Body weight (kg), height (cm), systolic and diastolic blood pressure (mm Hg) were measured after a 15-min rest, with the left arm at the level of the heart. The waistline circumference (cm) was measured midway between the lowest rib and the iliac crest parallel to the floor, with the participant fasting, wearing the thinnest clothing and standing upright.

Lipid profile, fasting blood glucose level, plasma clozapine and norclozapine levels were measured and recorded. Blood clozapine trough concentration was measured by High Performance Liquid Chromatography (HPLC).

Statistical Analysis

Statistical analyses were made using the IBM SPSS- Windows Version 22.0 software. Numerical variables were expressed by the mean, standard deviation or the median [minimum – maximum] value. Categorical variables were expressed by numbers and percentages. Normality in the distribution of the numerical values was tested by the Kolmogorov Smirnov test, and the homogeneity of the variances were analyzed by the Levene test. The difference between two independent groups of numerically expressed variables was assessed by the T test in independent groups, provided the parametric assumptions were met, or by the Mann-Whitney U-test if these assumptions were not met. Comparison of more than 2 independent groups was made by the one-way variation analysis when the parametric test assumptions were met. Correlation between numerical variables were analyzed by the Spearman correlation coefficient. The clinical scales with effects on the WHO-DAS-II score were determined by the multiple linear regression analysis (the hierarchical model). A result of $p<0.05$ was accepted to indicate statistical significance.

RESULTS

Sociodemographic and Clinical Data of the Participants

The participants of the study comprised 122 clozapine using schizophrenia patients who presented to the outpatient clinic of the Department of Psychiatry at Hacettepe University Faculty of Medicine. Demographically, they consisted of 57 (46.7%) females and 65 (53.3%) males, with a mean age of 41.4±10.65 years, mean education of 11.59±3.56 years; 86 (70.5%) being single, 23 (18.9%) married and 13 (10.7%) divorced. Clinically, the mean age at onset of illness was 21.79±6.23 years, with a median value of 17.5 years for duration of illness and a median value of 96 months for the duration of clozapine use. The mean duration of clozapine use and the median value for the interval between the onset of illness and the initiation of clozapine treatment were 118.31±92.74 months and 98 months, respectively. The mean dose of clozapine prescribed per participant was 381.35±163.69 mg, with the mean plasma clozapine and norclozapine levels being, respectively, 828.11±445.5 ng/mL and 364.66±200.17 ng/mL, and the clozapine/norclozapine ratio being 2.45±0.89. The data on the blood levels of metabolic parameters and the body measurements of the participants are shown in Table 1.

Table 1. Sociodemographic and Clinical Characteristics of Participants (n=122)

	n (%)	
Gender		
Female	57 (46.7%)	
Male	65 (53.3%)	
Marital Status		
Single	86 (70.5%)	
Married	23 (18.9%)	
Divorced	13 (10.7%)	
Cigarette Use		
No	75 (61.5%)	
Yes	47 (38.5%)	
Lifetime cigarette use		
No	55 (45%)	
Yes	67(55%)	
	Mean ± SD	**Median**
Age	41.4±10.65	
Duration of education (years)	11.59±3.56	
Age at onset of illness (years)	21.79±6.23	
Duration of illness (years)	19.61±8.84	17.5
Time interval before clozapine therapy (month)	118.31±92.74	98
Duration of clozapine use (month)	110.08±66.74	96
Clozapine dose (mg/day)	381.35±163.69	350
Clozapine plasma level* (ng/mL)	828.11±445.5	
Norclozapine plasma level (ng/mL)	364.66±200.17	
Clozapine /norclozapine	2.45±0.89	
Metabolic blood variables		
Total cholesterol (mg/dL)	222.59±48.16	
HDL (mg/dL)	49.54±14.65	
LDL (mg/dL)	152.61±37.4	
Triglycerides (mg/dL)	201.49±109.95	
VLDL (mg/dL)	40.3±21.96	
Cholesterol / HDL	4.74±1.22	
Fasting blood glucose (mg/dL)	105.25±29.71	
Body measurements		
Body mass index	30.75±6.46	
Systolic blood pressure (mmHg)	117.85±11.25	
Diastolic blood pressure (mmHg)	77.15±9.13	
Waistline circumference (cm)	106.76±14	

n: number, SD: standard deviation, *Clozapine levels have not been measured in 2 participants

Table 2. Clinical Assessment Scores (n = 122)

	Mean ± SD	Median
PANSS		
Positive	12.31±5.01	
Negative	18.93±7.99	
General psychopathology	27.48±7.5	
Total	58.56±17.52	56
WHO-DAS-II	27.95±19.37	23.96
CGI		
Disease severity	3.56±1.08	3
Side effect severity	2.17±0.72	2
UKU number of symptoms	8.7±0.45	8
	n (%)	
GAS		
21-40	11 (9%)	
41-60	66 (54.1%)	
61-80	37 (30.4%)	
>80	8 (6.6%)	

n: number, SD: standard deviation, PANSS: Positive and Negative Syndrome Scale, WHO-DAS-II: Disability Assessment Schedule-II, CCI: Clinical Global Impression Scale, UKU: UKU Side Effect Rating Scale, GAS: Global Assessment Scale

Results of the evaluations based on clinical scales are presented in Table 2. The mean group scores were 58.56±17.52 on the PANSS, 27.95±19.37 on the WHO-DAS-II. The mean number of symptoms on the UKU was 8.7±0.45. The median scores on the CGI for disease severity and the side effects severity were, respectively 3 and 2. The groupings according to the score intervals on the GAS were 9% for scores of 21-40, 54.1%, for scores of 41-60, 30.4% for scores of 61-80 and 6.6% for scores >80 .

It was determined that 47 (38.5%) participants were using cigarettes, and 20 out of the 75 (61.5%) were non-smokers who had used cigarettes in the past. The mean package/year was 23.3±2.34 for the lifetime smoking. The participants were grouped as smokers and non-smokers and intergroup differences of clozapine dose, the plasma clozapine and norclozapine levels and the clozapine/norclozapine ratio were determined. The clozapine dose used was found to be significantly higher (p=0.02) in the smoker group, the differences being statistically not significant in the other respects.

It was determined that while 35 of the patients were on clozapine monotherapy, 31 were using additional antipsychotics, 62 were on antidepressants, 10 were using benzodiazepine and 16 were on mood stabilizer/antiepileptic agents.

Clozapine Related Side Effects

On the basis of the UKU results, the side effect complaints were ranked as 87.7% for sialorrhea, 70.5% for fatigue, 61.5% for sedation, 56.6% for constipation, 37.7% for urinary incontinence, 35.3% for dizziness, 24.6% for tachycardia, and 18.8% for blurred vision. Common side effects are listed in Table 3, classified according to their severity. The levels of complaints were grouped on the basis of the UKU scoring of severity of side effects (0= none, 1=mild severity and 2-3=moderate to severe), and the relationships of the groups with the duration of clozapine use, clozapine dose, plasma levels of clozapine and norclozapine, and the clozapine/norclozapine ratio were evaluated (Table 4).

Participants expressing problems of sialorrhea, fatigue, sedation, constipation and urinary incontinence were evaluated in all 3 groupings of side effect severity. As the numbers of participants were low, moderate/severe side effect complaints of dizziness, blurred vision and tachycardia were grouped in the "present/not present" category. A statistically significantly correlation was determined between

Table 3. The Distribution and the Severity of the Frequently Observed Side Effects* (n = 122)

Side Effects	None	n (%) Present UKU side effect severity			
		1- Mild	2 Moderate	3- Severe	Total
Hypersalivation	15 (12.3%)	59 (48.4%)	19 (15.6%)	29 (23.8%)	107 (87.7%)
Fatigue	36 (29.5%)	57 (46.7%)	24 (19.7%)	5 (4.1%)	86 (70.5%)
Sedation	47 (38.5%)	47 (38.5%)	16 (13.1%)	12 (9.8%)	75 (61.5%)
Constipation	53 (43.4%)	45 (36.9%)	15 (12.3%)	9 (7.4%)	69 (56.6%)
Urinary incontinence	76 (62.3%)	35 (28.7%)	5 (4.1%)	6 (4.9%)	46 (37.7%)
Dizziness	79 (64.7%)	39 (32%)	3 (2.5%)	1 (0.8%)	43 (35.3%)
Tachycardia	92 (75.4%)	25 (20.5%)	5 (4.1%)	0 (0%)	30 (24.6%)
Blurred vision	99 (81.2%)	22 (18%)	1 (0.8%)	0 (0%)	18.8%)

*Side effects strongly associated with clozapine treatment were evaluated; side effects expressed by >20 patients were included, weight gain is separately shown

Table 4. Relationship Between Side Effect Severity and Clinical Variables (n= 122)

	Duration of Clozapine use (month)	Clozapine dose (mg)	Clozapine level (ng/mL)	Norclozapine level(ng/mL)	Clozapine/ Norclozapine
Hypersalivation					
Mean ±SD (n)					
None	132.73±68.24 (15)	340±171.34 (15)	622.36±383.31 (14)	337.89±245.62 (14)	2.02±0.81 (14)
Mild	104.07±59.14 (58)	396.19±183.17 (59)	863.61±430.25 (58)	380.06±193.98 (58)	2.51±0.95 (58)
Moderate/Severe	110.27±74.41 (48)	376.04±134.08 (48)	845.23±472.15 (48)	353.88±196.23 (48)	2.51±0.85 (48)
p*	0.336	0.478	0.181	0.697	0.154
Fatigue					
Mean ±SD (n)					
None	110.34±63.67 (36)	363.19±168.98 (36)	789.42±373.64 (36)	388.78±200.25 (36)	2.22±0.72 (36)
Mild	107.95±61.97 (56)	354.3±169.5 (57)	808.96±424.05 (56)	351.52±197.88(56)	2.54±1.04 (56)
Moderate/Severe	113.9±80.36 (29)	378.45±147.86 (29)	916.16±562.77 (28)	359.97±209.05 (28)	2.59±0.74 (28)
p*	0.928	0.671	0.484	0.681	0.163
Sedation					
Mean ±SD (n)					
None	110.45±66.99 (47)	394.68±176.46 (47)	900.86±496.06 (46)	389.96±191.14 (46)	2.35±0.78 (46)
Mild	112.35±70.99 (46)	403.72±166.16 (47)	796.55±407.01 (46)	348.03±198.7 (46)	2.55±1.01 (46)
Moderate/Severe	105.75±61.06 (28)	321.43±122.8 (28)	760.44±416.03 (28)	350.45±219.42 (28)	2.47±0.89 (28)
p*	0.919	0.084	0.352	0.555	0.548
Constipation					
Mean ±SD (n)					
None	102.4±68.89 (53)	325.47±145.98 (53)	787.59±431.94 (53)	346.19±211.12 (53)	2.51±0.88 (53)
Mild	113.11±65.85 (44)	437.78±165.8 (45)	887.62±428.95 (43)	383.64±190.44 (43)	2.54±1.05 (43)
Moderate/Severe	121.5±64.16 (24)	398.96±162.6 (24)	811±508.31 (24)	371.47±193.44 (24)	2.18±0.57 (24)
p*	0.477	0.020	0.541	0.652	0.244
Urinary incontinence					
Mean ±SD (n)					
None	107.71±65.18 (76)	399.34±169.66 (76)	849.17±456.33 (74)	373.45±203.07 (74)	2.49±0.95 (74)
Mild	107.79±61.78 (34)	375±159.62 (35)	817.89±424.21 (35)	360.61±194.09 (35)	2.44±0.81 (35)
Moderate/Severe	133.55±91.28 (11)	277.27±84.75 (11)	718.97±461.66 (11)	318.5±211.55 (11)	.22±0.88 (11)
p*	0.471	0.065	0.659	0.694	0.642
Dizziness					
Mean ±SD (n)					
None	113.05±68.95 (78)	373.73±170.26 (79)	792.44±414.91 (78)	336.18±183.67 (78)	2.53±0.92 (78)
Present	104.7±62.99 (43)	395.35±151.8 (43)	894.35±495.83 (42)	417.57±220.3 (42)	2.31±0.84 (42)
p**	0.512	0.488	0.234	0.033	0.189
Tachycardia					
Mean ±SD (n)					
None	108.07±68.12 (91)	384.78±161.55 (92)	838.58±484.26 (90)	357.93±201.05 (90)	2.5±0.89 (90)
Present	116.2±63.1 (30)	370.83±172.47 (30)	796.69±305.58 (30)	384.87±199.52 (30)	2.32±0.93 (30)
p**	0.565	0.687	0.581	0.526	0.342
Blurred vision					
Mean ±SD (n)					
None	109.74±70.14 (98)	367.42±157.85 (99)	826.8±462.42 (97)	367.52±208.08 (97)	2.45±0.87 (97)
Present	111.57±51.05 (23)	441.3±178.16 (23)	833.63±374.77 (23)	352.64±166.21 (23)	2.48±1.03 (23)
p**	0.906	0.051	0.948	0.750	0.857

*Variance analysis (ANOVA) **t-test for independent samples n: counts, SD: standard deviation
Levels of side effects were grouped according to UKU side effect severity score (0 points=none; 1 point= mild; 2-3 points= moderate/severe)

constipation and clozapine dose. Correlations with statistical significance were not determined between the rest of the side effect complaints and the clinical variables.

On the basis of current measurements and the information on history acquired from the participants and/or hospital files, the difference between the current body weight and that before starting clozapine treatment were compared and the calculated weight gain was attributed to clozapine use. Lest the certainty of data would be affected by the difficulty of recalling the past, the weight gain by the participants was grouped with ranges of increments. It was found that weight gain was nil in 25.8% of the participants, 1-5 kg in 15.7%, 6-10 kg in 23.6%, 11-15 kg in 16.9%, 16-20 kg in 14.6% and >20 kg in 29.2%.

The three adverse side effects that the participants subjectively found to be the most effective were asked to be stated in

the order of severity. Increased salivation was expressed by 71, constipation by 39, sedation by 33, and fatigue by 32 participants. Although weight gain was observed to be generalized, only 6 of the patients expressed discomfort about it.

Metabolic Syndrome

Body measurements and metabolic blood parameters were measured and the participants were queried on using any medication apart from the psychotropic agents. Checking the collected data for meeting metabolic syndrome diagnosis showed that 44.3% met the ATP-III, 50% met the ATP-IIIA and 54.1% met the IDF criteria. The participants with and without metabolic syndrome diagnoses were compared with respect to age, duration of illness, duration of clozapine use, clozapine dose and plasma levels and the total scores on the WHO-DAS-II and the PANSS. The groups of participants diagnosed with metabolic syndrome on the ATPIII criteria had a significantly higher mean age (p=0.037) than the others. The group diagnosed with respect to the IDF criteria had significantly lower clozapine/norclozapine ratio (p=0.035) and a significantly higher mean package/year cigarette use (p=0.017). The groups did not differ on the basis of the other clinical variables (Table 5).

When questioned on the use of non-psychiatric medication, it was found that 13 of the 122 participants were using insulin, 7 were on hypertensive agents, 3 were on antihypertensive agents and 3 on antilipidemic agents.

Table 5. Comparison of Participants with and without Metabolic Syndrome (n = 122)

			ATP-III				ATP-IIIA				IDF			
			n	**Mean**	**SD**	**p***	**n**	**Mean**	**SD**	**p***	**n**	**Mean**	**SD**	**p***
Age	METABOLIC SYNDROME	No	68	40.12	11.21	0.136	61	39.39	10.51	0.037	56	39.75	10.66	0.115
		Yes	54	43.02	9.79		61	43.41	10.51		66	42.80	10.54	
Duration of illness (year)		No	68	19.49	9.32	0.866	61	18.78	8.64	0.359	56	19.00	7.77	0.487
		Yes	54	19.76	8.27		61	20.34	9.04		66	20.12	9.68	
Duration of Clozapine use (month)		No	67	103.88	63.06	0.257	60	104.18	63.09	0.336	56	103.04	58.53	0.261
		Yes	54	117.78	70.90		61	115.89	70.20		66	115.96	72.81	
Clozapine dose (mg/day)		No	68	370.59	137.2	0.435	61	375.41	138.33	0.690	56	387.50	141.82	0.704
		Yes	54	394.91	192.45		61	387.3	186.62		66	376.14	181.1	
Clozapine level (ng/mL)		No	66	831.11	450.22	0.935	59	843.72	461.85	0.707	56	844.99	463.02	0.709
		Yes	54	824.45	443.87		61	813.01	432.42		66	814.30	433.74	
Norclozapine level (ng/mL)		No	66	343.3	179.49	0.197	59	342.46	378.17	0.234	56	334.85	179.25	0.141
		Yes	54	390.79	221.79		61	386.15	218.71		66	389.07	214.05	
Clozapine/norclozapine		No	66	2.54	0.90	0.256	59	2.57	0.93	0.171	56	2.64	0.93	0.035
		Yes	54	2.35	0.89		61	2.34	0.96		66	2.30	0.85	
						p**				**p****				**p****
WHO-DAS-II		No	68	26.19	16.68	0.663	61	26.73	17.11	0.916	56	26.24	16.58	0.809
		Yes	54	30.20	22.28		61	29.20	21.48		66	29.42	21.5	
PANSS total		No	68	59.97	15.25	0.438	61	57.18	15.86	0.525	56	57.09	15.85	0.473
		Yes	54	60.57	19.99		61	59.95	19.08		66	59.82	18.86	
Cigarette use (Lifetime package/year)		No	68	12.59	20.65	0.157	61	11.33	19.99	0.058	56	9.23	15.33	0.017
		Yes	54	13.49	15.50		61	14.64	16.85		66	16.17	20.36	

* t-test for independent samples, **Mann-Whitney U test, n:numbers, SD: standard deviation ATP III: US National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III - Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (2001); ATP IIIA: ATPIII Adapted-Adult Treatment Protocol; IDF: International Diabetes Federation, WHO-DAS-II: Disability Assessment Schedule-II,, PANSS: Positive and Negative Syndrome Scale

Results on Disability

Disability of the participants was evaluated on the WHO-DAS-II and the scores obtained were checked for correlation with age at onset of illness, the period taken until the initiation of clozapine treatment, the number of UKU side effect symptoms, the total scores on the CGI and the PANSS. A statistically significant correlation was determined between the increase in the number of UKU side effect symptoms and the increase in the severity of the disability. Also a positive correlation was found between the severity of the disability and the PANSS total score (r=0.697; p<0.001). The severity of disability correlated negatively with age at onset of illness (r=-0.197; p=0.030) and the CGI score (r=-0.548; p<0.001).

In order to find out the factors predicting disability, multiple linear regression analysis was carried out including the UKU results, the PANSS total score and the age at onset of illness. Results indicated that the PANSS total score and the number of UKU side effect symptoms predicted the WHO-DAS-II score (Table 6).

Table 6. Multiple Regression Analysis for Variables Predicting Disability (WHO-DAS-II)

	B	SH	β	t	p
UKU number of symptoms	0.959	0.25	0.244	3.826	<0.001
PANSS total	0.728	0.72	0.658	10.181	<0.001
Age at onset of illness	0.254	0.186	0.082	1.395	0.175
R^2= 59.8% F=58.555 p<0.001					

WHO-DAS-II: Disability Assessment Schedule-II, UKU-Side Effect Rating Scale, PANSS: Positive and Negative Syndrome Scale, SE: Standard error, β: Standardised coefficient; R^2:Determination Coefficient

DISCUSSION

The results of the study have shown that frequently observed side effects of clozapine ranked as hypersalivation (87.7%), fatigue (70.5%), sedation (61.5%), constipation (56.6%), urinary incontinence (37.7%), dizziness (35.3%), tachycardia (24.6%) and blurred vision (%18.8). When the clozapine side effects were classified as common (≥1/100), uncommon (≥1/1000) and rare (≥1/10000), the common complaints included hypersalivation, sedation, constipation, weight gain, nocturnal enuresis, hypotension, dizziness, tachycardia, blurred vision, seizures, hypertension, gastroesophageal reflux, non-malignant fever, blood dyscrasias and dysarthria (De Berardis et al. 2018). In this study, the evaluation of the severity of side effects is considered to be an important effort which enables an evaluation beyond the simple classification of side effects according to their presence.

Clozapine related increase in salivation was reported by others to vary in the 30-92% range (Maher et al. 2016, Praharaj et al. 2006, Syed et al. 2008). This prevalence was determined as 87.7% in our study and agrees with the 91.8% prevalence reported by Maher et al. (2016). The complaints of the participants varied as mild (48.4%), moderate (15.6%) and severe (23.8%). Our result on severe hypersalivation complaint exceeds that reported as 16.3-18.4% by Maher et al. (2016). Sedation complaint was expressed by 61.5% of our participants, the effect having been perceived as moderate to severe by 38.5% and as mild by 23% of the participants. Ramos Perdigues et al. (2016) reported that 64.7% of their patients slept for ≥ 9 hours per day. Fatigue was experienced by 70.5% of our participants, this observation being in agreement with the 79% prevalence reported by Kishi et al. (2013). Fatigue symptoms are being evaluated together with sedation and sleepiness (Citrome 2017), and in our study the participant complaints on fatigue and sedation were at close levels. The prevalence of constipation complaint was 56.6% in our study, the severity being perceived as mild (36.9%), and moderate/severe (19.7%), and the observed prevalences among our participants appears to be high as compared to 31.2% reported in the meta-analysis by Shirazi et al. (2016). Our result on the prevalence of urinary incontinence was 37.7% and the severity was expressed to be mild. The prevalence of clozapine caused nocturnal urinary incontinence was previously reported as 20.7% (Harrison-Woolrych et al. 2011), and persistence of this side effect was seen in 25% of the patients (Lin et al. 1999), the reported levels being lower than our finding. Complaints on dizziness (35%) and tachycardia (24.6%) were both experienced mildly by the majority of the participants of our study. In the third phase of the CATIE study, 24% of clozapine using patients were reported to experience loss of consciousness with severe orthostatic hypotension (Stroup et al. 2009). Tachycardia of >100beats/min was observed in nearly half of the clozapine using patients (Rostagno et al. 2011). In our study the side effects of tachycardia and dizziness were recorded as the subjective complaints of the participants and this may be one of the explanations for the differences in these results.

Hypersalivation, sedation and constipation draw attention as the side effects experienced at a severe level. These are also included among the subjective expressions of the participants such that, of the 3 most disturbing side effects, hypersalivation was ranked as primary complaint by 35 of

71 (58.2%) participants; constipation was ranked primary by 29 of 39 (32%); sedation was ranked primary by 12 of 33 (27.1%) and fatigue was ranked primary by 12 of 32 (26.2%) participants. It was thought that more complaints were expressed as the side effect severity increased and caused more difficulty in coping.

The side effect severity levels were grouped on the basis of the UKU scores and the groups were evaluated on the basis of the causative factors including the duration of clozapine use, clozapine dose, plasma levels of clozapine and norclozapine and the clozapine/norclozapine ratio. Statistically significant correlations were determined between dizziness and the plasma level of norclozapine and also between constipation and clozapine dose which confirmed the report by De Hert et al. (2011). Hypersalivation, fatigue, sedation, urinary incontinence, tachycardia and blurred vision did not correlate significantly with any of the tested factors.

A review of the results of 69 studies on the response to clozapine treatment and the side effects indicated that only 8 studies had looked into the relationship between the plasma level of clozapine and the side effects; in 4 of these studies significant relationships were not determined (Remington et al. 2013) and only in 1 study by Yusufi et al. (2007) the frequently observed side effects were evaluated in relation to their severity in 103 patients by grouping the plasma clozapine level as below and above 250 ng/mL. Statistically significant correlation was found between dosage in excess of 250 ng/mL and one or more complaints of moderate/severe non-neurological side effects that did not correlate with clozapine dose. Also, these side effects were not evaluated separately. Therefore, the investigation in our study of the relationships between each side effect and clozapine dose and plasma level is a significant contribution to the literature.

Prevalence of metabolic syndrome among the participants of our study was determined to be 44.3% on the basis of the ATP-III criteria, 50% on the ATP-IIIA criteria and 54.1% on the IDF criteria. These results show a parallelism with those of Lamberti et al. (2006) who reported that 53.8% of their patients met the diagnostic criteria for metabolic syndrome. A previous study carried out in our clinic on 149 schizophrenia patients using differing antipsychotic agents, with only 106 of whom were on clozapine or olanzapine treatment, determined metabolic syndrome prevalences of 44.3%, 53% and 55.7% on, respectively, the ATP-III, ATP-IIIA and the IDF diagnostic criteria (Yoca et al. 2019). Our results obtained with only clozapine using participants has contributed to this study.

The participants of our study with and without a metabolic syndrome diagnosis were compared with respect to age, gender, duration of illness, duration of clozapine treatment, clozapine dose and plasma level, the WHO-DAS-II and PANSS total scores and lifetime cigarette use. They were found to differ with respect to the factor of age on the basis of the ATP-IIIA criteria and with respect to clozapine/norclozapine ratio and the number of packages per year cigarette smoking on the basis of the IDF diagnostic criteria. In contrast to the results of our study, cigarette smoking was reported not to affect metabolic syndrome development in a group of patients 23% of whom were on clozapine treatment (Schorr et al. 2009); and, in a previous research in our clinic with patients 73% of whom were on clozapine treatment, lifetime smoking was not found to affect metabolic syndrome development (Yoca et al. 2019). In both of these studies, a statistically significant relationship was not determined between the presence of metabolic syndrome and the factors of age, gender, duration of illness and cigarette use.

Having included in our study only participants treated with clozapine, it is seen that clozapine dose and plasma level, and clinical variables such as duration of illness and of clozapine use did not significantly affect the development of metabolic syndrome. It is believed that rather than the effect of the drug per se, the individual differences among patients, multiple factors including the combined burden of the therapy, reduced self-care, incorrect nutrition, lack of exercise and cigarette use play a role in the development of metabolic syndrome in schizophrenia (Zhu et al. 2004).

In our study querying 122 participants on the use of non-psychiatric drugs showed that 13 were on insulin for diabetes mellitus, 7 were using antihypertensive agents and 3 were on antilipidemic agents. It is noteworthy that, given around 50% prevalence of metabolic syndrome among the participants, the observed drug use appeared to be low. This suggested that they were not benefiting adequately from healthcare, similarities having been observed in the results of past studies made in our country (Yazıcı et al. 2011, Yoca et al. 2019).

Schizophrenia is a heterogeneous mental disorder with a course of impairment on thinking, perception, emotions and behavior resulting in serious disability. There is not a study in the literature on the relationship between the frequently observed clozapine side effects and disability. Our study determined that the increase in disability correlated with the clozapine dependent increase in the number of side effects, the increase in the severity of the psychopathology and with the early age of onset of illness. Also, the number of side effects and the severity of the psychopathology were

found to predict disability. Similar to our results, previous evaluation of 60 schizophrenia patients on the WHO-DAS-II demonstrated a significant relationship between disease severity and disability, with the disease severity predicting the level of disability (Ertuğrul and Uluğ 2002).

A systematic review of 104 studies evaluating the difficulties experienced by schizophrenia patients reported that disability and functioning were evaluated in 36% and quality of life and wellbeing were evaluated in 23.1% of these studies, while 55.8% of the studies were concerned with treatment methods in relation to the severity and the course of the experienced difficulties, with only 6.7% of the studies being on treatment caused side effects. An emphasis was made on the paucity of investigations on this subject (Switaj et al. 2012). The adversity of clozapine side effects leads to different outcomes in disability. In treatment resistant schizophrenia, although clozapine might reduce disease severity, disability can be augmented against expectations with the burden of the developing metabolic side effects, the sedentary lifestyle and inadequacies of the daily activity (Harvey et al. 2019). Despite associating disability in schizophrenia with inadequate response or resistance to antipsychotic treatment, there is not clear data pointing to decreased disability, with most studies focusing on decreases in aggression and the number of hospitalizations (Harvey et al. 2019). In order to demonstrate with clarity, the relationship between disability and clozapine treatment, there must be comparative and observational work with clozapine and other antipsychotic agents. In our study, the WHO-DAS-II score correlated negatively with CGI results, demonstrating that as disability advanced, wellbeing and functionality of the participants deteriorated. The existence of a strong association in schizophrenia between disability and the daily life activities has been known (McKibbin et al. 2004).

The cross-sectional and retrospective design, the difficulties faced in reaching hospital files and with patient memory when clinical characteristics were investigated, participant being on psychotropic agents in addition to clozapine and the lack of a control group of participants treated with antipsychotic agents other than clozapine are among the limitations of our study.

There are limited number of studies on the relationship between the common side effects of clozapine treatment and clozapine dose and plasma levels, with most of the existing work focusing on the number of the side effects. Our results have indicated that each side effect should be evaluated on its own with objective measurements or observations. A multidisciplinary approach is needed for monitoring the patients with schizophrenia and enable them to reach healthcare services. For ensuring the positive effects of clozapine treatment on the disability and functioning of the patients, determination and control of the side effects appears to be important.

REFERENCES

Anıl Yağcıoğlu AE, Ertuğrul A (2011) Antipsikotik ilaçların kardiyovasküler yan etkileri. Psikiyatride Güncel 1:251-65.

Asenjo Lobos C, Komossa K, Rummel-Kluge C et al (2010) Clozapine versus other atypical antipsychotics for schizophrenia. Cochrane Database Syst Rev 10:CD006633.

Bleakley S, Taylor D (2013) The Clozapine Handbook. 1. ed. Warwickshire, Lloyd-Reinhold Communications LLP, p. 36 -119.

Citrome L (2017) Activating and sedating adverse effects of second-generation antipsychotics in the treatment of schizophrenia and major depressive disorder: absolute risk increase and number needed to harm. J Clin Psychopharmacol 37:138-47.

Citrome L, McEvoy JP, Saklad SR (2016) Guide to the management of clozapine-related tolerability and safety concerns. Clin Schizophr Relat Psychoses 10:163-77.

Cornier MA, Dabelea D, Hernandez TL et al (2008) The metabolic syndrome. Endocr Rev 29:777-822.

De Berardis D, Rapini G, Olivieri L et al (2018) Safety of antipsychotics for the treatment of schizophrenia: a focus on the adverse effects of clozapine. Ther Adv Drug Saf 9:237-56.

De Hert M, Hudyana H, Dockx L et al (2011) Second-generation antipsychotics and constipation: a review of the literature. Eur Psychiatry 26:34-44.

De Leon J, Armstrong SC, Cozza KL (2005) The dosing of atypical antipsychotics. Psychosomatics 46:262-73.

De Leon J, Odom-White A, Josiassen RC et al (2003) Serum antimuscarinic activity during clozapine treatment. J Clin Psychopharmacol 23:336–41.

Endicott J, Spitzer R, Fleiss J et al (1976) The global assessment scale. Arch Gen Psychiatry 33:766-71.

Ertuğrul A, Uluğ B (2002) The influence of neurocognitive deficits and symptoms on disability in schizophrenia. Acta Psychiatr Scand 105:196-201.

Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (2001) Executive summary of the third report of the National Cholesterol education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). JAMA 285:2486–97

First MB, Spitzer RL, Gibbon M et al (1997) DSM-IV Eksen I Bozuklukları İçinYapılandırılmış Klinik Görüşme (SCID-I/CV) (Çev.: A. Çorapçıoğlu). Ankara, Hekimler Yayın Birliği, 1999.

Fukuda K, Straus SE, Hickie I et al (1994) The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. Ann Intern Med 121:953-9.

Grundy SM, Brewer B, Cleeman JL et al (2004) Definition of metabolic syndrome: report of the National Heart, Lung, And Blood Institute/ American Heart Association Conference on scientific issues related to definition. Circulation 109:433–8

Gugger JJ, Ehret MJ (2016) Chapter 4 - Orthostatic Hypotension. Life-threatening effects of antipsychotic drugs, 1st Ed. Manu P, Flanagan RJ, Ronaldson KJ (Ed), San Diego, Academic Press, p. 81 - 101.

Guy, W. (1976) ECDEU assessment manual for psychopharmacology-revised (DHEW Publ No ADM 76-338), MD, US Department of Health, Education, and Welfare. Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, NIMH Psychopharmacology Research Branch, Division of Extramural Research Programs, Rockville,1076, p. 217-22.

Harrison-Woolrych M, Skegg K, Ashton J et al (2011) Nocturnal enuresis in patients taking clozapine, risperidone, olanzapine and quetiapine: comparative cohort study. Br J Psychiatry 199:40-4.

Harvey PD, Strassnig MT, Silberstein J (2019) Prediction of disability in schizophrenia: Symptoms, cognition, and self-assessment. J Exp Psychopathol 10: 1–20

Henderson DC, Cagliero E, Gray C et al (2000) Clozapine, diabetes mellitus, weight gain, and lipid abnormalities: A five-year naturalistic study. Am J Psychiatry 157:975-81.

Hirsch L, Yang J, Bresee L et al (2017) Second generation antipsychotics and metabolic side effects: a systematic review of population-based studies. Drug Saf 40:771–81.

International Diabetes Federation (2005) The IDF Consensus Worldwide Definition of the Metabolic Syndrome. International Diabetes Federation, Brussels

Kay SR, Fiszbein A, Opler LA (1987) The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull13:261-75.

Kishi T, Fujita K, Furukawa O et al (2013) Efficacy and tolerability of clozapine in Japanese patients with treatment resistant schizophrenia: results from a 12-week, flexible dose study using raters masked to antipsychotic choice. Asian J Psychiatr 6:200-7

Kostakoğlu AE, Batur S, Tiryaki A et al (1999) Pozitif ve negatif sendrom ölçeğinin (PANSS) Türkçe uyarlamasının geçerlilik ve güvenilirliği. Türk Psikoloji Dergisi 14:23-32.

Lamberti JS, Olson D, Crilly JF et al (2006) Prevalence of the metabolic syndrome among patients receiving clozapine. Am J Psychiatry 163:1273-6.

Lameh J, Burstein ES, Taylor E, et al (2007) Pharmacology of N-desmethylclozapine. Pharmacol Ther 115: 223–31.

Leucht S, Cipriani A, Spineli L et al (2013) Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. Lancet. 382:951–62.

Lin CC, Bai YM, Chen JY (1999) A retrospective study of clozapine and urinary incontinence in Chinese in-patients. Acta Psychiatr Scand 100:158-61.

Lingjaerde O, Ahlfors UG, Bech P et al (1987) The UKU side effect rating scale. A new comprehensive rating scale for psychotropic drugs and a cross-sectional study of side effects in neuroleptic-treated patients. Acta Psychiatr Scand Suppl. 334: 1-100.

Mackin P (2008) Cardiac side effects of psychiatric drugs. Hum Psychopharmacol 23(Suppl. 1):3-14.

Maher S, Cunningham A, O'Callaghan N et al (2016) Clozapine-induced hypersalivation: an estimate of prevalence, severity and impact on quality of life. Ther Adv Psychopharmacol 6:178-84.

McEvoy JP, Lieberman JA, Stroup TS et al (2006) CATIE Investigators. Effectiveness of clozapine versus olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia who did not respond to prior atypical antipsychotic treatment. Am J Psychiatry 163:600-10.

McKibbin C, Patterson TL, Jeste DV (2004) Assessing disability in older patients with schizophrenia: results from the WHODAS-II. J Nerv Ment Dis 192:405-13.

Miller DD (2000) Review and management of clozapine side effects. J Clin Psychiatry 61 (Suppl. 8):14-7.

Naber D, Moritz S, Lambert M et al (2001) Improvement of schizophrenic patients' subjective well-being under atypical antipsychotic drugs. Schizophr Res 30;50:79-88.

Olianas MC, Dedoni S, Ambu R et al (2009) Agonist activity of n-desmethylclozapine at δ-opioid receptors of human frontal cortex. Eur J Pharmacol 607:96–101.

Özkürkçügil A, Aydemir Ö, Yıldız M et al (1999) DSM-IV eksen I bozuklukları için yapılandırılmış klinik görüşmenin Türkçeye uyarlanması ve güvenilirlik çalışması. İlaç ve Tedavi Dergisi 12:233-6.

Palmer SE, McLean RM, Ellis PM et al (2008) Life-threatening clozapine-induced gastrointestinal hypomotility: an analysis of 102 cases. J Clin Psychiatry 69:759-68.

Papanastasiou E (2013) The prevalence and mechanisms of metabolic syndrome in schizophrenia: a review. Ther Adv Psychopharmacol 3:33-51.

Praharaj SK, Arora M, Gandotra S (2006) Clozapine-induced sialorrhea: pathophysiology and management strategies. Psychopharmacology (Berl) 185:265-73.

Raedler TJ (2010) Cardiovascular aspects of antipsychotics. Curr Opin Psychiatry 23:574-81.

Ramos Perdigués S, Sauras Quecuti R, Mané A et al (2016) An observational study of clozapine induced sedation and its pharmacological management. Eur Neuropsychopharmacol 26:156-61.

Remington G, Agid O, Foussias G, et al (2013) Clozapine and therapeutic drug monitoring: is there sufficient evidence for an upper threshold? Psychopharmacology (Berl) 225:505-18.

Remington G, Lee J, Agid O et al (2016) Clozapine's critical role in treatment resistant schizophrenia: ensuring both safety and use. Expert Opin Drug Saf 15:1193–203.

Rostagno C, Domenichetti S, Pastorelli F et al (2011) Usefulness of NT-pro-BNP and echocardiography in the diagnosis of subclinical clozapine-related cardiotoxicity. J Clin Psychopharmacol 31:712–6.

Rummel-Kluge C, Komossa K, Schwarz S et al (2010) Head-to-head comparisons of metabolic side effects of second generation antipsychotics in the treatment of schizophrenia: a systematic review and meta-analysis. Schizophr Res 123:225-33.

Schorr SG, Sloof CJ, Bruggeman R et al (2009) The incidence of metabolic syndrome and its reversal in a cohort of schizophrenic patients followed for one year. J Psychiatr Res 43: 1106–11

Shirazi A, Stubbs B, Gomez L et al (2016) Prevalence and Predictors of Clozapine-Associated Constipation: A Systematic Review and Meta-Analysis.Int J Mol Sci 17:863.

Simon V, van Winkel R, De Hert M (2009) Are weight gain and metabolic side effects of atypical antipsychotics dose dependent? A literature review. J Clin Psychiatry 70:1041-50.

Sockalingam S, Shammi C, Remington G (2007) Clozapine-induced hypersalivation: a review of treatment strategies. Can J Psychiatry 52:377-84.

Solmi M, Murru A, Pacchiarotti I et al (2017) Safety, tolerability, and risks associated with first- and second-generation antipsychotics: a state-of-theart clinical review. Ther Clin Risk Manag 13:757–77.

Stroup TS, Lieberman JA, McEvoy JP et al (2009) Results of phase 3 of the CATIE schizophrenia trial. Schizophr Res 107:1–12.

Switaj P, Anczewska M, Chrostek A et al (2012) Disability and Schizophrenia: A Systematic Review of Experienced Psychosocial Difficulties. BMC Psychiatry 12:193.

Syed R, Au K, Cahill C, Duggan L et al (2008) Pharmacological interventions for clozapine-induced hypersalivation. Cochrane Database Syst Rev 16:CD005579.

Taylor D, Paton C, Kapur S (2015) Maudsley Prescribing Guidelines. 12. ed. Oxford, Wiley-Blackwell. 165-85.

Uluğ B, Ertuğrul A, Göğüş A, Kabakçı E (2001) Yetiyitimi değerlendirme çizelgesinin (WHO-DAS-II) şizofreni hastalarında geçerlilik ve güvenilirliği. Turk Psikiyatri Derg 12:121-30.

Waters F, Naik N, Rock D (2013) Sleep, fatigue, and functional health in psychotic patients. Schizophr Res Treatment 2013:425826.

Wetterling T (2001) Bodyweight gain with atypical antipsychotics. A comparative review. Drug Saf 24:59-73.

World Health Organization (2011) Clozapine and life-threatening gastrointestinal hypomotility. WHO Drug Information 25:29-30.

World Health Organization (2011) World report on disability 2011. Downloaded from https://www.who.int/disabilities/world_report/2011/report.pdf on May 10, 2020.

Yazıcı MK, Anıl Yağcıoğlu AE, Ertuğrul A et al (2011) The prevalence and clinical correlates of metabolic syndrome in patients with schizophrenia: findings from a cohort in Turkey. Eur Arch Psychiatry Clin Neurosci 261:69-78.

Yoca G, Anıl Yağcıoğlu AE, Eni N et al (2019) A follow-up study of metabolic syndrome in schizophrenia. Eur Arch Psychiatry Clin Neurosci 27 Nisan 2019, online publishing.

Yusufi B, Mukherjee S, Flanagan R et al (2007) Prevalence and nature of side effects during clozapine maintenance treatment and the relationship with clozapine dose and plasma concentration. Int Clin Psychopharmacol 22:238–43

Zhu S, St-Onge MP, Heshka S et al (2004) Lifestyle behaviors associated with lower risk of having the metabolic syndrome. Metabolism 53:1503-11.

Zipursky RB, Reilly TJ, Murray RM (2013) The myth of schizophrenia as a progressive brain disease. Schizophr Bull 39:1363–72.

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