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The Role of the Central and the Peripheral Neuropeptides in Weight Gain and Metabolic Changes Related to Olanzapine

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ABSTRACT

Objective: This study aimed to examine the role of central and peripheral neuropeptides in olanzapine-induced weight gain and metabolic changes.

Materials and Methods: Thirty patients who would receive olanzapine treatment were evaluated at the beginning of the treatment at the 2nd and 8th weeks. Weight, waist circumference, the central neuropeptides pro-opiomelanocortin (POMC) and neuropeptide Y (NPY), and the peripheral adipokine leptin and the peripheral peptide cholecystokinin (CCK) levels were measured in each control. In addition, biochemical parameters such as fasting blood glucose (FBG), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), total and direct bilirubin, very-low-density lipoprotein (VLDL), low-density lipoprotein (LDL), high-density lipoprotein (HDL), total cholesterol, and triglyceride (TG) were measured.

Results: There were statistically significant differences weight and waist circumference levels compared to the initial levels. As observed in previous studies in the literature, changes in biochemical parameters including AST, ALT, total and direct bilirubin, LDL, TG, total cholesterol, and HDL levels were statistically significant. Levels of the neuropeptides POMC and NPY tended to increase at early stages and decrease at later stages of the treatment, while CCK and leptin levels kept increasing throughout the treatment period. The changes in POMC and CCK levels were statistically significant.

Conclusion: The results suggest that POMC and CCK may play a role in olanzapine-related weight gain.

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KEYWORDS: Neuropeptide, olanzapine, weight gain

INTRODUCTION

Olanzapine is a commonly used antipsychotic drug for various psychiatric conditions, including bipolar mood disorder and major depression with psychotic features. Its metabolic side effects, including weight gain, limit olanzapine use despite the clinical benefits. Studies show that olanzapine is one of the most common excessive weight gain-causing antipsychotic drugs.[1,2]

Weight gain is a predisposing factor for various major and life-threatening conditions such as dyslipidemia, hypertension, diabetes, atherosclerosis, and metabolic syndrome. Physical slowness and social pressure caused by impaired physical appearance due to weight gain affect patient's compliance with drug use negatively. Weight gain and weight gain-related physical and psychological health problems are the main factors for impaired patient compliance with drug use.[3] Since regular and scheduled use of the medication is one of the essential components for preventing the exacerbation and the recurrence of psychotic diseases, weight gain as a side effect is an obstacle for treatment compliance. Thus, during the last

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decade, many studies investigating the possible mechanisms underlying antipsychotic drug-related weight gain have been performed. Nutrition physiology and the feeding-fasting cycles are mainly controlled by various central neuropeptides, which are released by the hypothalamus (neuropeptide Y, pro-opiomelanocortin, cocaine- and amphetamine-regulated transcript, agouti-related protein), peripheral peptides (ghrelin, cholecystokinin), adipokines (leptin, adiponectin) and hormones (insulin).[4] While peripheral mechanisms of antipsychotic drug-related weight gain were commonly investigated in the past, central mechanisms have been more commonly scrutinized recently. Recent studies report that the primary mechanism behind antipsychotic drug-related weight gain is the stimulation of the hypothalamic appetite-regulating mechanism.[5,6] Leptin, which is released by the adipose tissue and regulates theorexigenic and anorexigenic peptides in the hypothalamic arcuate nucleus (ARC), has been one of the most investigated agents.[7-9]

In addition to leptin, orexigenic neuropeptides regulating the central food intake control mechanisms and serotonin and dopamine receptors on the neuropeptide releasing neurons have been the main targets of the studies.[5,6] Pro-opiomelanocortin (POMC) and cocaine and amphetamine-regulated transcript (CART) are anorexygenic neuropeptides while neuropeptide Y (NPY) and agouti-related protein (AgRP) are orexygenic neuropeptides. It has been suggested that olanzapine changes the balance of the neuropeptide release via effecting the receptors on the central hypothalamic appetite-regulating neurons and thereby causes weight gain.[10] The results of the studies regarding this mechanism are still not precise, and further studies are needed to understand the mechanism clearly. In many studies, neuropeptide levels were measured twice: once at the beginning and once at the end of the study. However, as repetitive measurements were not performed, these studies did not provide enough data on the compensatory mechanisms. Many studies had a limited number of patients, which affected the generalizability of the results in a negative way. There are not enough data about the interactions of the central and the peripheral variables that participate in the control of food intake.

The primary aim of this study was to show the changes in body weight and waist circumference after olanzapine prescription and investigate the relationship of these changes with the central and the peripheral peptides. The secondary aim of the study was to evaluate the effects of olanzapine treatment on various metabolic parameters such as fasting blood glucose (FBG), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), total and direct bilirubin, very-low-density lipoprotein (VLDL), low-density lipoprotein (LDL), high-density lipoprotein (HDL), total cholesterol, and triglyceride (TG).

MATERIALS AND METHODS

Ethical Committee Approval

Necmettin Erbakan University Meram Faculty of Medicine Clinical Research Ethics Committee approved the study vide Decision number 2017/141 dated July 05, 2017.

Study Participants

Psychiatric patients who applied to the outpatient clinics with psychotic conditions such as schizophrenia, schizoaffective disorder, acute psychotic attack, bipolar disorder, and depression with psychotic features, aged 18-65 years, and who were going to receive olanzapine treatment for the first time were included in the study. Eighty percent ($n=24$) of the patients were female and 20% ($n=6$) were male. The mean age was 40.06 years (range 19-63 years). About 33.3% ($n=10$) of the patients were with acute psychosis attacks for the first time, 66.6% ($n=20$) had a previous diagnosis of a psychotic disease such as schizoaffective disorder, bipolar disorder, and depression with psychotic features (Table 1).

Exclusion criteria were as follows: age <18 and >65 years, history/current use of olanzapine, additional metabolic or endocrine disease history which could affect the study test results (diabetes mellitus, liver disease, lipid metabolism diseases, etc.), previous metabolic syndrome diagnosis, additional and possibly weight-effecting medication

Table 1. Sociodemographic Characteristics of Participants

	n	%
Gender		
Female	24	80
Male	6	20
Marital status		
Single	12	40
Married	12	40
Divorced	6	20
Disease		
Acute psychosisattacks	10	33.3
Others[a]	20	66.6

Note: Participants were on average 40.06 years old (range 19-63 years).
[a]Reflects the number and percentage of patients previously diagnosed with a psychotic illness such as schizoaffective disorder, bipolar disorder, and depression with psychotic features.

use (hypolipidemic agents, anti-diabetic medication,β blockers, etc.). Inclusion and exclusion criteria were taken into consideration during the patient selection.

Forty patients who met the inclusion criteria were included in the study. Consent of these patients was obtained from the ethics committee of our hospital with the approval form dated May 18, 2017, version no. 2. Ten patients who did not participate in regular follow-ups were excluded during the study period. Ten patients in the study group were diagnosed with acute psychosis first episode based on DSM-IV-TR.[11] These patients had no history of using any psychotropic medication. Olanzapine (5-20 mg/day) was prescribed in this group, and olanzapine treatment was continued during the follow-up period. The remaining 20 patients were previously diagnosed with bipolar mood disorder, schizoaffective disorder, or depression with psychotic features, and lithium was used as a mood stabilizer. Olanzapine (clinicians consented to doses varying between 5 and 20 mg/day) was added to the lithium treatment of these patients.

Anthropometric measurements and blood sampling were studied, and variables such as height, weight, and waist circumference were measured and recorded at three different times at the beginning, in the 2nd week, and in the 8th week of the study. The central (POMC, NPY) and peripheral neuropeptides (cholecystokinin) and adipokine (leptin) levels were examined in blood samples taken from the antecubital vein. All blood samples were centrifuged at 3500 rpm for 10 min. Serum samples were stored at -80°C until the analysis.

Laboratory Analysis

At the beginning and in the 2nd and 8th weeks of the study, FBG, AST, ALT, GGT, ALP, LDH total and direct bilirubin, LDL, HDL, total cholesterol, VLDL and insulin levels were analyzed in the biochemistry laboratory of Necmettin Erbakan University, and the results were recorded. Serum leptin, NPY, POMC, and CCK (cholecystokinin) levels were quantitatively assessed by using commercially available enzyme-linked immunosorbent analyses kits (Biovendar Research and Diagnostic Products, RayBiotech, Maybiosource, and RayBiotech respectively).

Statistical Analysis

Statistical analyses were performed with Statistical Package for the Social Sciences (SPSS) version 23.0 (IBM SPSS Corp.; Armonk, NY, USA). The Kolmogorov-Smirnov test was used to analyze the distribution of the data. This test suggested that the distribution was abnormal. Therefore, we ran the Wilcoxon signed-rank test to compare continuous variables between baseline and after treatment data. A comparison of parameters was performed with the Mann-Whitney-U test to analyze continuous variables between single and multiple medication users.

A *P*-value of <.005 was considered statistically significant.

RESULTS

The sociodemographic characteristics of the participants are shown in Table 1.

Table 2. Comparison of Changes in Weight, Waist Circumference, and Metabolic Parameters

Mean ± SD	Initial (0)	1st Control (1)	2nd Control (2)	Statistical Comparisons[a]
Weight (kg)	65.33 ± 12.89	69.06 ± 13.17	70.8 ± 13.35	2 > 1 > 0
Waist circumference (cm)	81.26 ± 10.17	83.76 ± 10.57	86.06 ± 11.92	2 > 1 > 0
AST(IU/L)	22.73 ± 14.56	28.86 ± 14.47	22.03 ± 8.77	1 > 0=2
ALT (IU/L)	18.86 ± 10.57	32.70 ± 23.49	19.86 ± 9.42	1 > 0=2
Total bilirubin (mg/dL)	0.50 ± 0.24	0.52 ± 0.38	0.76 ± 0.65	2 > 0=1
Direct bilirubin (mg/dL)	0.18 ± 0.10	0.20 ± 0.19	0.26 ± 0.17	2 > 0=1
ALP (U/L)	65.42 ± 19.28	70.19 ± 22.41	71.64 ± 25.67	0=1=2
LDH (U/L)	259.74 ± 53.63	343.44 ± 64.72	301.71 ± 57.98	0=1=2
FBG (mg/dL)	97.66 ± 26.49	102.68 ± 37.34	94.09 ± 31.01	0=1=2
Insulin (mg/dL)	23.38 ± 21.93	26.85 ± 40.12	20.39 ± 20.41	0=1=2
LDL (mg/dL)	106.98 ± 33.61	122.07 ± 38.34	121.60 ± 35.69	1=2 > 0
Triglyceride(mg/dL)	121.46 ± 67.04	159.10 ± 96.02	135.22 ± 64.02	1 > 0=2
Total cholestrol (mg/dL)	182.96 ± 43.39	203.96 ± 42.00	198.65 ± 47.29	1=2 > 0
HDL (mg/dL)	48.25 ± 12.20	50.09 ± 10.80	52.04 ± 11.09	2 > 0=1

Note: AST: aspartate transaminase; ALT: alanin transaminase; ALP: alkaline phosphatase; LDH: lactate dehydrogenase; FBG: fasting blood glucose; LDL: low-density lipoprotein cholesterol; HDL: high-density lipoprotein cholesterol.
Results are expressed as mean ±standard deviation.
[a]TheWilcoxon signed ranks test.

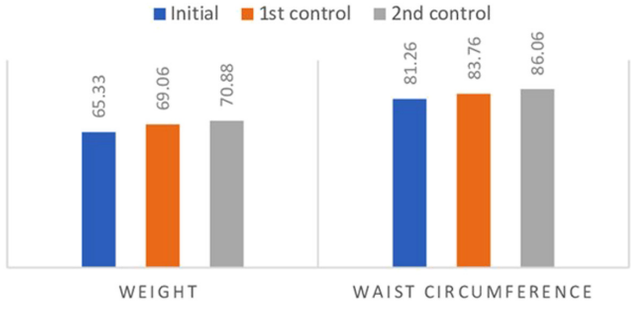

Figure 1. Changes in weight and waist circumfrence.

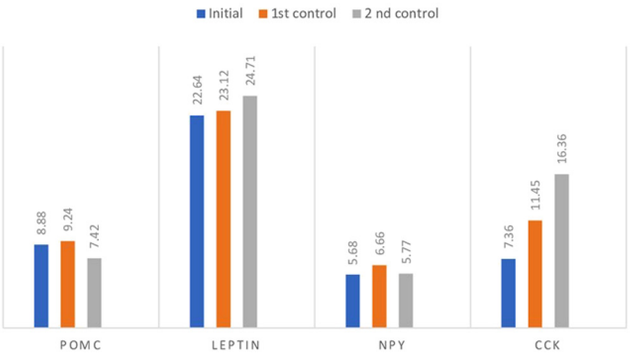

Figure 2. POMC, leptin, NPY, CCK changes (POMC: proopiomelanocortine, NPY: neuropeptide Y, CCK: cholecystokinin).

Table 2 shows the changes in weight, waist circumference, and blood parameters such as AST, ALT, total and direct bilirubin, ALP, LDH, FBG, insulin, LDL, triglyceride, total cholesterol, and HDL from the baseline to the first control and the second control.

There were statistically significant differences between the weight at initial measurement and the two control measurements. Control measurements were found to be significantly higher than the initial measurement. The mean weight increase was 3.73 kg at the 1st control ($P = .00$) and 5.55 kg at the 2nd control ($P = .00$) (Figure 1, Table 2).

There were statistically significant differences in waist circumference between the initial measurement and the two control measurements as with weight gain ($P < .05$). Control measurements were found significantly higher than the initial measurement. The mean waist circumference increase was 4.8 cm for the 2nd control (Figure 1, Table 2).

The changes in AST and ALT values were similar. These values tended to increase in the 1st control compared to the initial values, but in the 2nd control, they tended to decrease to the approximate initial values. While the increase and decrease in ALT values were statistically significant ($P < .05$), there was no statistically significant difference in the change in AST values ($P > .05$). The changes in control values according to the initial values of total and direct bilirubin, LDH, ALP, FBG, insülin, LDL, triglyceride, total cholesterol, and HDL levels are as shown in Table 2. While the increase in LDL, triglyceride, and total cholesterol values was statistically significant ($P < .05$), the other changes were not statistically significant ($P > .05$) (Table 2).

Table 3 shows the changes in POMC, leptin, CCK, and NPY from the baseline to the 1st control and the 2nd control.

While POMC levels increased in the 1st control compared to the initial levels, it decreased in the 2nd control compared to the 1st control. While the initial increase values were not statistically significant ($P = .346$), the decrease was statistically significant ($P = .013$) (Figure 2, Table 3).

Leptin levels tended to increase during the study period, but this increase was not statistically significant ($P > .05$) (Figure 2, Table 3).

CCK levels tended to increase as with leptin levels. While the initial increase values was not statistically significant ($P > .05$), the increase in values between the 1st control and 2nd control was statistically significant ($P = .036$) (Figure 2, Table 3).

NPY increased mildly for the 1st control and tended to decrease later, but these changes were not statistically significant ($P > .05$) (Figure 2, Table 3).

When patients using lithium in addition to olanzapine treatment and patients who did not use lithium were compared, it was observed that the mean of initial and mean of second control weight values and the mean of second control waist circumference values of the patients using lithium treatment in addition to olanzapine were

Table 3. Comparison of Changes in Neuropeptide Levels

Mean ± SD	Initial (0)	1st Control (1)	2nd Control (2)	Statistical Comparisons[a]
POMC	8.88 ± 3.92	9.24 ± 4.16	7.42 ± 4.05	1 > 0=2
Leptin	22.64 ± 18.20	23.12 ± 15.10	24.71 ± 17.32	0=1=2
NPY	5.68 ± 2.41	6.66 ± 7.65	5.77 ± 1.76	0=1=2
CCK	7.36 ± 17.48	11.45 ± 24.40	16.36 ± 26.41	2 > 0=1

Note: POMC: proopiomelanocortin; NPY: neuropeptide Y; CCK: cholecystokinin.
Results are expressed as mean ± standard deviation.
[a]The Wilcoxon Signed Ranks test

Table 4. Comparison of Variables Between Patients Using Lithium in Addition to Olanzapine Treatment and Patients Not Using Additional Lithium

Variables	Mean of Initial Values			Mean of 2nd Control Values		
	Olanzapine ($n=10$)	Lithium+olanzapine ($n=20$)	*P*	Olanzapine ($n=10$)	Lithium+olanzapine ($n=20$)	*P*
Weight	56.70 ± 6.76	69.65 ± 13.15	**.006**	60.60 ± 6.44	76.02 ± 12.99	**.001**
Waist Circumference	76.00 ± 7.10	83.90 ± 10.58	**.027**	77.50 ± 6.60	90.34 ± 11.77	**.002**
AST	19.80 ± 8.91	24.20 ± 16.70	.566	21.40 ± 7.08	22.35 ± 9.66	.947
ALT	20.30 ± 13.64	18.15 ± 8.99	.825	18.20 ± 10.10	20.70 ± 9.21	.261
Total biluribin	0.53 ± 0.23	0.49 ± 0.25	.598	0.78 ± 0.43	0.75 ± 0.77	.209
Direct biluribin	0.16 ± 0.08	0.19 ± 0.12	.959	0.26 ± 0.14	0.26 ± 0.19	.798
ALP	55.55 ± 9.77	70.64 ± 21.20	.045	59.33 ± 11.94	78.56 ± 28.92	.106
FBG	103.70 ± 35.02	94.65 ± 21.48	.982	110.60 ± 32.66	85.84 ± 27.34	.090
Insulin	25.86 ± 27.57	22.07 ± 19.04	.748	25.52 ± 20.96	17.37 ± 20.08	.547
LDL	106.37 ± 28.90	107.28 ± 36.45	.878	123.63 ± 36.03	120.47 ± 36.50	.666
Triglyceride	112.90 ± 73.77	125.75 ± 64.99	.495	137.40 ± 58.25	134.01 ± 68.63	.905
Total cholesterol	174.90 ± 33.17	187.00 ± 47.97	.597	203.80 ± 47.10	195.94 ± 48.44	.422
HDL	45.54 ± 7.08	49.61 ± 14.06	.567	52.52 ± 6.75	51.79 ± 12.97	.371
POMC	9.44 ± 3.00	8.59 ± 4.35	.708	7.24 ± 4.06	7.51 ± 4.15	.860
Leptin	15.12 ± 12.08	26.60 ± 19.85	.183	19.17 ± 12.43	27.63 ± 19.06	.271
NPY	5.29 ± 1.60	5.88 ± 2.75	.455	5.26 ± 1.28	6.03 ± 1.55	.202
CCK	2.52 ± 3.15	9.91 ± 21.22	.580	15.45 ± 26.17	16.82 ± 27.20	.877

Note: POMC: proopiomelanocortin; NPY: neuropeptide Y; CCK: cholecystokinin.
Results are expressed as mean ± standard deviation.
P < .05 between patients using lithium in addition to olanzapine treatment and patients not using additional lithium (Mann-Whitney U-test).

statistically significantly higher than the patients who did not use lithium. Regarding the mean of initial and the mean of second control values of all the other parameters, there was no statistically significant difference between these two groups (Table 4).

DISCUSSION

Olanzapine is one of the most frequently used drugs in psychiatry, and one of its important side effects is drug-induced weight gain. Weight gain is vital due to treatment compliance problems and life-threatening results. Therefore, in recent years there have been many studies about this subject.[12-17]

Although knowledge about the role of the hypothalamus, neuropeptides, peripheral peptides that regulate neuropeptides, and adipokines in the control of body weight has increased, in current studies, the hypothalamus, central neuropeptides, peripheral peptides, and the changing balance between them are important issues. POMC, CART, NPY, and AgRP synthesized and released in the hypothalamus ARC in the central region are frequently investigated. However, the mechanisms are still unclear.

This study makes a significant contribution to previous studies on this subject. In this study, in addition to showing olanzapine'seffect on weight and waist circumference, peptides that play essential roles in nutrient uptake were evaluated to investigate the molecular mechanisms underlying drug-induced weight gain in patients who undergo olanzapine treatment. In our study examining the mechanism of weight gain, the most important reason for choosing olanzapine among atypical antipsychotics was its prominent weight-gaining effect and the fact that it is a commonly used molecule in psychiatry practice.[2,5,6,16] Therefore, easy access to the target number of patients was achieved. In the same group of patients, an orexigenic central neuropeptide (NPY), anorexigenic peptide (POMC), leptin, as the central regulator of neuropeptide balance, and CCK, a peptide that has not been frequently studied before, were investigated. Thus, the subject could be evaluated from a comprehensive perspective. In addition, by analyzing the first and second control values of the same patients, data on the occurrence of changes in the early and later stages and the balance between variables could be obtained.

The increase in weight and waist circumference during the treatment period was in accordance with the literature. It was found that there was a statistically significant weight

gain in the 8th week of the treatment with an 8.49% rate. Waist circumference was increased around 4.8 cm in the 8th week of the treatment, parallel to the weight gain.

Increased NPY levels, a central orexigenic neuropeptide, were an expected result in the olanzapine treatment process. The increase in NPY levels after olanzapine treatment was similar to the literature.[18,19] It is known that 5HT1b receptors are present in the cell body of NPY and AgRP neurons in the ARC and on the axons of inhibitory GABAergic intermediate neurons between NPY, AgRP neurons, and POMC neurons.[20-22] The increase observed in NPY levels can be explained by the antagonist effect of olanzapine on the 5HT1b receptor, whereas the increase in appetite and food intake can be explained as a result of the increase in NPY levels. The 5HT1b receptors are present in the axons of the inhibitory GABAergic intermediate neurons between NPY, AgRP neurons, and POMC neurons, while the 5HT2c receptor is present in the cell body of POMC neurons in the ARC.[21] The direct action of olanzapine is expected to reduce POMC levels by antagonism of the 5HT1b receptor on the axons of inhibitory GABAergic intermediate neurons between NPY, AgRP neurons, and POMC neurons, and antagonism of 5HT2c receptors in POMC neurons. In terms of POMC, the results were different than expected, but consistent with previous studies. With an unexpected effect, POMC increase was observed in the early period, and the actually expected decrease in POMC related to the drug appeared in the later stages of the treatment. In recent studies, the results were similar.[10,23] This result suggests that a compensation mechanism may have been activated due to the increase in NPY. It also suggests that there may be other more complex mechanisms in POMC release, and receptors other than serotonin may be involved in this pathway. In a recent study, it was found that alpha melanocyte stimulating hormone expression, a metabolite of POMC, was controlled by the dopaminergic system via the D2 receptor and the POMC is suppressed by the effect of dopamine on the D2 receptor.[24] Therefore, the increase in the POMC level in the early stages of treatment observed in this study and other studies suggest that it may be in a compensatory mechanism due to the increase in NPY and may be due to the antagonistic effect of olanzapine on D2 receptors.

Leptin is an adipokine that tries to control weight gain by suppressing orexigenic NPY and AgRP neuropeptides and increasing anorexigenic CART, POMC neuropeptides synthesized from ARC in the case of satiety. It has been observed to increase with weight in most of the previous studies evaluating the weight gain mechanisms.[9,25,26] In this study, leptin levels were increased in parallel with the duration of treatment. We think that this increase in leptin levels is due to increased TG levels and leptin resistance caused by weight gain, as stated in previous studies. Increased leptin might be acting as an important compensation mechanism trying to control early weight gain due to olanzapine use, especially at the early stage. Olanzapine-induced weight gain might be slower in the later stages of treatment due to increased leptin level compensation.

CCK is not a commonly studied parameter of weight gain. It is known primarily as an enzyme controlled by cholinergic muscarinic M3 receptors. In previous studies, a positive correlation between M3 receptor antagonism and CCK increase and weight gain was found.[27] Muscarinic receptors are present in the ventromedial nucleus and arcuate nucleus. Knowledge about olanzapine's effects on central M3 receptors is limited.[28] Continuous increase in CCK levels during the treatment in this study can be explained by the antagonist effect of olanzapine on the M3 receptor. It can be predicted that increasing CCK may play a role as a compensatory factor that helps to control weight gain due to the effect of reducing nutrient intake.

The evaluation of CCK to investigate the relationship of a peripheral peptide, antipsychotic effects, and weight gain has opened a new path, and it should be supported with new studies in order to determine this relationship clearly.

There are some limitations in this study in which we evaluate the role of central neuropeptide and peripheral peptides in the relationship between olanzapine and weight gain. Although the target number calculated with power analysis was reached, it was difficult to find patients using only olanzapine. The absence of a significant difference between neuropeptide levels in patients who did not use additional mood stabilizers (lithium) and those treated with lithium before olanzapine treatment suggest that lithium treatment does not have an additional negative effect on appetite and metabolic parameters. Nevertheless, a more significant number of patients can only be achieved with long-term multicenter studies. In the study, cerebrospinal fluid (CSF) from the central nervous system was not obtained. Therefore, the variables were evaluated by peripheral measurement, which was emphasized to reflect the central measurements. According to hypothetical views on defined neuropeptides and receptors, accuracy can be achieved by demonstrating these peptides at the level of gene expression and direct sampling from CSF.

CONCLUSION

The network in the central nervous system is very complex. Since various peripheral variables in addition to hypothalamic mechanisms also play a role in appetite regulation, it is not possible to claim that we can definitely explain appetite regulation with this study. In order to eliminate uncertainties, it is necessary to examine the central and environmental variables with more advanced methods.

Conflict of Interest: The authors have no conflicts of interest to declare.

Peer-review: Externally peer-reviewed.

Ethical Committee Approval: Ethical committee approval was received from the Clinical Research Ethics Committee of Necmettin Erbakan University Meram School of Medicine (2017/141, July 05, 2017).

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