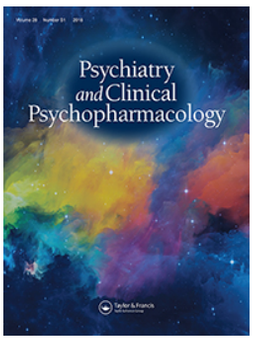

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Psychiatry and Clinical Psychopharmacology

ISSN: 2475-0573 (Print) 2475-0581 (Online) Journal homepage: https://www.tandfonline.com/loi/tbcp21

Outstanding Awards Brief Reports

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To cite this article: Ferhat Can Ardic, Samet Kose, Mustafa Solmaz, Filiz Kulacaoglu, Yasin Hasan Balcioglu, Emrah Yıldız, Gülçin Elboğa, Abdurrahman Altındağ, Mehmet Arslan, Ali Metehan Çalışkan, Duygu Göktaş, İkbal İnanlı, Saliha Çalışır, İbrahim Eren, Gokhan Unal, Feyza Aricioglu, Yasemin Yulaf, Funda Gümştaş, Sebla Gökçe, Yankı Yazgan, Çağdaş Öykü Memiş, Doğa Sevincok, Bilge Doğan, Ayşe Kutlu, Burcu Çakaloz, Levent Sevinçok, Tuğba Mutu, Esra Yazici, Derya Guzel, Atila Erol, Nazan Aydın, Hasan Mervan Aytaç, Doğan Yılmaz, Pınar Çetinay Aydın, Gökşen Yüksel Yalçın, Cana Canbay, Merve Terzioğlu & Aysel Özer (2018) Outstanding Awards Brief Reports, Psychiatry and Clinical Psychopharmacology, 28:sup1, 271-296, DOI: 10.1080/24750573.2018.1467612

To link to this article: https://doi.org/10.1080/24750573.2018.1467612

Published online: 13 Jun 2018.

PSYCHIATRY AND CLINICAL PSYCHOPHARMACOLOGY, 2018
VOL. 28, NO. S1, 271–296
https://doi.org/10.1080/24750573.2018.1467612

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10th International Congress on Psychopharmacology & 6th International Symposium on Child and Adolescent Psychopharmacology

Reliability, validity, and factorial structure of the Turkish version of the structured inventory of malingered symptomatology (Turkish SIMS)

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ABSTRACT

Objective: Smith and Burger developed the Structured Inventory of Malingered Symptomatology (SIMS) in 1997 as a self-report measure for malingering of psychiatric symptoms. The SIMS consists of 75 dichotomous (True–False) items that form into five subscales Psychosis (P), Neurologic Impairment (NI), Affective Disorder (AF), Amnestic Disorders (AM), Low Intelligence (LI), with each subscale containing 15 items. In this study, we aimed to examine the reliability, validity, and factor structure of the SIMS in a Turkish forensic psychiatry sample.

Methods: A sample of 103 forensic patients (9 female, 94 male), aged 18–75, undergoing an inpatient forensic evaluations for competency assessment for criminal responsibility were recruited from a large forensic hospital in Turkey. The study protocol was approved by the local ethics committee. Socio-demographic information of the participants was collected and the SIMS, Miller Forensic Assessment of Symptoms Test (M-FAST), the Scales of Psychological Well-being, 36-Item Short Form Survey (SF-36), Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI) were administered. All statistical analyses were performed by using SPSS version 23.0 for Windows.

Results: The Cronbach's alpha coefficients for the Turkish SIMS were ranging from 0.42 to 0.87. The lowest alpha coefficient was observed for the Amnestic Disorders (0.46). For the whole scale, Cronbach's alpha coefficient was found to be 0.93. The test–retest (at after 1 week) correlation coefficients for Psychosis (P), Neurologic Impairment (NI), Affective Disorder (AF), Amnestic Disorders (AM), Low Intelligence (LI), and whole scale were found to be 0.97, 0.97, 0.95, 0.91, and 0.96, respectively. A positive and statistically significant correlation was found between the Turkish SIMS and BDI ($r = 0.593$, $p < .01$), BAI ($r = 0.578$, $r < 0.01$), M-FAST subscale Reported versus Observed Symptoms ($r = 0.660$, $p < .01$), M-FAST subscale Extreme Symptomatology ($r = 0.686$, $p < .01$), M-FAST subscale Rare Combinations ($r = 0.729$, $p < .01$), M-FAST subscale Unusual Hallucinations ($r = 0.698$, $p < .01$), M-FAST subscale Unusual Symptom Course ($r = 0.568$, $p < .01$), M-FAST subscale Negative Image ($r = 0.514$, $p < .01$), M-FAST subscale Suggestibility ($r = 0.426$, $p < .01$), and M-FAST Total ($r = 0.794$, $p < .01$) scores. Principal axis factor analyses with promax rotation were performed and four-factor solution that accounted for 39.87% of the variance observed.

Conclusions: Our preliminary findings suggested that Turkish SIMS was a valid and reliable tool with a robust factorial structure for further use in detecting malingering of forensic psychiatric cases in Turkey.

KEYWORDS
Structured inventory of malingering symptomatology; reliability; validity; factor structure; malingering

Introduction

The American Psychiatric Association (1980) officially defined malingering in the Diagnostic and Statistical Manual of Mental Disorders-Third Edition (DSM-III). Prior to that time, the absence of an official definition was due to an earlier debate whether malingering constitutes a distinct psychiatric disorder. The DSM-III stated malingering as not a mental disorder *per se* but a condition that deserves a focus of attention or treatment. In other words, although malingering is not in and of itself a psychiatric disorder, it does

have clear psychological implications. Under the current nosology of the Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition (DSM-5), malingering is defined as the intentional production of false or grossly exaggerated physical or psychological symptoms, motivated by external incentives. The DSM-5 instructs clinicians to strongly suspect the presence of malingering when any combination of the following indicators are present: (a) the existence of a medicolegal context, (b) explicit discrepancy between the reported impairment and objective observation, (c) lack of cooperation during the diagnostic evaluation and non-adherence to treatment, and (d) the presence of antisocial personality disorder [1].

When malingering was considered in differential diagnosis, clinicians are expected to ascertain the motivations and level of conscious awareness that accompany symptoms reported by individuals rather than identifying certain diagnostic criteria during presentation [2]. Among the differential conditions to be considered in the malingering cases are factitious disorders, in which the motivation is internal such as assuming a sick role and somatoform disorders, in which the condition and the presentation of symptoms are not viewed as intentional. Different types of external motivations might have impact on the presentation of malingering, including avoiding military duty or work, efforts to obtain financial compensation, efforts to evade criminal prosecution, and obtaining drugs [2].

The frequency of malingering differs across settings; however, the base rate of malingering psychiatric symptoms in sanity and competence cases has been reported to range between 15.7% and 45% [2]. The evaluation of malingering of psychiatric disorders is crucial in forensic settings. Failure to detect malingering may lead to vital adverse consequences for the administration of justice [3]. The higher frequency of malingering in forensic cases is indisputably related to the fact of the diminished or excluded responsibility of the psychiatric patients in criminal jurisdictions and the temptation of the offenders to evade criminal prosecution. Detecting simulated or exaggerated symptoms is a major challenge in forensic psychiatry. Rogers suggested that any psychological examination conducted in a compensation-seeking context should include an assessment of the likelihood of malingering [2].

There have been three types of instruments used in the detection of malingering: (a) structured interviews, (b) general psychological or cognitive instruments, and (c) tests specifically designed for the detection of malingering. Although structured interviews contributed to systematic assessment of psychiatric disorders, this method is time-consuming and requires a trained evaluator. Both personality measures and cognitive/intellectual assessment instruments may be effective in the detection of malingering; however, length of administration, need for specialized administration training and high reading levels would limit their extensive use in clinical settings. Some measures were specifically developed to determine the presence of malingered psychopathology (e.g. the Miller Forensic Assessment of Symptoms Test – M-FAST) [4]. Although the M-FAST has been shown utility in clinical settings function, there remains the need for an instrument that screens more than general psychopathology since malingerers often feign symptoms of more than one condition.

Smith and Burger developed the Structured Inventory of Malingered Symptomatology (SIMS) in 1997 as a self-report measure designed to assess symptoms of both feigned psychopathology and cognitive function [5]. The SIMS is a 75-item, multiaxial, self-administered screening measure used for detection of malingering across a variety of clinical and forensic settings. The SIMS includes dichotomous (True–False) items that form into five subscales namely Psychosis (P), Neurologic Impairment (NI), Amnestic Disorders (AM), Low Intelligence (LI), Affective Disorder (AF); each subscale containing 15 items. The Psychosis (P) subscale assesses the degree to which a respondent endorses bizarre or unusual psychotic symptoms not typically seen in actual psychotic patients. The Neurologic Impairment (NI) subscale assesses the degree to which a respondent endorses illogical or highly atypical neurological symptoms. The Amnestic Disorders (AM) subscale items indicate the degree to which a respondent endorses symptoms of memory impairment that are inconsistent with patterns of impairment seen in brain injuries or dysfunctions. The Low Intelligence (LI) assesses the degree to which a respondent fabricates/exaggerates intellectual deficits by failing simple general fund of knowledge items. The Affective Disorder (AF) subscale assesses the degree to which a respondent reports atypical symptoms of depression and anxiety [5].

In this present study, we aimed to examine the reliability, validity, and factor structure of the SIMS in a Turkish forensic psychiatry sample.

Methods

A sample of 103 forensic patients (9 female, 94 male), aged 18–75, undergoing an inpatient forensic evaluations for competency to stand trial (CST) were recruited from a large forensic hospital in Turkey. The study protocol was approved by the local Ethics Committee. The Turkish SIMS has been translated into Turkish by Samet Kose and back-translated into English by Filiz Kulacaoglu who was blinded to the original items. The content equivalence of SIMS items was examined, and necessary changes were made as some items being irrelevant to Turkish culture. Socio-demographic information of the participants was

Table 1. SIMS Total and Subscale Means, Standard Deviations, Cronbach's Alpha, and Test–retest Cronbach's Alpha.

SIMS subscales	M	SD	α	Test–Retest α
Psychosis (P)	4.94	4.19	0.87	0.97
Neurologic Impairment (NI)	5.85	4.50	0.88	0.98
Amnestic Disorders (AM)	6.12	4.91	0.71	0.67
Low Intelligence (LI)	6.00	2.07	0.32	0.83
Affective Disorder (AF)	6.77	3.14	0.69	0.96
TOTAL SIMS	29.70	16.29	0.93	0.95

collected and the SIMS, the Miller Forensic Assessment of Symptoms Test (M-FAST), the Scales of Psychological Well-Being, 36-Item Short Form Survey (SF-36), Beck Depression Inventory (BDI), and Beck Anxiety Inventory (BAI) were administered. For examining test–retest reliability, the Structured Symptomatology of Malingered Symptoms was reapplied to 36 patient selected from whole sample one week after the initial administration. All statistical analyses were performed by using SPSS version 23.0 for Windows.

Results

The average age of 103 participants in the study was 34.89 with a standard deviation of 12.29, and it ranged from 18 to 75. The sample consisted of 9 female (8.7%) and 9 male (91.3%) patients. The majority of the patients who participated in the study were single (48.5%) and 27 (26.2%) were married, and 26 patients were divorced or separated. The mean scores and standard deviations for the SIM scale and its subscales are presented in Table 1.

The Cronbach's alpha coefficients for the Turkish SIMS were ranging from 0.32 to 0.88. The lowest Cronbach's alpha coefficient was observed for the Low Intelligence (0.32). For the whole scale, Cronbach's alpha coefficient was found to be 0.93. The test–retest correlation coefficients for all dimensions were relatively high and statistically significant. The test–retest (at after 1 week) correlation coefficients for Psychosis (P), Neurologic Impairment (NI), Amnestic Disorders (AM), Low Intelligence (LI), Affective Disorder (AF), and whole scale were found to be 0.97, 0.98, 0.67, 0.83, 0.96, and 0.95, respectively.

Convergent and Discriminant validity were examined by correlations between the SIMS scores and M-FAST scores. A positive and statistically significant correlation was found between the Turkish SIMS and M-FAST subscale Reported versus Observed Symptoms ($r = 0.675$, $p < .01$), M-FAST subscale Extreme Symptomatology ($r = 0.713$, $p < .01$), M-FAST subscale Rare Combinations ($r = 0.751$, $p < .01$), M-FAST subscale Unusual Hallucinations ($r = 0.710$, $p < .01$), M-FAST subscale Unusual Symptom Course ($r = 0.588$, $p < .01$), M-FAST subscale Negative Image ($r = 0.528$, $p < .01$), M-FAST subscale Suggestibility ($r = 0.440$, $p < .01$), and M-FAST Total ($r = 0.816$, $p < .01$) scores.

In addition, The BDI was positively correlated with P ($r = 0.539$, $p < .01$), NI ($r = 0.591$, $p < .01$), AM ($r = 0.524$, $p < .01$), AF ($r = 0.687$, $p < 0.01$), and SIMS Total ($r = 0.620$, $p < 0.01$). The BAI was positively correlated with P ($r = 0.543$, $p < .01$), NI ($r = 0.547$, $p < 0.01$), AM ($r = 0.523$, $p < 0.01$), AF ($r = 0.646$, $p < 0.01$), SIMS Total ($r = 0.597$, $p < .01$).

Principal components analysis with promax rotation was performed to optimize factor loadings and to facilitate the interpretation of different factors. Both a four- and a five-factor solution were performed following inspection of the plot of Eigenvalues. Only four-factor solution provided clear loadings of the scales and four-factor solution accounted for 39.87% of the variance observed.

Discussion

In this study, we aimed to examine the reliability, validity, and factor structure of the SIMS in a Turkish forensic psychiatry sample. The main results of the study confirmed that the Turkish SIMS was observed to have stable and reliable psychometric properties. The internal consistency coefficients of the Turkish SIMS scale and subscales showed that the scale was reliable. The Cronbach's alpha coefficients for the Turkish SIMS were ranging from 0.32 to 0.88. The lowest Cronbach's alpha coefficient was observed for the Low Intelligence (0.32) and the highest Cronbach's alpha coefficient was observed for the Neurologic Impairment (0.88). Additionally, the positive correlation coefficients between the first and the second administration of the Turkish SIMS revealed high test–retest reliability. On examination of the relationship between the SIMS scale and other measures of malingering, the SIMS subscales demonstrated moderate-to-high correlations with and M-FAST subscales and M-FAST Total scores. The positive correlations between Turkish SIMS and the BDI and BAI further gave support to the validity of the scale. Our principal components factor analysis with promax rotation provided a four-factor

Table 2. Correlations between the SIMS Total and Subscales Scores and Total Scores of M-FAST, BAI, and BDI.

		M-FAST total	BAI total	BDI total
P	*r*	0.792	0.543	0.539
	p	0.000**	0.000**	0.000**
NI	*r*	0.777	0.547	0.591
	p	0.000**	0.000**	0.000**
AM	*r*	0.687	0.523	0.524
	p	0.000**	0.000**	0.000**
LI	*r*	0.448	0.185	0.213
	p	0.000**	0.061	0.031*
AF	*r*	0.691	0.646	0.687
	p	0.000**	0.000**	0.000**
TOTAL SIMS	*r*	0.816	0.597	0.620
	p	0.000**	0.000**	0.000**

*Correlation is significant at the 0.05 level (two-tailed).
**Correlation is significant at the 0.01 level (two-tailed).

solution with clear loadings of the scales, which accounted for 39.87% of the variance observed. This was consistent with the original study.

In conclusion, the SIMS is a brief 75-item, self-report screening measure of multiple domains of malingered symptomatology, which includes psychiatric and neurocognitive disorders. In addition, higher SIMS subscale scores might signal a need for further scrutiny for emotional distress, given the possibility of comorbidity between malingering and psychopathology. The Turkish version of the SIMS had sound psychometric properties in our sample of Turkish forensic patients with its satisfactory internal consistency, test–retest reliability, concurrent validity, and factorial structure (Table 2).

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Circadian rhythm neuropeptide levels among bipolar disorder patients

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ABSTRACT

Objective: According to the previous studies, it has been noted many times that circadian rhythm is disrupted in bipolar disorder. This suggests that BPD may also have circadian rhythm disorders in the aetiology [1–3]. We aimed to examine somatostatin (SST), neuropeptide-Y (NPY), arginine vasopressin (AVP), vasoactive intestinal peptide (VIP), and cortisol levels, which are known as neuropeptide markers related to circadian rhythm in patients with bipolar disorder euthymic period.

Methods: Thirty-nine patients diagnosed as bipolar disorder euthymic episode according to DSM-5 and 38 healthy controls enrolled into the study. Serum somatostatin (SST), neuropeptide-Y (NPY), arginine vasopressin (AVP), vasoactive intestinal peptide (VIP), and cortisol measurements were done in biochemistry laboratory of Gaziantep University.

Results: When SST, NPY, VIP, AVP and cortisol levels were compared between bipolar disorder euthymic episode patients and control group, SST, NPY, VIP, and cortisol levels were significantly lower in the patient group than in the control group ($p = .001$, $p = .001$, $p = .001$, $p = .001$). According to the correlation analysis, SST levels were found to have strong positive correlations with VIP and AVP ($r = 0.777$, $p = .001$ for VIP; and $r = 0.574$, $p = .001$ for AVP).

Conclusions: SST, NPY, VIP, AVP, and cortisol levels were lower in bipolar disorder euthymic episode patients when compared with controls in concordance with many of the previously conducted studies [4]. In the earlier studies, data have been obtained about the effects of neuropeptide markers related to circadian rhythm on behaviour, sleep, anxiety, and relevant hypotheses have been established [5]. In the light of these studies in the literature, our study suggests that bipolar disorder may be associated with a decrease in circadian rhythm-related neuropeptide levels in one of the causes of behavioural and sleep disturbances seen in the clinical features of patients with bipolar disorder euthymic episode. To the best of our knowledge, this study is the first one to examine SST, NPY, VIP, AVP, and cortisol levels in euthymic episode of bipolar disorder together; therefore, it may significantly contribute to the literature.

KEYWORDS
Bipolar disorder; circadian rhythm; neuropeptide; SST; NPY

Bipolar Disorder (BPD) is a disorder characterized by a history of recurrent mania, depression, or mixed episodes without a specific pattern, during which time a person can return to a fairly healthy mood; it has a lifelong recurrent episode of impaired functioning and is a chronic illness. While the lifetime prevalence rate for BPD is assumed to be 1.2%, studies covering bipolar disorder types I and II in recent years give frequency ratios up to 5%. Genetic, biochemical (neurotransmitters, hormones, and others), pharmacology, anatomic, immunologic, intracellular reporters and ion systems, circadian rhythm, sleep, cognitive processing, psychosocial factors, and ignition phenomine are all responsible for the aetiology of BPD but a single hypothesis showing the role of these factors in disease formation has not yet been established and the exact cause of the disease has not been elucidated. It is thought that the underlying factor in the majority

of psychiatric diseases is the gene–environment interaction. It has been noticed in ancient times that a certain rhythm is observed in many biological activities of living things. This system, called circadian rhythm, is a rhythm of about 24 h, which contains a number of physiological, behavioural, and psychological parameters and also plays a key role in the sleep/wake cycle. Circadian rhythm disturbance is associated with many medical problems. The abnormality of this system plays a key role in many psychiatric disorders such as major depression, anxiety disorder, and schizophrenia (1).

Increased evidence supports the existence of circadian rhythm disorders in bipolar disorder. Circadian rhythm-specific gene polymorphism was found in broad genome-related studies (GWAS). When the relationships between circadian rhythm and anxiety disorder (AB) and major depressive disorder (MDD) were examined, it was found that there was a more significant relationship between circadian clocks in the morning hours. In bipolar disorder, significant neuropathological connections have been identified in circadian rhythm disorders.

Somatostatin (SST) and Neuropeptide-Y (NPY) expressions have been linked to the formation of circadian rhythm disorders in MDD and AB. Potent anxiolytic and antidepressant effects of NPY and SST have been found. In addition, both SST and NPY in mouse amygdala have been shown to be significantly associated with circadian regulation of anxiety-like behaviour. In addition, GWAS-related molecular-based studies support neuropeptide and circadian rhythm association. Increased severity of change in circadian rhythm-related changes in SST in bipolar patients, particularly in samples taken in the morning and at MDB and EU. In addition, SST expression in the suprachiasmatic nucleus supports the association with circadian rhythm. Abnormal SST expressions in the amygdala and suprachiasmatic nucleus are associated with abnormal circadian rhythm disturbances in mood disorders. It has also been found that arginine has an effect on circadian rhythm regulation in vasopressin (AVP) and vasoactive intestinal peptide (VIP) (2).

Although cortisol changes are known to affect mood disorders, they are thought to be a predisposing effect of mood disorders in other neuropeptide signalling pathways. Investigating the role of circadian rhythm neuropeptides in psychiatric disorders suggests that these diseases may help to develop our current limited knowledge of biology and therapy, and that circadian rhythm neuropeptides may have the potential to play a role as new therapeutic targets. In our study, it is aimed to evaluate the levels of circadian rhythm-related neuropeptide markers (SST, VIP, NPY, AVP, and cortisol) in patients with Bipolar Disorder.

The achievement of the project will clarify the relationship between circadian rhythm disturbance and aetiology of bipolar disorder and provide us with a wider knowledge of the treatment. It is believed that clarification of the pathogenesis of the disease may contribute to national and international scientific accumulation and may be a guide for preventive and therapeutic medicine approaches (3).

Normal distribution fitness of numerical data was tested by Shapiro–Wilk test. Student *t*-test was used for comparison of normal dividing variables in two groups. The Mann–Whitney *U* test was used to compare normal non-dispersive variables in two groups. The relationship between categorical variables was tested by Chi-square test. Relations between variables were tested with the correlation coefficient. SPSS 22.0 package program was used in the analyses. $p < .05$ was considered significant.

Thirty-nine bipolar disorder euthymic patients and 38 healthy controls were included in the study. Twenty (51.4%) of the patients were male and 19 (48.7%) were female. Eighteen (47.4%) of the control group were male and 20 (52.6%) were female. The mean age was 33.85 ± 9.56 in the patient group and 32.24 ± 7.96 in the control group. There was no difference between the groups in terms of age, gender, bipolar disorder, and control group of euthymic patients ($p > .05$). No significant difference was found between the two groups when the bipolar disorder and the control group were compared in terms of marital status ($p > .05$). When SST, VIP, NPY, and cortisol values were significantly higher in the patient group than in the control group ($p = .001$, $p = .001$, $p = .015$, $p < .05$) and $p = .001$), statistical significance was not found in the ADH level in both groups ($p = .772$).

In our study, patients continued their current therapies and there were no differences in terms of circadian rhythm neuropeptides when the drugs used were classified as typical antipsychotics, atypical antipsychotics, mood stabilizers, and combinations ($p > .005$).

No correlation was found between age, gender, marital status, educational status, duration of illness, number of hospitalizations, drugs used, SST, VIP, NPY, APV, and cortisol values. There was no statistically significant relationship between CGI, HAMD scores and SST, VIP, NPY, APV, and cortisol levels.

In our study, the socio-demographic characteristics, SST, VIP, NPY, AVP, and cortisol levels of bipolar disorder (euthymic period) patients who applied to Gaziantep University, Department of Psychiatry were compared. This research is based on the fact that information about circadian rhythm and related neuropeptide levels of bipolar disorder (euthymic) patients is limited in the literature. Obtained data are discussed in the light of current information.

There was no statistically significant difference in the socio-demographic characteristics of age, gender,

and marital status between the BPB group and the control group. This can be considered as a positive feature in terms of reducing possible confounding factors in the comparison between the two groups in the study.

In our study, bipolar disorder was statistically significantly lower in the euthymic patients compared to the control group in terms of SST, VIP, NPY, and cortisol levels. Although the AVP value was lower in BPD groups, we did not find statistical significance. We observed a strong positive linear relationship between AVP levels of patients and SST, VIP, and cortisol in the positive direction. Cortisol levels and SST, VIP, and together with SST and VIP levels were observed. We observed a linear relationship between the strong positive and the strong. There was no relationship between NPY and other neuropeptides (SST, VIP, AVP, and cortisol).

Harry et al. have shown that amygdala SST and NPY neurons are anaemic in anxiety modulation in a study of mice. SST-deficient mice show anxiety-like behaviours as well as behavioural, neuroendocrine, and molecular abnormalities similar to those seen in anxiety and depressed individuals. Furthermore, in studies on mouse amygdala, SST and NPY have been found to be associated with increased anxiety periods. Thus, the morning shift of amygdala SST may be associated with circadian abnormalities that contribute to worse symptom severity.

Increased evidence also supports the role of SST in regulating rhythm in SCN. The SST showed that it was rhythmically expressed in rodent SCN at constant darkness, and that this was controlled by the molecular clock and not by light stimulation. Moreover, SST is expressed by a subpopulation of SCN neurons that are synaptic to VIP and AVP neurons in this region. These two neuropeptides are expressed as two neuronal populations critical to the regulation of circadian and SCN output signals (4).

It has been shown that SST inhibits VIP rhythms in SCN, and *in vivo* SST depletion in SCN has led to locomotive activity 51 min in progress. Similar depletion in the SCN slices leads to phase progression of neuronal shot rhythms. Furthermore, the application of SST *in vitro* to SCN causes phase progression or phase delays in neuronal firing rhythms depending on the duration of the application given in circadian time, reflecting phase progression and phase delay effects of light pulses. A genetic polymorphism for SST receptor 5 (SSTR5) expressed in abundant quantities in SCN has been associated with BD. Genetic polymorphisms for two molecules suggest that they regulate SST expression (5).

Despite evidence of reduced neuropeptides in multiple brain regions in the BD and their relationship to anxiety and circadian rhythms, neuropeptide expression and evidence of their association with circadian rhythms in mood disorders. The limitation of our study was that all the patients evaluated had been using psychotropic drugs. Patient group without psychotropic use could not be created. For this reason, it was not possible to prevent the effect of drugs on hormones. Although blood pressure instability, hypovolemia, hyponatremia, hyper osmolality, and other serum PEP activity affecting peripheral vasopressin levels, such as those for serum vasopressin levels, occur at the same time interval (between 08.00 am and 09.00 am); all samples are kept in equal conditions and at the same time, The fact that variables are not considered is another limitation of this study.

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Sexual satisfaction in male patients with bipolar disorder and their healthy spouses

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ABSTRACT

Objective: Bipolar disorder (BD) is a chronic disorder with recurrent depressive and manic/hypomanic episodes that negatively affect social and professional functionality. Only a limited number of studies have evaluated sexual functions in patients with bipolar disorder (BD) and their spouses. Dell'Osso et al. reported that patients with BD had a higher lifelong sexual dysfunction rate when compared to controls. Similarly, Hariri et al. found that patients with BD in remission experience more sexual problems than healthy controls. In addition, a decline in sexual satisfaction level of the patients' partners following the onset of the disorder was reported. The aim of the present study was to compare the sexual problem levels of male patients with BD and their healthy spouses with those of healthy couples and to examine the potential factors that affect sexual problems.

Methods: The study was a cross-sectional design conducted at the Konya Research and Training Hospital. Sixty male outpatients with BD in remission and their healthy female spouses were included as couples in the study. All patients were under medication. Another 40 healthy couples were included as the control group. Participants were assessed with the socio-demographic data form, Hamilton Depression Rating Scale (HDRS), Hamilton Anxiety Rating Scale (HARS), Young Mania Rating Scale (YMRS), and Golombok Rust Inventory of Sexual Satisfaction (GRISS).

Results: Logistic regression analysis which included the GRISS total score of the partner as one of the dependent factors was conducted to identify the sexual satisfaction differences between groups. Erectile dysfunction scores of male patients with BD were higher than healthy male controls (OR: 1.22, $p = .043$). Sexual communication score of patients' spouses were higher than healthy female controls ($p = .005$, OR = 1.33). Sexual problems were identified in 62% of patients and in 53% of patients' spouses, based on the GRISS total score. The subgroup logistic regression analyses revealed that sexual satisfaction was associated with depressive symptoms in patients (OR: 1.81, $p = .010$). Moreover, sexual satisfaction of patients' spouses was associated with patients sexual satisfaction (OR: 1.06, $p = .011$).

Conclusions: Male patients with BD experience more problems in terms of ED, and their spouses experience more problems in terms of sexual communication compared to the healthy controls. Increased depressive symptom levels were correlated with patients' sexual dissatisfaction. Sexual dissatisfaction in the patients' spouses was also correlated with the patients' sexual dissatisfaction.

KEYWORDS

Bipolar disorder; sexual satisfaction; sexual dysfunction; depression; sexual health

Objective

Bipolar disorder (BD) is a chronic disorder with recurrent depressive and manic/hypomanic episodes that negatively affect social and professional functionality. Only a limited number of studies have evaluated sexual function in patients with bipolar disorder (BD) and their spouses. It has been reported that patients with BD and their spouses experienced more sexual problems than healthy controls. The aim of the present study was to evaluate the sexual satisfaction level and sexual problems in male patients with BD and their healthy spouses and to reveal potential factors that affect sexual satisfaction.

Method

Study setting and subjects

This study was conducted at the Konya Training and Research Hospital Psychiatry Clinic from December 2014 to April 2015. The subjects included 60 married heterosexual male outpatients being treated in the Mood Disorders Unit and diagnosed with BD I and II in remission according to DSM-IV-TR, along with their healthy spouses who had no known psychiatric or physical conditions. The control group consisted of 40 healthy married couples.

Inclusion criteria for patients with BD were age from 18 to 65 years, being married to the same spouse for at least 1 year, being sexually active during the last 1 month, being euthymic for a minimum of 2 months (scoring 7 or below according to the Hamilton Depression Rating Scale [HDRS], scoring 5 or below according to the Young Mania Rating Scale [YMRS]), and using the same treatment for a minimum of 2 months.

Inclusion criteria for patients' spouses were age between 18 and 65 years, and being physically and psychiatrically healthy. Healthy couples meeting the aforementioned criteria for the patients' spouses were taken as the control group.

Exclusion criteria were defined as follows for all participants: having any known organic disorder that can cause SD (e.g. diabetes, hypertension, thyroid disease, or urological, infectious, neurological, or gynaecological disorders); having mental retardation; having a history of alcohol or drug addiction or abuse; and, for females, being pregnant or in the postpartum period. Patients with any additional psychiatric Axis I diagnosis other than BD or a history of pre-BD SD or hypersexuality were also excluded.

Informed signed consent was obtained from all participants for the research before admittance to the research. Ethical approval was obtained from the Ethics

Committee of the Selçuk University Faculty of Medicine (Number: 2014/300).

Assessment instruments

Considering the objectives of the study, individual socio-demographic data forms, created by the researchers, were applied individually for patients, patients' spouses, and the control group.

We administered the Hamilton Depression Rating Scale (HDRS, 17-item version) to assess depressive symptom severity, Young Mania Rating Scale (YMRS, 11-item version) to assess manic symptom severity, Hamilton Anxiety Rating Scale (HARS, 14-item version) to assess anxiety severity, and Golombok Rust Inventory of Sexual Satisfaction (GRISS, 28-item version individually for females and males) to assess the sexual satisfaction level. All scales are used in Turkish form and the validity and reliability of all scales are approved. The psychiatric assessments and scale applications were conducted by the psychiatrists involved in the study.

Statistical analysis

Statistical analyses were conducted using SPSS (Statistical Package for The Social Sciences) v22.0 for Windows.

The differences in the sexual satisfaction level were assessed by comparing patients to healthy male controls and by comparing the patients' spouses to the healthy spouses of those controls. Individual logistic regression analyses (enter method) for males and females were applied to the variables showing statistically significant difference ($p < .05$) between the groups, in order to distinguish the sexual satisfaction level and to control for the effects of potential confounding factors. The sexual functionality of a partner is a further confounding factor that affects a person's sexual satisfaction; therefore, all participants were matched with the GRISS total score of their partners, and the GRISS total score of the partner was also included in the analysis.

The relationship between sexual problems in patients and the socio-demographic, clinical, and disorder-related variables was identified by dividing patients with (GRISS total standard score >5) and without sexual problems into two groups for this comparison. The variables predicting the existence of sexual problems were identified using logistic regression analysis applied to the variables showing statistically significant differences ($p < .05$). The age and sexual dissatisfaction level of the partners were also included in the models. Patients' spouses were subjected to the same statistical procedures.

Descriptive statistics, including the average, standard deviation (SD), and median, were used for continuous data, whereas frequency and percentages were used for discrete data. The Kolmogorov–Smirnov/Shapiro–Wilk test was conducted to evaluate the compliance of the data with normal distribution. The Chi-square/Fisher's Exact Test was used to identify the difference between the frequencies of the discrete data. The two groups were compared using the Student *t*-test for continuous data with a normal distribution and the Mann–Whitney *U* test for continuous data without a normal distribution. The Hosmer–Lemeshow test was used for the goodness of fit of the model in the multivariate analysis. The significance level was taken as $p < .05$ (two-tailed).

Results

The study sample consisted of a total of 200 participants, including 60 patient couples (60 male patients and their healthy female spouses) and 40 healthy couples (40 healthy males and their healthy female spouses) as the control group.

Comparisons of participants according to gender

The patient group consisted of 56 (93.3%) male patients diagnosed with BD I and 4 (6.7%) male patients diagnosed with BD II; all 60 patients were in remission. The average onset age and the duration of the disorder were 28.60 (SD=9.33) years and 183.98 (125.37) months, respectively. The mean number of manic and depressive episodes were 5.70 (5.79) and 3.05 (3.62), respectively. All patients were under treatment when included in the study, with 13 (21.7%) using only mood stabilizers and 47 (78.3%) using both mood stabilizers and atypical antipsychotics.

No significant difference was identified between patients and healthy males in terms of age, educational background, employment, or HARS. The Body Mass Index (BMI) and HDRS scores were statistically significantly higher in the patient group than in the healthy male controls ($p = .014$, $p = .006$, respectively). The scores in sexual intercourse frequency, sexual communication, and erectile dysfunction (ED) were significantly higher in the patients than in the healthy male controls, as was the GRISS total score ($p = .002$, $p = .039$, $p < .001$, $p = .001$, respectively).

The HDRS scores were statistically significantly higher in the patients' spouses than in healthy males ($p = .042$). No difference was identified between patients' spouses and the healthy females in terms of the age, educational background, employment, BMI, HARS, or GRISS total score, whereas scores for frequency and communication were significantly higher in the patients' spouses ($p = .003$, $p < .001$, respectively).

The logistic regression model applied to patients and healthy males revealed that erectile dysfunction scores of male patients with BD were higher than healthy male controls ($p = .043$, OR=1.22). The model applied to patients' spouses and healthy females revealed that sexual communication score of patients' spouses were higher than healthy female controls ($p = .005$, OR = 1.33).

Comparison of patients and their spouses according to sexual dissatisfaction

SD was identified in 62% ($n = 37$) of patients according to the GRISS total score. Comparison of patients with and without SD revealed high HARS and HDRS scores for patients with SD, and the spouses of those patients also had a high GRISS total score ($p = .020$, $p < .001$, $p = .022$, respectively). There was no statistically significant difference between patients with and without SD in terms of age, educational background, employment, BMI, HARS, YMRS, age of onset of BD, duration of BD, number of episodes, or medication type (only mood stabilizers or mood stabilizers +antipsychotics).

SD was identified in 53% ($n = 32$) of patients' partners, according to the GRISS total scores. Only spouses of those with SD showed a high level of GRISS total score ($p = .004$). There was no statistically significant difference in terms of age, educational background, employment, BMI, HDRS, or HARS.

The logistic regression model conducted for patients indicated that sexual satisfaction was associated with depressive symptoms ($p = .010$, OR = 1.81). The model created for patients' spouses revealed GRISS total score of the patients as a predictor of SD in their partners ($p = .011$, OR = 1.06).

Discussion

Our results revealed that male patients with BD experienced higher ED than controls. Psychotropic drugs used in BD treatment are known to cause SD. Furthermore, subsyndromal symptom experiences during euthymic periods and negative consequences of the disorder can negatively affect sexual functionality. Dell'Osso et al. reported that patients with BD had a higher lifelong sexual dysfunction rate when compared to controls [1]. Similarly, Hariri et al. found that patients with BD in remission experience more sexual problems than healthy controls [2]. These results support our findings.

The subgroup logistic regression analyses revealed that sexual satisfaction was associated with depressive symptoms in patients, after controlling for the confounding factors. The literature reports an association between the existence of depressive symptoms below the syndromal depression level and SD [3]. However, the relation between depressive symptoms and SD can be bidirectional. The causality relationship between these variables cannot be explained based on our findings.

Sexual communication problems of patients' spouses were higher than healthy female controls. A few studies have addressed SD in spouses of male patients with BD. A study evaluating spouses of patients with BD in remission (28 females, 37 males) suggested that the sexual satisfaction level declined in patients' spouses following the onset of the disorder [4]. Caregiver burden and increased responsibility for patients' spouses might have influenced sexuality negatively.

The subgroup regression analyses revealed that only GRISS total score of the patients was a factor affecting the SD of their spouses. Several previous studies have indicated that sexual functions are mutually affected in partners and that a sexual problem existing with one of the partners can lead to SD in the other partner [5].

This study has some limitations. Our study design was cross-sectional, so no inference can be made regarding causality of the results. Another limitation is the small sample size. Furthermore, due to the small sample size, no assessment was made based on drug type, dosage, or prolactin level.

Conclusions

The results from this study revealed that male patients showed higher scores of ED and their spouses showed higher scores of sexual communication when compared to healthy controls. A correlation was identified between sexual dissatisfaction in male patients with BD and their depressive symptom levels. The SD of the patients was correlated with the SD of their healthy spouses. The findings indicate that assessment of especially subsyndromal depressive symptoms of patients with BD and provision of necessary medical interventions can reduce the sexual problems of both the patients and their spouses.

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Alpha-7 nicotinic acetylcholine receptor positive allosteric modulators improve GABAergic deficits induced by subchronic MK-801 model of schizophrenia in rats

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ABSTRACT

Objective: Schizophrenia is a chronic and young-onset psychiatric disorder, having 0.5–1% prevalence and characterized by positive, negative, and cognitive symptoms. While current treatments improve most of the positive symptoms, they are not successful enough to prevent negative and cognitive symptoms. Additionally, they may cause serious side effects such as tardive dyskinesia and metabolic syndrome. Therefore, new drug development became an important target for schizophrenia treatment. Glutamatergic hypoactivity has been shown to play a fundamental role in the pathophysiology of schizophrenia, and *N*-methyl-D-aspartate receptor (NMDAR) antagonists such as MK-801 and Phencyclidine are widely used for modelling schizophrenia in rats [1]. Deficits in glutamic acid decarboxylase (GAD) 67 and parvalbumin expressions are well-known molecular findings of schizophrenia [2]. Recent studies have shown that alpha-7 nicotinic acetylcholine receptors (nAChR) play an important role in the neurobiology of the disease. Besides, agonists and positive allosteric modulators (PAMs) of nAChR might be valuable candidates for schizophrenia treatment [3]. In this study, we examined the effects of alpha-7 nAChR partial agonist (A-582941), type I PAM (CCMI), type II PAM (PNU-120596), and their combinations (A-582941+CCMI and A-582941+PNU-120596) on hippocampal GAD67 and parvalbumin gene expressions in subchronic MK-801 model of schizophrenia in rats.

Methods: Male Wistar Hannover rats were divided into nine groups ($n = 6$ per group): Control, Vehicle (Dimethyl sulfoxide), MK-801 (0.2 mg/kg), MK-801+Clozapine (5 mg/kg), MK-801+A-582941 (1 mg/kg), MK-801+CCMI (1 mg/kg), MK-801+PNU-120596 (3 mg/kg), MK-801+A-582941+CCMI (0.33/0.33 mg/kg), MK-801+A-582941+PNU-120596 (0.33/1 mg/kg). MK-801 (0.2 mg/kg) was intraperitoneally (i.p.) injected twice a day for 7 days. After a week of washout period, treatments were administered once a day for 10 days. Rats were decapitated 24 h after the last dose of treatments. Real-time polymerase chain reaction (RT-PCR) was conducted to determine the levels of parvalbumin and GAD67 gene expressions in hippocampus. For each sample, the level of target gene transcripts was normalized to GAPDH. Cp values were calculated with 2^{-ddCT} method according to the following formula: $2^{-ddCT} = 2^{-(Ct\ target - Ct\ target\ reference)}/2^{-(Ct\ control - Ct\ control\ reference)} \times 100$. One-way analysis of variance (ANOVA) followed by Dunnett's *post hoc* test was used for statistical analyses in GraphPad Prism software.

Results: MK-801 administration significantly decreased parvalbumin and GAD67 gene expressions compared to control group ($p < .01$). Clozapine ($p < .05$), CCMI ($p < .01$), PNU-120596 ($p < .01$), A-582941+CCMI ($p < .001$), and A-582941+PNU120596 ($p < .001$) treatments reversed MK-801-induced parvalbumin deficit. CCMI ($p < .001$), A-582941+CCMI ($p < .01$), and A-582941+PNU-120596 ($p < .05$) treatments increased GAD67 gene expressions compared to MK-801 group.

Conclusions: In our study, it was shown that CCMI, PNU-120596, and their combinations with A-582941 but not A-582941 alone, improved GABAergic deficits of schizophrenia in rats. Our results showed a clear superiority of alpha-7 nAChR PAMs (CCMI and PNU-120596) to a partial agonist (A-582941) on molecular findings of schizophrenia. Additionally, among others, CCMI was found to be the most promising candidate in our study. In addition to CCMI, the combination of alpha-7 agonist and PAM might be a valuable approach for schizophrenia treatment.

KEYWORDS

A-582941; CCMI; PNU-120596; MK-801; nicotinic acetylcholine receptor; schizophrenia

Introduction

Schizophrenia is a chronic, lifelong, young-onset psychiatric disorder, which has about 0.5–1% prevalence. Clinical aspects of the disease consist of three main symptom clusters: positive (hallucination, delusion), negative (anhedonia, amotivation, etc.), and cognitive (learning, memory, and attention deficits) symptoms. Typical and atypical antipsychotics are used for the pharmacological therapy of schizophrenia. The effect

of typical antipsychotics is based on the antagonism of dopaminergic D2 receptors, whereas the effects of atypical antipsychotics are mainly based on the blockade of both dopaminergic and serotonergic receptors. Either typical or atypical antipsychotics have beneficial effects on most of the positive symptoms of schizophrenia while they are not successful enough to prevent negative and cognitive symptoms. In addition to this, serious side effects occur by the usage of typical (extrapyramidal side effects) and atypical (metabolic syndrome and agranulocytosis) antipsychotics. For these reasons, developing the new strategies became an important target for schizophrenia treatment [1].

Hyperdopaminergic hypothesis is the oldest and most accepted theory for explaining the neurobiology of schizophrenia. According to the hypothesis, it has been thought that hyperactivity of the mesolimbic dopaminergic pathway causes positive symptoms of schizophrenia, whereas hypoactivity of the mesocortical pathway reveals negative and cognitive symptoms. The fact that the effects of typical and atypical antipsychotics are based on D2 receptor blockade is the main supportive data of this hypothesis [2]

Glutamatergic hypoactivity is one of the important hypotheses of schizophrenia. This hypothesis has stated that the hypoactivity of the glutamatergic neurotransmission, especially via *N*-methyl-D-aspartate (NMDA) receptors, reveals an imbalance between glutamatergic, gamma-aminobutyric asidergic (GABAergic), and dopaminergic systems. As a result of this imbalance, positive, negative, and cognitive symptoms occur in schizophrenic patients. In addition to this, the fact that NMDA receptor antagonists such as phencyclidine and ketamine reveal psychosis-like state in healthy volunteers is one main evidence of this theory. Moreover, acute and chronic antagonism of NMDA receptors causes schizophrenia-like behaviours in rodents. For this reason, NMDA receptor antagonists such as MK-801 and Phencyclidine are widely used for modelling schizophrenia in rodents [3].

GABA is one of the key neurotransmitters in the neurobiology of schizophrenia. Studies have shown that the numbers of the GABAergic interneurons decreased in the hippocampus of schizophrenic patients while the numbers of total neurons were unchanged. In addition to this, expressions of both 65 and 67 kDa isoforms of glutamic acid decarboxylase (GAD) enzyme were also decreased in these patients. Moreover, certain studies have indicated that the neuronal loss of the GABAergic interneurons occurs in especially parvalbumin-containing subtype. Supportively, preclinical studies have demonstrated that administration of the NMDA receptor antagonists decreases the number of GABAergic interneurons, expressions of GAD65/67, and parvalbumin. Therefore, it has been thought that reduced level of the GAD65/67 and parvalbumin expressions could be a good marker for schizophrenia [4].

It has been known that imbalance of cholinergic and dopaminergic neurotransmission plays a role in pathophysiology of schizophrenia. It has been demonstrated that there is a polymorphism on the alpha-7 nicotinic acetylcholine receptors (nAChR) encoding gene in schizophrenic patients. Moreover, postmortem studies indicated that alpha-7 nAChR binding capacity and expression were found to be decreased in patients. In addition to this, it has been reported that cigarette consumption of schizophrenic patients is higher than healthy smokers. It has been thought that this situation could be related to their self-treatment desire. In this manner, agonism of the alpha-7 nAChR became a remarkable target for schizophrenia. The first attempt focusing alpha-7 nAChR was the selective agonists of these receptors. It has been demonstrated that alpha-7 nAChR selective agonists such as A-582941 had beneficial effects on schizophrenia-like behaviours in rodents. Additionally, certain studies showed that these agonists could reverse the deficits on GAD67 and parvalbumin expressions in rodents. Despite the successful profile of alpha-7 nAChR agonists, it has been indicated that they cause a rapid desensitization of these receptors and reveal "invers U" dose–response curve in in vitro studies. Positive allosteric modulators (PAMs) of alpha-7 nAChR are the newer strategy compared to agonists for schizophrenia treatment. PAMs bind to allosteric site of the alpha-7 nAChR and indirectly facilitate neurotransmission, whereas agonists bind to orthosteric site of receptors and directly stimulate receptors. PAMs alone cannot stimulate a receptor, but they potentiate the effect of agonists. PAMs are divided into two classes according to their pharmacological profile; Type I and Type II PAMs. Type I PAMs increase agonist evoked maximum peak amplitude, whereas Type II increase both of peak amplitude and maximum peak duration in electrophysiological studies. As a difference from type I PAMs, type II PAMs also re-sensitize the agonist-desensitized alpha-7 nAChR. It has been reported that CCMI, a type I PAM, reveals procognitive effects in naive rats and antipsychotic-like properties in animal models of schizophrenia. Similarly, studies have demonstrated that PNU-120596, a type II PAM, showed procognitive effects and reversed schizophrenia-like behaviours in rats. The effects of CCMI or PNU-120596 on GAD67 and parvalbumin expressions, which are considered as repeated and reliable markers, are unknown yet [5–7].

In this study, we investigated the effects of alpha-7 nAChR partial agonist (A-582941), type I (CCMI) PAM, type II (PNU-120596) PAM, and their combinations (A-582941+CCMI and A-582941+PNU-120596) on hippocampal GAD67 and parvalbumin

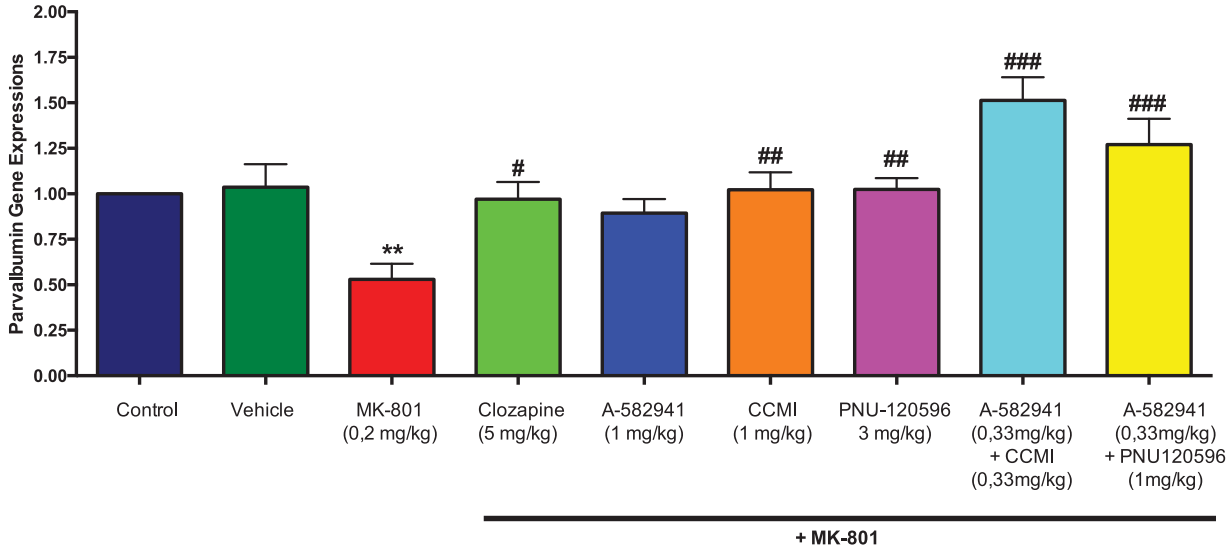

Figure 1. The effects of MK-801 and treatments on parvalbumin gene expressions in rats. Data are expressed as mean ± S.E.M and analysed by using one-way ANOVA followed by Dunnett *post hoc* test. **:$p < .01$ compared with the control group and #:$p < .05$, ##:$p < .01$, ###:$p < .001$ compared with the MK-801 group.

gene expressions in subchronic MK-801 model of schizophrenia in rats.

Material and methods

Male Wistar Hannover rats were divided into nine groups ($n = 6$ in each group): Control, Vehicle, MK-801, MK-801+Clozapine, MK-801+A-582941, MK-801+CCMI, MK-801+PNU-120596, MK-801+A-582941+CCMI, and MK-801+A-582941+PNU-120596. All drugs were dissolved in dimethyl sulfoxide and diluted by saline. MK-801 (0.2 mg/kg) was intraperitoneally (i.p.) injected twice a day for 7 days. After a week of washout period, Clozapine (5 mg/kg), A-582941 (1 mg/kg), CCMI (1 mg/kg), PNU-120596 (3 mg/kg), A-582941+CCMI (0.33/0.33 mg/kg), and A-582941+PNU-120596 (0.33/1 mg/kg) were administered once a day for 10 days. In this period, saline and dimethyl sulfoxide were injected to control and vehicle groups, respectively. Rats were decapitated 24 h after the last dose of treatments. Real-time polymerase chain reaction (RT-PCR) was conducted to determine the levels of parvalbumin and GAD67 gene expressions in hippocampus. Isolation of RNA, cDNA synthase, and quantitative PCR protocols were performed, respectively. Firstly, total RNA was isolated using RNAzol solution (MRC, 1 mL for 100 mg hippocampal tissue) according to the manufacturer's instructions. After RNA isolation, cDNA was synthased by commercial script cDNA synthase kit (Jena Bioscience) via 10 min 42°C, 60 min 50°C, and 10 min 70°C thermal cycle. RT-PCR was conducted using Agilent Stratagene

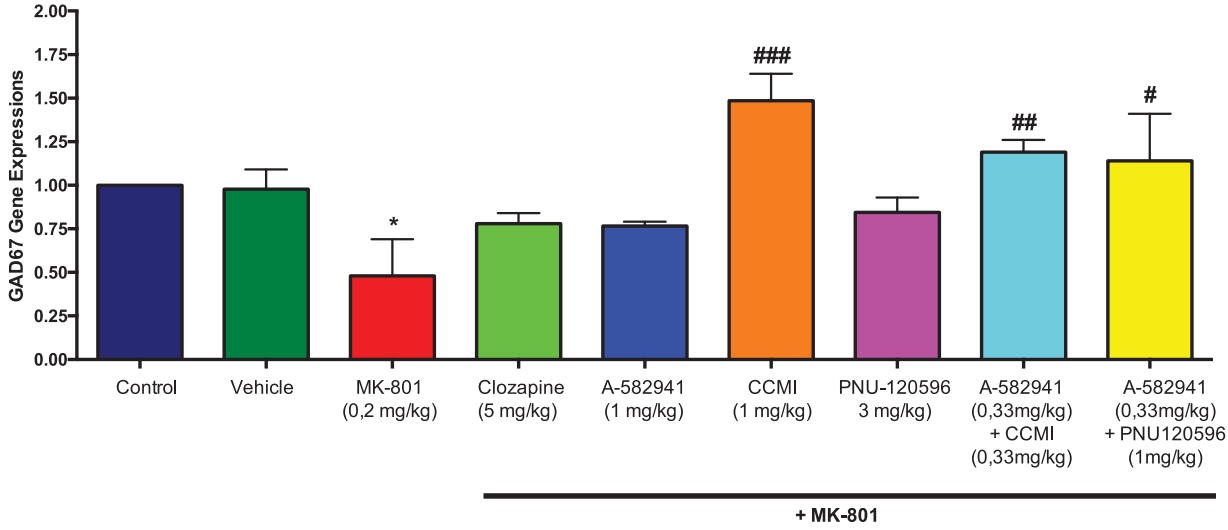

Figure 2. The effects of MK-801 and treatments on GAD67 gene expression in rats. Data are expressed as mean ± S.E.M and analysed by using one-way ANOVA followed by Dunnett *post hoc* test. *:$p < .05$ compared with the control group and #:$p < .05$, ##:$p < .01$, ###:$p < .001$ compared with the MK-801 group.

3005P (Agilent) via quantitative PCR GreenMaster-UNG/lowROX kit (Jena Bioscience). For each sample, the level of target gene transcripts was normalized to GAPDH. Cp values were calculated with 2^{-ddCT} method according to the following formula: $2^{-ddCT} = 2^{-(Ct\ target - Ct\ target\ reference)}/2^{-(Ct\ control - Ct\ control\ reference)} \times 100$. One-way analysis of variance (ANOVA) followed by Dunnett's *post hoc* test was used for statistical analyses in GraphPad Prism software.

Results

For parvalbumin gene, MK-801 administration significantly decreased its expression compared to the control group in the hippocampus of rats ($p < .01$). Clozapine ($p < .05$), CCMI ($p < .01$), PNU-120596 ($p < .01$), A-582941 + CCMI ($p < .001$), ve A-582941+PNU120596 ($p < .001$) treatments reversed the effect of MK-801 on this gene. Although A-582941 tended to increase the expression of parvalbumin, this effect was not found statistically significant (Figure 1).

In GAD67 gene expressions, MK-801 markedly reduced the level of expression compared with control group. CCMI, A-582941+CCMI, and A-582941+PNU-120596 treatments increased GAD67 gene expressions compared to MK-801 group ($p < .001$, $p < .01$, $p < .5$, respectively). Clozapine and PNU-120596 could not reverse the effect of MK-801 for GAD67 gene although they increased parvalbumin gene expressions in the hippocampal tissue of rats. A-582941 treatment could not reverse the effect of MK-801 on either parvalbumin or GAD67 gene expressions (Figure 2).

Conclusions

In our study, we firstly investigated the effects of A-582941, CCMI, PNU-120596, and their combinations on parvalbumin and GAD67 expressions in MK-801 model of schizophrenia in rats. We showed that sub-chronic MK-801 administration decreased GAD67 and parvalbumin gene expressions in the hippocampus of rats. We reported that A-582941 did not reverse the effect of MK-801 on either parvalbumin or GAD67 expressions. Additionally, Clozapine and PNU-120596 attenuated GABAergic deficits on parvalbumin, but not GAD67. CCMI and combination treatments ameliorated the effect of MK-801 on both parvalbumin and GAD67 gene expressions. Our results showed a clear superiority of alpha-7 nAChR PAMs (CCMI and PNU-120596) to a partial agonist (A-582941) on molecular findings of schizophrenia. To conclude, it can be said that even though all drug candidates (except A-582941) have beneficial effect on molecular markers of schizophrenia, CCMI is the most promising candidate for this scope. We also suggested that the combination of alpha-7 agonist and PAM might be a valuable approach for schizophrenia treatment.

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Executive functions profile in children and adolescents with or without ADHD: by using performance-based measures and homework and work habits questionnaire

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ABSTRACT

Objective: The first purpose of this study was to compare executive functions in children and adolescents with and without ADHD using performance-based measures. The second aim was to demonstrate how daily functions of the children and adolescents with ADHD are impaired using the developed questionnaire about Homework and Work Habits (HWH). Finally, we aimed to examine the relationship between HWH ratings and performance-based measures of executive functions.

Methods: A group of children between the age of 7 and 17 who met the DSM-IV criteria for the first time for ADHD ($n = 60$) as the patient group, and 7- to 17-year aged children and adolescents ($n = 60$) as the healthy control group were included in this study sample. Parents and teachers of the participants were asked to complete a form of Conner's Parent and Teacher Ratings and HWH ratings to evaluate performance-based executive functions. Participants completed the Wisconsin Card Sorting, Stroop Color and Word and Trail Making (B) tasks. In addition, HWH questionnaire was given to the children and adolescents and their intelligence level was evaluated by using the Wechsler Intelligence Scale for Children-Revised (WISC-R).

Results: ADHD group participants displayed lower performance on all of the performance-based executive functions measures and lower HWH scores compared to the controls. The HWH questionnaire was found to be significantly related with performance-based executive function tests negatively.

Conclusions: HWH questionnaire may be a more feasible and cost-effective method to evaluate executive functions compared to performance-based measures in children and adolescents. It can also be used to monitor levels of executive functions before and after medical management in children and adolescent with ADHD.

KEYWORDS

ADHD; executive functions; homework and work habits; children; adolescence

Introduction

One of the most common disorders which has been investigated most thoroughly is Attention Deficit Hyperactivity Disorder (ADHD). Impairment in executive functions shown in some of the ADHD cases [11] led many neuropsychological theories regarding ADHD to be put forward [1,7,8,9]. Executive functions (EF) are cognitive skills required to conduct targeted behaviour, and to adapt in accordance with environmental changes and needs. It is the cluster processes in which person uses him/herself and resources to reach a target [3]. There are studies reporting that deficiencies in executive functions play role in many psychiatric diseases or developmental disorders [5,6,11]. Therefore, there are attempts to develop methods to measure these skills as deficiencies in executive functions constitute an important component of understanding ADHD [2,9]. These attempts may be in the form of performance-based measurements as well as scales evaluating behaviour [4].

The first aim of this study was to compare executive functions in children and adolescents with and without ADHD using performance-based measures. The second aim was to demonstrate how daily functions of the children and adolescents with ADHD are impaired using the developed questionnaire about Homework and Work Habits (HWH). Finally, we aimed to investigate the relationship between HWH ratings and performance-based measures of executive functions.

Method

Study sample was chosen from children and adolescents between the ages of 7 and 17 who were diagnosed with ADHD according to diagnostic criteria of DSM-IV by random sampling method. ADHD group was composed of 60 children and adolescents between the ages of 7 and 17 (mean 10.92±2.13) accepting to participate in the study and diagnosed with ADHD after semi-structured interview who have only oppositional defiant disorder as comorbid disease. In order to control the effect of drugs on executive functions, children and adolescents using drugs were not included in the study and those diagnosed with ADHD for the first time were included in the study.

For control group, Child Behaviour Checklist (CBCL), which is a screening form for behavioural characteristics, was administered to parents of children between the ages of 7 and 17 referring to paediatrics outpatient clinic of Marmara University Hospital and from those who do not have psychopathology findings, especially ADHD, were invited to the study after being chosen by random sampling. Children meeting study criteria and consenting to participate were included in the study. The control group consisted of 60 healthy children and adolescents between the ages of 7 and 17 (mean age 10.46 ± 2.22).

The exclusion criteria of the study for ADHD and control groups were as follows: mental retardation or borderline intelligence (WISC-R verbal, performance and/or overall score <80), chronic or severe medical disease, seizure-like neurological disorder, psychosis history or symptoms, a mood or anxiety disorder, autism-spectrum disorder.

The aim of the present study was to address the relations between changes in executive functions in children and adolescents diagnosed with ADHD and having difficulty in "home work and work," which is

an important component of daily functions. In order to collect more data in this context, Wisconsin Card Sorting Test (WCST), Stroop Color Word Test (SCWT), and Trail Making Test-B form (TMT-B) were administered and performance-based executive functions of children and adolescents were evaluated. In addition, all children and adolescents were administered WISC-R test regarding the issue of home work/work habits. Children and adolescents were evaluated by performance-based tests and the scores obtained from home work habits (HWH) questionnaire filled by their parents. HWH questionnaires have three forms to be filled by the students, teacher, and parents respectively. Both teachers' and parents' forms contain 37 items, whereas the students' form contains 38 items.

Statistical analysis

The data were evaluated using the Statistical Package for the Social Sciences (version 20) program. Descriptive statistics are shown as mean, standard deviation, or frequency (%). A 95% confidence interval was used to assess the data. In the comparison of HWH parent, teacher, and student scores and the levels of performance-based executive functions, one-way analysis of covariance (ANCOVA) was used for controlling the effects of WISC-R scores on tasks and questionnaires. Linear regression analysis was used to define association between performance-based tasks and HWH questionnaires.

Results

There were no significant statistical differences between the groups in terms of age and gender ($p > .05$). The children in the ADHD group had lower IQ scores than the control group ($p < .05$).

The comparison of the HWH parent, teacher, and student scores and the levels of WCST-4, SCWT, TMT-B across groups is shown in Table 1. Children with ADHD had lower scores of all measurements than the healthy children after adjusting for overall IQ level.

In the result of linear regression analysis, all three forms of HWH questionnaires were found to be significantly associated with all three tasks which evaluated executive functions (Table 2).

Conclusions

In view of the finding of our study, it was founded that the ADHD group displayed lower performance in executive functions compared to control group. Similarly, there were significant differences between groups in terms of all HWH questionnaire levels. Significant differences between groups persisted after the IQ level was controlled for both performance-based tasks and questionnaires. Secondly, significant correlations were found between the scores of HWH and performance-based executive function tests. Linear regression analysis results supported the relationship between executive function tasks and questionnaire measures. It was demonstrated that an increase in all HWH scores can predict the quantity of the decrease in all executive function tests.

Children and adolescents with ADHD can experience difficulties in working without distraction, completing their homework and giving proper intervals while doing their homework due to the deficiencies in skills of adapting easily to changes in conditions, referred to as attention and flexibility measured by TMT-B. The fact was that each of the three forms of HWH questionnaire was associated with SCWT total time. It may be related to the inability of children and adolescents with ADHD to finish their homework on time, to adjust the duration of work, and to maintain their concentration on a subject without distracting their attention which was assessed in HWH questionnaires. ADHD children may have deficiencies in cognitive flexibility and difficulties in adapting to changing conditions and in finding solutions to the obstacles. These skills were evaluated by both performance-based tasks and HWH questionnaires in our

Table 1. Comparison of the scores of HWH questionnaires and performance-based executive function tasks between two groups.

	ADHD Mean ± SD	Control Mean ± SD	*F*	*p*
HWH-Parent Score	26.48 ± 9.90	44.65 ± 11.25	70,09	.000***
HWH-Teacher Score	25,08 ± 11.35	43.70 ± 11.05	45.70	.000***
HWH-Student Score	35.08 ± 12.84	44.84 ± 12.14	13.66	.000***
SCWT	124.69 ± 40.64	97.26 ± 26.60	8.50	.004**
TMT-B	93.75 ± 75.92	51.95 ± 29.77	5.42	.022*
WCST 4	3.18 ± 1.72	4.93 ± 2.03	11.67	.001**

Note: ADHD: Attention deficit hyperactivity disorder; HWH: Homework and work habits; SCWT: Stroop Color Word Test; TMT-B: Trail Making Test-B form; WCST: Wisconsin Card Sorting Test.
*$p < .05$.
**$p < .01$.
***$p < .001$.

Table 2. Evaluation of the relationship between performance-based measures and questionnaires by linear regression analysis.

Dependent variable	Independent variable	*C*	*B*	*p*	Corrected R^2 (%)
TMT-B	HWH-Parent	116.95	−1.24	.002**	7.0
	HWH-Teacher	118.72	−1.33	.001**	9.0
	HWH-Student	129.57	−1.41	.001**	9.0
SCWT	HWH-Parent	140.14	−0.82	.001**	8.7
	HWH-Teacher	135.84	−0.71	.002**	7.1
	HWH-Student	148.46	−0.93	.000**	11.0
WCST 4	HWH-Parent	1.92	0.06	.000**	15.7
	HWH-Teacher	2.31	0.05	.000**	12.0
	HWH-Student	2.25	0.04	.001**	8.1

Note: ADHD, Attention deficit hyperactivity disorder; HWH, Homework and work habits; SCWT, Stroop Color Word Test; TMT-B, Trail Making Test-B form; WCST, Wisconsin Card Sorting Test.
**$p < .01$.

study and we found significant relationships between them.

We think that HWH questionnaires may predict executive function scores and can be filled in a shorter time than executive function tests in clinical practice. It can also be used to follow changes in the levels of executive functions before and after medical treatment in children and adolescent with ADHD.

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Autistic/schizotypal traits in adult-onset and adolescent obsessive–compulsive disorder patients

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ABSTRACT

Objective: The primary aim of the present study was to examine whether adult-onset (AO) OCD patients would differ from subjects with juvenile OCD in terms of autistic and schizotypal traits, socio-demographic variables, and clinical characteristics. Our hypothesis was that juvenile OCD differs from adult-onset OCD with respect to autistic and schizotypal traits, and therefore, juvenile and adult-onset OCD are different subtypes of disorder.

Methods: Adolescent OCD patients (current age 12–17 years; $n = 29$) who were consecutively admitted to Child and Adolescent Psychiatry Department of Behcet Uz Child Diseases and Neurosurgery Research and Training Hospital were interviewed with the Kiddie Schedule for Affective Disorders and Schizophrenia-Present state and Lifetime version (KSADS-PL). Adult patients who were aged 18–65 years who had the diagnosis of OCD according to Diagnostic and Statistical Manual of Mental Disorders, 4th edition DSM-IV criteria were recruited from consecutive subjects who were admitted to the psychiatry department of the Adnan Menderes University (onset age and current age $\geq$ 18 years; $n = 60$). The severity and content of obsessive–compulsive symptoms were determined through Childhood Yale-Brown obsessive–compulsive scale (CYBOCS) and Yale-Brown Obsessive–Compulsive Scale (Y-BOCS). Autism symptoms were assessed by using the Turkish version of Autism-Spectrum Quotient (AQ). Schizotypal traits were assessed using Turkish version of 22-item Schizotypal Personality Questionnaire (SPQ-B).

Results: The course of OCD in AO patients was chronic, whereas adolescent patients had a more episodic course. The rates of lifetime aggressive, religious, and somatic obsessions were significantly higher in adolescent patients compared to AO patients. Adolescent patients had also more lifetime checking, ritualistic, and miscellaneous compulsions than AO patients. The mean number of lifetime obsessions, and compulsions were significantly higher in adolescents than in AO subjects. We have found that total, attention switching, and imagination scores of AQ in AO patients were higher than in adolescent patients. In contrast, adolescent patients had higher scores of total, cognitive-perceptual, interpersonal, and

KEYWORDS

Adolescents; adults; autistic traits; schizotypal traits; subtypes

disorganized scores of SPQ-B compared to AO patients. The correlation analysis in adolescent group revealed that total scores of AQ, and SPQ-B were significantly correlated with the mean number of lifetime obsession and compulsions. There were also significant correlations between total AQ scores and total, cognitive-perceptual, interpersonal, and disorganized scores of SPQ-B. In the AO group, total scores of AQ and SPQ-B were not correlated with the mean number of lifetime obsessions and compulsions. There were significant correlations between total AQ scores and total, cognitive-perceptual, interpersonal, and disorganized scores of SPQ-B.

Conclusions: Our findings suggested that autistic traits might have been related to development of OCD in adulthood, indicating a subgroup of patients in adults. Clinical profile of OCD adolescent patients seemed to be influenced by autistic and schizotypal traits, indicating an autistic and schizotypal subtype of OCD in this age group. We also suggest that the differences between adolescent and AO patients represent developmentally variable manifestation of OCD across juvenile and adult periods. OCD in adolescents seemed to be related to an autistic and schizotypal subtype of the disorder.

Obsessive–compulsive disorder (OCD) is a severe, heterogeneous neuropsychiatric disorders characterized by recurrent, distressing, unwanted thoughts and repetitive ritualistic behaviour. OCD is a common disorder, with a prevalence of 0.5–1% to 4% in childhood and adolescence. Previous studies reported that 30–80% of adults with OCD had a childhood onset of the disorder [1].

The term juvenile onset has been used to refer to cases that begin at any point in childhood or adolescence. Presently, it is unclear whether juvenile and adult-onset OCD are different subtypes of the disorder or are part of a developmental continuum. Some authors postulate that juvenile OCD is a developmental subtype determining its course throughout adult life. Juvenile OCD is reported to have certain important phenotypic characteristics that are different from those of adult OCD.

Autism is frequently a comorbid problem in OCD, both in paediatric and in adult populations. Some authors proposed an autistic subtype of OCD [2]. Schizotypal traits have been related to schizophrenia at conceptual, genetic, neurochemical, anatomical, and neurocognitive levels; 5–33% of the OCD patients have mild-to-severe levels of schizotypal traits, indicating a schizotypal subtype of OCD [3].

The evaluation of whether juvenile OCD differs from its adult counterpart has important clinical and research implications, though it is not yet clear if the differences represent a developmental subtype of OCD or developmentally variable manifestations of OCD across the life cycle. The primary aim of the present study was to investigate whether adult-onset (AO) OCD patients would differ from subjects with juvenile OCD in terms of autistic and schizotypal traits, socio-demographic variables, and clinical characteristics. Specifically, we compared autistic and schizotypal traits between two groups and examined the associations of these traits with OCD symptomatology. Our hypothesis was that juvenile OCD differs from adult-onset OCD with respect to autistic and schizotypal traits, and therefore, juvenile and adult-onset OCD are different subtype of disorder.

Method

Participants

Adolescent OCD patients (current age 12–17 years; $n = 29$) who were consecutively admitted to Child and Adolescent Psychiatry Department of Behcet Uz Child Diseases and Neurosurgery Research and Training Hospital were interviewed with the Kiddie Schedule for Affective Disorders and Schizophrenia-Present state and Lifetime version (KSADS-PL) by a board-certified child- and adolescent psychiatrist. In cases where autistic traits or disorders were suspected (these were not included in the KSADS-PL version used), a neuropsychiatric assessment was performed.

Adult patients who were aged 18–65 years who had the diagnosis of OCD according to Diagnostic and Statistical Manual of Mental Disorders, 4th edition DSM-IV criteria were recruited from consecutive subjects who were admitted to the psychiatry department of the Adnan Menderes University (onset age and current age ≥18 years; $n = 60$).

We defined age at onset as the age that the patient, or a family member, remembered as the beginning of the obsessive–compulsive symptoms. The severity and content of obsessive–compulsive symptoms were determined through Childhood Yale-Brown obsessive–compulsive scale (CYBOCS) and Yale–Brown Obsessive–Compulsive Scale (Y-BOCS).

Autism symptoms were rated by Turkish version of Autism-Spectrum Quotient (AQ). Schizotypal traits were assessed using Turkish version of 22-item Schizotypal Personality Questionnaire (SPQ-B).

Patients with a primary diagnosis of mental retardation, psychotic disorders, bipolar disorders, alcohol-/substance-use disorders, and autism were excluded from participation. Detailed information on demographic and clinical features of the sample (age

at onset of symptoms, gender, course, and the number of lifetime and current clinically significant obsessions and compulsions) was collected by self-report from clinical interviews or retrospective investigation of medical records. Sixteen participants in the adolescent group, and 48 patients in the adult group were under the drug treatment during the assessment. None of the patients were participating in psychotherapy at the time of participation. Informed consent was obtained from patients after the procedure had been fully explained.

Statistical analyses

The group differences were examined using chi-square, and Student's *t*-test, as appropriate. The correlations between several clinical variables of interest were examined with Spearman correlations. All statistical assessments were two-tailed, and we considered results to be significant at $p < 0.05$. We used SPSS version 18.0 statistical software (SPSS Inc., Chicago, IL, USA) to perform our analyses.

Results

As indicated in Table 1, the ratio of females to males was significantly higher in the AO group compared to the adolescent group ($p = .02$). The course of OCD in AO patients tended to be chronic, whereas adolescent patients had a more episodic course ($p = .02$). The frequency of lifetime aggressive ($p = .04$), religious ($p = .01$), somatic ($p = .005$) obsessions were significantly higher in adolescent patients compared to AO patients. Adolescent patients had also more lifetime checking ($p = .04$), ritualistic ($p = .001$), and miscellaneous compulsions ($p < .0001$) than AO patients. The mean number of lifetime obsessions ($p = .005$) and compulsions ($p < .0001$) were significantly higher in adolescents than in AO subjects.

We have found that total ($p = .01$), attention switching ($p = .01$), and imagination scores of AQ ($p = .02$) in AO patients were higher than in adolescent patients. In contrast, adolescent patients had higher scores of total ($p = .003$), cognitive-perceptual ($p = .02$), interpersonal ($p = .03$), and disorganized ($p = .003$) scores of SPQ-B compared to AO patients.

Table 1. The comparison of juvenile and adult-onset OCD patients with respect to several demographic and clinical variables.

	Juvenile OCD ($n = 29$)		Adult-onset OCD ($n = 61$)		Statistical analyses		
	n	%	*n*	%	χ^2	df	*p*
Gender					5.04	1	.025
Male/female	14/15	48.8/51.2	15/46	24.6/75.4			
Family history of any psychiatric disorders	9	40.9	18	30.9	0.78	1	NS
Course of OCD					5.37	1	.020
Chronic	9	31.0	32	55.2			
Episodic	20	79.0	26	44.8			
The mean *n* of lifetime obsessions							
Contamination	21	72.4	40	67.6	0.19	1	NS
Aggressive	20	69.0	28	47.5	3.62	1	.045
Sexual	7	24.1	11	18.6	0.36	1	NS
Hoarding	6	20.7	7	11.9	1.20	1	NS
Religious	16	55.2	16	27.1	6.61	1	.01
Somatic	13	44.8	10	16.9	7.82	1	.005
Miscellaneous	14	48.3	28	47.5	0.00	1	NS
The mean *n* of lifetime compulsions							
Cleaning	17	58.6	41	69.5	1.02	1	NS
Checking	25	86.2	39	66.1	3.96	1	.047
Ritualistic	22	75.9	22	37.3	11.5	1	.001
Counting	8	27.6	11	18.6	0.91	1	NS
Ordering	9	31.0	13	22.0	0.84	1	NS
Hoarding	5	17.2	6	10.2	0.88	1	NS
Miscellaneous	23	79.3	17	28.8	19.9	1	<.0001
	Mean	SD	Mean	SD	*T*	df	*p*
Mean number of life time							
Obsessions	3.34	1.61	2.37	1.42	3.00	86	.005
Compulsions	3.76	1.32	2.53	1.43	3.89	86	<.0001
CY-BOCS/Y-BOCS total	22.7	6.27	20.7	9.10	1.03	84	NS
Obsession	11.5	3.59	10.4	4.67	1.01	84	NS
Compulsion	11.2	3.0	10.2	4.74	0.97	84	NS
AQ Total	22.7	6.27	22.4	5.31	−2.56	88	.012
Social skill	3.79	2.00	4.41	1.98	−1.37	88	NS
Attention shifting	4.31	2.05	5.44	1.83	−2.63	88	.010
Attention to detail	4.90	2.32	5.00	1.90	−2.24	88	NS
Communication	2.79	2.14	3.15	1.78	−0.82	88	NS
Imagination	3.45	2.04	4.48	1.88	−2.35	88	.021
SPQ-B total	11.7	4.40	8.42	5.06	3.04	87	.003
Cognitive-perceptual	4.07	1.33	3.02	2.20	2.36	87	.020
Interpersonal	4.90	1.97	3.80	2.39	2.13	87	.035
Disorganized	2.79	2.04	1.60	1.56	3.04	87	.003

Table 2. Correlation analysis in juvenile OCD group.

	OA total	SPQ-B total	SPQ-B cognitive-perceptual	SPQ-B interpersonal	SPQ-B disorganized
Mean *n* of lifetime obsessions	0.37*	0.50**	0.32	0.38*	0.50**
Mean number of lifetime compulsions	0.55**	0.37*	0.39*	0.23	0.32
OA total		0.63***	0.42*	0.52**	0.59***

*$p < .05$.
**$p < .001$.
***$p < .0001$.

Table 3. Correlation analysis in adult-onset OCD group.

	OA total	SPQ-B total	SPQ-B cognitive-perceptual	SPQ-B interpersonal	SPQ-B disorganized
Mean number of lifetime obsessions	1.48	0.16	0.08	0.19	0.10
Mean number of lifetime compulsions	−0.04	−0.00	−0.02	0.00	0.00
OA total		0.55***	0.26*	0.58***	0.51***

*$p < .05$.
**$p < .001$.
***$p < .0001$.

The correlations between the severity of autistic and schizotypal traits, and clinical variables were examined separately in two groups. The correlation analysis in the adolescent group revealed that total scores of AQ, and SPQ-B were significantly correlated with the mean number of lifetime obsession ($p = .04$; $p = .006$, respectively), and compulsions ($p = .002$; $p = .04$, respectively). There were also significant correlations between total AQ scores and total ($p < .0001$), cognitive-perceptual ($p = .02$), interpersonal ($p = .004$), and disorganized ($p = .001$) scores of SPQ-B (Table 2).

In the AO group, total scores of AQ and SPQ-B were not correlated with the mean number of lifetime obsessions and compulsions. There were significant correlations between total AQ scores and total ($p < .0001$), cognitive-perceptual ($p = .04$), interpersonal ($p < .0001$), and disorganized ($p < .0001$) scores of SPQ-B (Table 3).

Discussion

The main purpose of the present study was to examine the differences between adolescent and AO OCD patients with respect to autistic and schizotypal traits, and their associations with OCD symptomatology. We hypothesized that OCD is a distinct disorder in adolescents and in AO patients, based on the differences in autistic and schizotypal traits.

Our results demonstrated that OCD profile of adolescents was different from AO patients. The course of OCD in AO patients tended to be chronic, whereas adolescent patients had a more episodic course ($p = .02$). Consistent with some of the previous findings, the mean number of lifetime obsessions, and compulsions; and the presence of lifetime aggressive, religious, and somatic obsessions; checking, ritualistic, and miscellaneous compulsions in adolescent OCD patients were significantly higher than those with AO. When the two groups were compared, we have found that adolescent OCD patients had more schizotypal traits, while AO subjects were more likely to have schizotypal traits. We suggested that autistic traits might be related to development of OCD in adulthood, indicating a subgroup of patients, as Bejerot et al. [2] pointed out. In contrast, OCD in adolescents seemed to be related to schizotypal traits. This finding supports the previous studies which suggested that schizotypal traits in OCD are associated with earlier onset of OCD [3]. The most prominent finding of this study is that the associations of autistic and schizotypal traits with OCD symptomatology differed between adolescent OCD subjects and the OCD patients with AO. The severity of total autistic and schizotypal traits in adolescent OCD patients was significantly associated with the number of lifetime obsessions and compulsions, in contrast to AO patients. Therefore, clinical profile of OCD adolescent patients seemed to be influenced by autistic and schizotypal traits, indicating an autistic and schizotypal subtype of OCD in this age group. In addition, the close relationship between autistic and schizotypal traits in both adolescent and AO OCD patients might suggest their roles in development of OCD from adolescence to adulthood.

The findings of the present study must be interpreted with caution due to small sample size. We did not assess the correlation between the content of OCS with autistic and schizotypal traits. In addition, we did not control for a comorbid diagnosis of autistic disorder which might be associated with autism and schizotypal features. Since the majority of our sample was under drug treatment, we did not measure the relationship between autistic/schizotypal traits and current OCD severity. Future research with larger samples might help us to better understand the complex influence of autistic and schizotypal traits in adolescent and adult subjects with OCD.

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The relationship of oxytocin, vasopressin, and atrial natriuretic peptide levels with cognitive functions in patients with schizophrenia

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ABSTRACT

Objective: Studies with regard to schizophrenic patients have found significant social cognition and impairment in other neurocognitive functions. The aim of this study was to examine neurocognition and social cognition levels in patients with schizophrenia and compare those with healthy controls, to examine the effects of cognitive functions on disease severity, symptoms, and function, to examine the effects of blood oxytocin, vasopressin, and atrial natriuretic peptide levels on cognitive capacity in patients, and to compare these with healthy controls.

Method: Sixty-three chronic schizophrenic patients at Sakarya University Research and Training Hospital were admitted to the study, as were 60 healthy controls. The control group and the patient group were matched in terms of age, gender, and duration of education, and care was taken to ensure that there was no significant difference in terms of IQ scores. Socio-demographic data form, the Rey Auditory Verbal Learning Test (VLT), the Trail Making Test A-B (TMT), the Stroop Test, the Wechsler Memory Scale-Visual Production Subscale (WMS-V), and the Facial Emotion Recognition Test have been administered to all subjects. In addition, the structured clinical interview for DSM-4 (SCID-I), PANSS (positive and negative syndrome scale), Clinical Global Impression – Severity (CGI-s), and the Global Assessment of Functioning (GAF) scale have been administered to the patients participating in the study. Before applying the tests, 10 mL of venous blood were taken from all participants and analysed using ELISA.

Results: In the healthy control group, some neurocognitive tests showed a statistically significant improvement with oxytocin, and it was also found that there was a correlation between social cognitive performances. Blood vasopressin level did not different between the groups and it was found that in the healthy control group, statistically significant decrease in performance was observed in some social and neurocognitive field tests. Blood ANP levels did not differ between the groups. A statistically significant difference was found in the healthy control group that blood ANP levels affected social cognition in the positive direction.

Conclusions: Despite the wide variety of treatment options, the inability to achieve a complete remission goal in schizophrenia treatment, especially the limited presence of antipsychotics on negative findings and cognitive functions, led to the search for other molecules that may be involved in the aetiology of schizophrenia. In our study, the relationship between the levels of oxytocin and atrial natriuretic peptides in terms of social cognition was determined in the healthy control group and our study was the first to examine the association between atrial natriuretic peptide and cognitive functions. In addition to oxytocin and vasopressin, our study has contributed to the literature in terms of finding that ANP may be related to cognitive function. These new studies will help us to understand the effects of neuropeptides on neurocognition and social cognition and establish a relationship in schizophrenia patients. They will also offer us an alternative perspective to explain behavioural and memory findings in schizophrenia patients and will also help us develop new treatment strategies in these areas.

KEYWORDS

Atrial natriuretic peptide; cognitive functions; oxytocin; schizophrenia; vasopressin

Introduction

Studies with regard to schizophrenic patients have found significant social cognition and impairment in other neurocognitive functions. The reduction in the prevalence of delusions and hallucinations during the remission period of schizophrenic patients, and the absence of a decline in the rate of cognitive impairment, indicates the prevalence of cognitive impairments in schizophrenia, and is one of the most important symptom clusters [1]. The deficiency of antipsychotic drugs in this area has led to a search for new treatments, so oxytocin and vasopressin have been the subject of many studies investigating their

effects on cognitive capacity. However, the results obtained from the various studies are contradictory, and there is no study yet that has investigated the association between atrial natriuretic peptide and cognitive functions, and a neuropeptide uses similar mechanisms to oxytocin. The aim of this study was to investigate neurocognition and social cognition levels in schizophrenia patients and compare those with healthy controls, to examine the effects of cognitive functions on disease severity, symptoms, and function, to investigate the effects of blood oxytocin, vasopressin, and atrial natriuretic peptide levels on cognitive capacity in patients, and compare these with healthy controls.

Method

Sixty-three chronic schizophrenic patients at Sakarya University Educational Research Hospital were admitted to study, as were 60 healthy controls. The inclusion criteria for patients were as follows: 1. Diagnosis of schizophrenia according to DSM-4 and DSM-5 criteria; 2. Between the ages of 18 and 65; 3. Be at least a primary school graduate; 4. Have been in remission for at least 6 months; 5. 6 months prior to inclusion in the investigation, no admission to a psychiatric clinic; and 6. Have been in receipt of regular antipsychotic treatment for the last 6 months. Control group inclusion criteria: 1. According to DSM-IV and DSM-V criteria, there is no psychiatric diagnosis with regard to the participant and in the participant's family; 2. Between the ages of 18 and 65; 3. Be at least a primary school graduate. Exclusion criteria for both groups: 1. Neurological/metabolic disease history affecting cognitive function (known); 2. Sensory impairment that may cause neurocognitive limitations (such as loss of hearing/blindness); 3. Those with mental retardation; 4. Those with alcohol or substance abuse; 5. Those who have received electroconvulsive therapy in the last six months; 6. Those who are pregnant and lactating; 7. Those with hypertension and known cardiovascular disease. The control group and the patient group were matched in terms of age, gender, and duration of education, and care was taken to ensure that there was no significant difference in terms of IQ scores. Socio-demographic data form, the Rey Auditory Verbal Learning Test (VLT), the Trail Making Test A-B (TMT), the Stroop Test, the Wechsler Memory Scale-Visual Production Subscale (WMS-V), and the Facial Emotion Recognition Test which included photos with six facial emotions (happy, sad, fearful, angry, surprised, disgusted, and neutral facial expressions) have been applied to all subjects. In addition, the structured clinical interview for DSM-4 (SCID-I), PANSS (positive and negative syndrome scale), Clinical Global Impression – Severity (CGI-s), and the Global Assessment of Functioning (GAF) scale have been applied to the patients participating in the study. We planned to measure neurocognition using the Rey Auditory Verbal Learning Test (VLT), the Trail Making Test A-B (TMT), the Stroop Test, and the Wechsler Memory Scale-Visual Production Subscale (WMS-V) and measure social cognition with the facial emotion recognition test. Before applying the tests, 10 mL of venous blood was taken from all participants and analysed using ELISA. In the analysis of the data, the percentage distributions of the variables were obtained, and the centrality and prevalence measures (mean, standard deviation) were calculated for the continuous variables, the dependent and independent variables were evaluated using the chi-square test, the Student's *t*-test, and the Pearson correlation test.

Results

There were no significant differences in age, gender, and years of education between the patients and the healthy group in the study. When the clinical history of the patient group is examined, the group mean duration of illness was 14.13 ± 9.31 years; the mean age at onset was 26.93 ± 10.08 years; the average number of hospitalizations is 2.71 ± 2.98. The equivalent dose of treatment the patient group was using was 876.19 ± 370.14. The PANSS negative symptoms subscale scores were found to be 12.22 ± 3.19, the PANNS general symptoms subscale was 26.06 ± 9.33, the PANSS negative symptoms subscale scores were found to be 12.10 ± 3.03 in the patient group. There was a statistically significant difference between VLT, TMT A-B, Stroop Test, WMS-V, and the facial emotion recognition test between the patient group and the healthy control group. The Patient group showed worse performance in terms of the neurocognitive and social cognitive tests. There was also a significant relationship between the GAF scale and the Rey Auditory Verbal Learning Test (VLT), the Trail Making Test A (TMT A), Stroop 1 duration, the number of colour errors (Stroop 2), and correct recognition of the sad, surprised, disgusted, and neutral facial expressions in the patient group. Clinical Global Impression – Severity (CGI-s) had a negative correlation with correct recognition of the number of scared and disgusted facial expressions in the patient group. Neurocognitive performance and social performance were found to be related to each other in the patient group. There was no significant difference between the blood oxytocin levels of the healthy control group and the patient group. There was no significant relationship between VLT, TMT A-B, WMS-V, and the Stroop test and the blood oxytocin levels in the patient group. There was no significant relationship between the correct recognition of the number of facial expressions and the blood oxytocin levels in the patient group. There was a positive correlation between the

response times with regard to the happy, sad, and disgusted facial expressions and the blood oxytocin levels in the patient group. In the healthy control group, some neurocognitive tests (TMT-B, WMS-V, and Stroop test) showed a statistically significant improvement with oxytocin. There was a positive correlation with the number of correct recognitions (sad, angry, and fearful facial expressions) and the blood oxytocin levels in the healthy control group. There was a negative correlation between the response times in terms of facial emotion (all facial emotions) and the blood oxytocin levels in healthy control group. While the neurocognitive tests in the patient group were not affected by oxytocin, oxytocin in the healthy group was improved in the neurocognitive tests. While oxytocin increased social cognition in the healthy control group, oxytocin had a negative effect on the oxytocin social cognition in the patient group. There was no significant difference between the blood vasopressin levels of the healthy control group and the patient group. Vasopressin was not correlated with neurocognitive and social cognition tests in the patient group. In the healthy control group, a statistically significant decrease in performance was observed in some social and neurocognitive field tests (Stroop 1, short-time verbal memory, happy, and neutral recognition response times). There was no significant difference between the blood atrial natriuretic peptide levels of the healthy control group and the patient group. There was a significant correlation between long-term memory and TMT-B in the patient group, which worsened the performance. There was a statistically significant correlation between the facial emotion recognition response time (happy and total facial emotion recognition response time) and atrial natriuretic peptide in the healthy group. ANP improved social cognition in the healthy group.

Conclusion

Despite the wide variety of treatment options, the inability to achieve a complete remission goal in schizophrenia treatment, especially the limited presence of antipsychotics on negative findings and cognitive functions, led to the search for other molecules that may be involved in the aetiology of schizophrenia. There are many studies in the literature that particularly agree that oxytocin is related to cognitive functions and is predictive of social cognition [2]. In the healthy control group, some neurocognitive tests showed a statistically significant improvement with oxytocin. In addition, it was found that there was a correlation between social cognitive performance and blood oxytocin levels. However, oxytocin in the patient group reduced social cognition. In the healthy group, social cognition and neurocognition were more closely correlated with oxytocin than in the patient group. This suggests that the role of oxytocin is mediated by factors such as amygdala, prefrontal cortex, and dopaminergic systems and, receptor concentration, and it is conceivable that the level of oxytocin in schizophrenia patients, where this mediator system is impaired, as well as the level of neurophysiological integrity in the regions where oxytocin receptors are concentrated [3]. The ANP level worsened some neurocognitive test performances in the patient group. Previously, this effect of ANP has been shown to suppress anxiety via the HPA (hypothalamus–pituitary–adrenal axis), which may reduce the positive effect of anxiety on learning [4]. A similar mechanism may have been used in our study. There was a positive correlation between ANP and social cognition in the healthy group. This finding supports the view that CRP (corticotropin-releasing factor) neurons in the amygdala are associated with ANP and that ANP may play a neuromodulator role in olfactory/limbic information processing [5]. In our study, the relationship between the levels of oxytocin and atrial natriuretic peptides in terms of social cognition was determined in the healthy control group and our study was the first to investigate the association between atrial natriuretic peptide and cognitive functions. In addition to oxytocin and vasopressin, our study has contributed to the literature in terms of finding that ANP may be related to cognitive function. These new studies will help us to understand the effects of neuropeptides on neurocognition and social cognition and establish a relationship in schizophrenia patients. They will also offer us an alternative perspective to explain behavioural and memory findings in schizophrenia patients, and will also help us develop new treatment strategies in these areas.

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Extrapyramidal and metabolic side effects of haloperidol decanoate: a 12-month follow-up study

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ABSTRACT

Objective: It is believed that first-generation antipsychotics may cause more extrapyramidal side effects and second-generation antipsychotics also may cause more metabolic syndrome, cardiovascular disease, and type-2 diabetes. However, there are still a lot of controversial studies about this subject in the literature. In particular, recent studies have shown that there is no difference in terms of efficacy and drug tolerability between these two drug groups. The aim of our study is to monitor if extrapyramidal side effects and changes of metabolic parameters were developed in a 12-month follow-up study with Haloperidol Decanoate (HD).

Methods: Fifty-four patients who were diagnosed with schizophrenia and hospitalized in Bakırkoy Mental Health and Neurological Diseases Hospital consecutively were included in this naturalistic study. The first examination at the inpatient clinic was named as Assessment 0, and the interview after HD was applied was named as Assessment 1. The next four Assessments (Assessment 2–5) were conducted as weekly follow-up. In the next month, it was organized as twice a week (Assessment 6–7) and next assessments (8–18) once in a month. The following parameters except the clinical efficacy and plasma levels were evaluated:
(1) Assessment of clinical efficacy of haloperidol decanoate and functionality
(2) Plasma levels of haloperidol
(3) Extrapyramidal symptoms and metabolic side effect
(4) The compliance of long-term treatment

Results: Fifty-four patients with schizophrenia consisting of 41 women and 13 men were included in the study. There were no severe side effects like neuroleptic malignant syndrome and acute dystonia during our follow-up study. There were only significant correlations between the beginning high dose of haloperidol and EPS scores in the positive direction. There were no statistically significant differences between measurements in the weight variable, but there was a significant difference in waist circumference. The first measurement of waist circumference was significantly higher from both the mid- and final measurements. Among all of these blood measures, only prolactin levels increased significantly over time with the use of haloperidol. There were no statistically significant differences between values of other metabolic parameters (fasting blood glucose, triglyceride, HDL, iron, Hgb, PRL, and HbA1c). In our study, half of the patients still used haloperidol depot at the end of the year and the remaining half of these patients had the following percentages: 14.8% ($n = 8$) had an atypical antipsychotic, 7.4% ($n = 4$) was treated with mood stabilizer and another antipsychotic, 7.4% ($n = 4$) had another depot antipsychotic, and 20.4% ($n = 11$) had left treatment completely. When the causes of dropout from follow-up study were evaluated, it was learnt that 37.14% of patients had changed their treatment after clinician changing, 37.14% of patients discontinued treatment since lack of social support, and 25.71% of patients left treatment with their own desire or side effects.

Conclusions: This study pointed out that the HD was still an effective and tolerable drug for patients with schizophrenia. It is also important to replicate these results in a hospital where severe patients with non-adherence story are treated. As a result, clinicians must choose the best treatment to meet the needs of their patients, leaving the fears and prejudices about the first-generation antipsychotics.

KEYWORDS
Haloperidol decanoate; extrapyramidal; metabolic; side effects; compliance

Introduction

There are two classes of long-acting antipsychotics recently in use. These two classes of drugs, which are also known as first- and second-generation antipsychotics, are thought to have unique advantages and disadvantages. It is believed that first-generation antipsychotics may cause more extrapyramidal side effects like acute dystonia, akathisia, and tardive dyskinesia, and second-generation antipsychotics also may cause more metabolic syndrome, cardiovascular disease, and type 2 diabetes. However, there are still a lot of confusing studies about this subject in the literature. In particular, recent studies have shown that there is no difference in terms of efficacy and drug tolerability between these two drug groups (1). There are also several studies that have opposite results in terms of cost effectiveness of these two antipsychotic drugs (2). The aim of our study is to monitor if extrapyramidal side effects and changes of metabolic parameters were developed in a 12-

month follow-up study with Haloperidol Decanoate (HD).

Method

Fifty-four patients who were diagnosed with schizophrenia and hospitalized in Bakırkoy Mental Health and Neurological Diseases Hospital consecutively were included in this naturalistic study. First assessment had started with being hospitalized, and the second one at the first day of HD. Then, it would be once a week at the first month, every 15 days at the second month, and then once a month. The first examination at the inpatient clinic was named as Assessment 0, the interview after HD was applied was named as Assessment 1. The next four Assessments (Assessment 2–5) were conducted as weekly follow-up. In the next month, it was organized as twice a week (Assessment 6–7), and next assessments (8–18) once in a month. Among the following parameters, only the extrapyramidal symptoms and the metabolic side effect profile of the following parameters and the change of these side effects with medication dose and the effect on adherence to treatment will be given in this article. Assessment of clinical efficacy of haloperidol decanoate and functionality, plasma levels of haloperidol, and the compliance of long-term treatment will be evaluated in a different study.

1. Assessment of clinical efficacy of haloperidol decanoate and functionality: After the patients were diagnosed as a schizophrenia with Structured Clinical Interview for DSM-IV axis I disorders (SCID-CV), the Brief Psychiatric Rating Scale (BPRS), Scale for the Assessment of Positive Symptoms (SAPS), and Scale for the Assessment of Negative Symptoms (SANS) were used to evaluate clinical efficacy of HD. Global Assessment of Functioning (GAF) was used for the calculation of functionality.
2. Plasma levels of haloperidol: Analyses of plasma level were performed with a mass spectrometer (LC/MS, Agilent 1200 Series) instrument connected to a reverse-phase HPLC system with a C18-type chromatographic column.
3. Extrapyramidal symptoms and metabolic side effects: The Simpson–Angus Scale (SAS) was used to evaluate extrapyramidal side effects at each visit. The measurements of waist circumference and weight were controlled at each visit. Fasting blood glucose, triglyceride, HDL, iron, haemoglobin (Hgb), Prolactin (PRL), and HbA1c were measured at 0, 2, 5, 8, and 12th month.
4. The compliance of long-term treatment: Since this is a natural follow-up study, some of the patients continued to treatment until the 12th month of treatment, but some of them stopped treatment or were removed from the follow-up due to the treatment protocol change. Patients who were still in treatment at other centres were found out by examining the pharmacy information system and hospital records. These patients were evaluated in a group of patients who continued haloperidol treatment in terms of treatment compliance. However, the drug plasma level of the patients who were followed up for only 12 months and came to regular controls were evaluated for parameters of side effect monitoring.

Results

Fifty-four patients with schizophrenia consisting of 41 women and 13 men were included in the study. The mean age of the patients was 42.30 ± 10.22, the mean duration of education was 5.93 ± 3.17 years, the mean duration of disease was 14.15 ± 8.51 years, and the mean number of hospitalization was 6.24 ± 9.78 (Table 1).

There were no severe side effects like neuroleptic malignant syndrome and acute dystonia during our follow-up study and the means of SAS scores were beginning score: 1.33 ± 3.45, mid-score: 1.53 ± 1.76, end-score: 0.73 ± 1.28, and low SAS scores existed during the treatment. There was only significant correlation between the beginning high dose of haloperidol and EPS scores in the positive direction.

The changes in metabolic measurements of patients who completed the study over time were compared. There is only statistically significant difference between the measures of the PRL values during the study period ($p < .007$). According to the results of the bipartite comparison, the first PRL value was significantly lower than third ($Z = -3.411$, $p = .001$), fourth ($Z = -2.831$, $p = .0046$), and fifth ($Z = -2.985$, $p = .003$) values. No statistically significant difference was found between the other measurements of PRL value ($p > .005$). Among all these measures, only prolactin levels increased significantly over time with the use of haloperidol. There was no statistically significant difference between values of other metabolic parameters (Fasting blood glucose, triglyceride, HDL, iron, Hgb, PRL, and HbA1c) (Table 2).

There was also no statistically significant difference between measurements in the weight variable, but

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

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)
Simpson-Angus Baseline Score	0–13	1.40 ± 2.55 (0)
GAF Baseline Score	15–75	33.07 ± 11.35 (35)

Table 2. Comparison of changes in metabolic measurements of patients.

*** *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)	χ^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

there was a significant difference in the waist circumference ($p < .01$). The first measurement of waist circumference was significantly higher ($p < .016$) from both the mid- and final measurements.

In our study, half of the patients still used haloperidol depot at the end of the year and the remaining half of these patients had the following percentages: 14.8% (*n*: 8) had an atypical antipsychotic, 7.4% (*n*: 4) was treated with mood stabilizer and another antipsychotic, and 7.4% (*n*: 4) had another depot antipsychotic; 20.4% (*n*: 11) had left treatment completely. When the causes of dropout from follow-up study were evaluated, it was learnt that 37% of patients had changed their treatment after the changing diagnosis by the clinician or due to antipsychotic side effect, 33.3% of patients discontinued treatment since lack of social support, and 29.6% of patients left treatment with their own desire. While extrapyramidal side effect was the most important factor in terms of non-adherence in the literature (3), only five patients dropped out from study due to the doctor-documented side effects.

Conclusion

In the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study and The Cost Utility of the Latest Antipsychotics in Schizophrenia Study Band 1 (CUtLASS-1) which is a randomized controlled trial (RCT), which compared the first-generation antipsychotic (FGA) with atypical antipsychotics in schizophrenia groups, there were no significant differences in rates of objectively assessed extrapyramidal side effects between the SGA and FGA patients. There are also a lot of studies about extrapyramidal and metabolic side effects in the literature. In a previous study, paliperidone palmitate (PP) and HD were compared and it was shown that PP was not superior in efficacy, and also caused higher level of prolactin and weight gain, and HD had caused higher in akathisia compared to paliperidone (4). In another study, PP and HD were compared and it was shown that PP is more advantageous than HD in terms of efficacy and tolerability of side effects (5). The current meta-analysis consists of fifteen antipsychotics and a mutual comparisons between antipsychotics showed that haloperidol had the least effect over weight gain. In our study, there was no significant weight change in the measurements during a year, and even the measurement of waist circumference decreased over time. The reason for this event may be the use of atypical antipsychotics in past treatments of these patients.

In the literature, it was published that PRL is elevated moderately by olanzapine, intermediately by haloperidol and strongly by risperidone in multicentre, double-blind, randomized clinical trials (6). In contrast, another study where prolactin levels were not significantly affected by the usage of olanzapine and haloperidol, although elevated prolactin levels persisted in most patients were treated with risperidone. Among all these measures, only prolactin levels increased significantly over time with the use of haloperidol in our study. There was no significant statistical change in other metabolic parameters.

In previous studies, it was studied that when the haloperidol dose is increased in the treatment, the extrapyramidal side effects also increase (7). Similar to this study, there was also statistically significant correlation between the beginning high dose of haloperidol and EPS scores in parallel with each other, and no statistically significant relationship was found between the low dose of prolonged treatment and EPS scores. When we evaluated the side effects, patients did not report symptoms such as neuroleptic malignant syndrome or acute dystonia, and SAS scores were at acceptable limits. It is important that only five patients left study due to side effects and half of the patients continued HD treatment for 1-year follow-up.

This study points out that the HD is still an effective and tolerable drug for patients with schizophrenia. It is also important to obtain these results in a hospital where severe patients with non-adherence story are treated. As a result, clinicians must choose the best treatment to meet the needs of their patients, leaving the fears and prejudices about the first-generation antipsychotics.

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