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Mental health action plan 2021-2023: What to say? What to do?

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The agenda of the world and the country is full of events and developments that negatively affect the mental health of individuals, groups, communities, and all organized and unorganized layers of society. War, individual and social violence, environmental disasters, earthquakes and other natural (!) disasters, economic crisis, poverty, job murders and many other events with global effects shape mental health. But is a mental health policy that reads all these processes correctly being implemented? Turkey's official health authority continues to develop the National Mental Health policy text and the National Mental Health Action Plan discourse in the extension of the Health Transformation Program, adding new targets every year.

The World Health Organization defines mental health policy as a set of principles, values and goals designed to promote mental health and reduce the social burden of mental disorders. Since mental health is closely related to human development and quality of life, mental disorders constitute a significant burden of disease worldwide, and the participation of many different sectors is required to implement mental health initiatives, the WHO recommends that countries develop mental health policies, action plans and programs (1). Although the WHO's emphasis on multisectoralization sounds good, the fact that it does not always point to public structures as sectors seems to create a mental framework that allows the private sector to take part in mental health services. The fact that the main objective is to reduce the burden of illness and improve the quality of life gives the impression that it recommends a secondary and tertiary preventive perspective to countries, focusing on reducing the burden of the disease, rather than preventing the occurrence of mental illnesses that impair the quality of life, eliminating stress factors and developing a primary preventive mental health service for stress factors. This naturally means that although it is called Community Mental Health Services, it is understood that it proposes a policy that focuses on the individual, or more precisely on the sick individual.

The official health authority in Turkey has so far acted accordingly. The National Mental Health Action Plan, which was prepared on the basis of the National Mental Health Policy Text of 2006 (3,4), which we have previously discussed in our journal (2), aims to establish a mental health service network that puts the needs of individuals at the center and ensures that services are provided to individuals "adequately through appropriate methods". Updates are made in this direction every two years. The aim is to adopt an individual-oriented approach in mental health services that will support people with mental health problems to continue their lives in a way that minimizes the need for hospitalization or minimizes the duration of hospitalization (1). The motto of the Mental Health Action Plan for the 2021-2023 period is stated as "Implementing an integrated community-based mental health service model in mental health services, monitoring, protecting and improving the mental health of individuals". As a service model, it is envisaged that Community Mental Health Teams consisting of one full-time psychiatrist, two nurses, at least one part-time psychologist and one social worker will be established to provide integrated mental health services including primary health care services, community-based mental health services, social care support services and regional specialized services for individuals with complex needs for a population of approximately 250,000 people. The units where the teams will work in this service process are family physicians,

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healthy life centers, mental health service units attached to hospitals, Community Mental Health Centers, polyclinics and units to be opened within general hospitals.

Although the name of the community mental health centers, which today number nearly 200 across the country, evokes a service for the community, it will be seen that they have a function and quality that follows the treatment, follow-up and rehabilitation needs of people with chronic mental disorders such as schizophrenia, schizo-affective disorder, other psychotic disorders, bipolar disorder, and serves as a neighborhood polyclinic of the inpatient unit to which they are attached. It does not have the purpose, plan and function of providing services to the "sector" in the real sense, that is, to a region and population-based services, to improve the mental health of people who do not have mental health problems, to immunize them, to prevent the occurrence of mental disorders, to enable early diagnosis and treatment if the disease occurs, to protect and strengthen mental health by interacting with the community in the community. Awareness activities do not go beyond conferences and brochures. The Community Mental Health Teams envisaged to be established do not have a defined purpose in this direction.

It is understood that these mental health policies, which have been transformed into action plans, do not have a communitarian perspective, and that the multi-sectoral approach refers only to the work to be carried out with certain public and private institutions. Apart from the Ministry of Health and the Ministry of Family and Social Policies, the other public institutions planned to cooperate with are the Ministry of Interior, the Ministry of Justice and the Presidency of Religious Affairs, suggesting that the agenda is related to more political preferences beyond health protection and promotion. The Psychiatric Association of Turkey, Turkish Medical Association other physicians' organizations, health sector unions, mental health field associations, mental health workers' associations, patient associations, etc. are not among the organizations planned to cooperate with. As non-governmental organizations, it is seen that there is a tendency to assign a task to some foundations, congregations and sects in parallel with the tendency towards conservatism in health. The fact that the Mental Health Law could not come from the commissions to the parliamentary agenda and could not be enacted is also an important reality that needs to be thought about...

The goals and objectives set out in the 2011 Mental Health Action Plan have not been fully achieved. The number and quality of health manpower is still insufficient and unbalanced. The planned Community Mental Health Teams have not yet been established. The existing Community Mental Health Center teams are still far from a healing-oriented approach that focuses on the patient, not the disease (5). The main goal and demand should be to create a discussion ground where the process will be critically discussed with the active participation of the official health authority, all institutions and health organizations that have a voice and function in this field, and patient associations, and to take action in line with the feedback obtained in this discussion (5).

Psychiatry, psychiatric journals that contribute to the production of scientific knowledge in the field, and the Psychiatric Association of Turkey in particular, are expected to always keep the National Mental Health Policy and the mental health action plans updated according to the needs of the political power on their agenda, to carry out effective studies with a critical perspective, and to bear the responsibility of being the main actor in the development and implementation of policies. Then add and discuss the following questions. What should be done?

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A comparison for thyroid functions and clinical features in deficit and non-deficit schizophrenia

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SUMMARY

Objective: The primary occurrence and persistence of negative symptoms observed in patients with schizophrenia is deficit syndrome. Although the association between thyroid hormones and schizophrenia symptoms has been reported, no studies have investigated thyroid function in patients with deficit schizophrenia (DS). This study aims to investigate the clinical features and thyroid function in DS patients by comparing them with patients with non-deficit schizophrenia (NDS) and a control group.

Method: 33 subjects from DS, 35 subjects from NDS and 35 healthy control subjects were included in the study. Patients with schizophrenia were classified into DS and NDS using the deficit syndrome table. Thyroid function was assessed by the levels of TSH, free T3 (fT3), and free T4 (fT4). Sociodemographic data and clinical characteristics were evaluated using the Sociodemographic Data Form, the Positive Symptoms Evaluation Scale (SAPS), the Negative Symptoms Evaluation Scale (SANS), and the Calgary Depression in Schizophrenia Scale (CDSS).

Results: There was no significant difference between DS and NDS groups in terms of age, gender, marital status and education ($p>0.05$). The percentage of unemployed was significantly higher in the DS group than in the NDS group ($p=0.005$). There were 14 (42.4%) suicide attempts in the DS group and 11 (31.4%) in the NDS group, and there was no significant difference between the groups ($p>0.05$). There was no significant difference between the groups when comparing the thyroid functions of the DS, NDS and healthy control groups regarding fT4, fT3 and TSH ($p>0.05$). There was no significant correlation between TSH, free T3, free T4 and total SANS, total SAPS and CDSS scores ($p>0.05$).

Discussion: According to our study thyroid function is not different in DS, NDS and healthy controls and is not associated with positive, negative and depressive symptoms in patients with schizophrenia.

Key Words: Schizophrenia, deficit syndrome, thyroid hormones, signs and symptoms

INTRODUCTION

Negative symptoms consist of emotional limitation, alogy, anhedonia, social decline and avolition (1). Nevertheless, negative symptoms are associated with significant functional disability, decreased quality of life, and increased care needs (2,3). These negative symptoms may be temporary or permanent. According to the source, they are classified as primary if they are related to schizophrenia, and secondary if they are due to another reason such as drug side effects, psychotic symptoms, depressive comorbidity, lack of stimuli (4). The presentation of primary and persistent negative symptoms in schizophrenia is called the schizophrenia deficit syndrome (5). This group of patients with deficit schizophrenia (DS) is thought to constitute one-third of patients with schizophrenia (6). Studies comparing the differences between the deficit schizophrenia group (DS) and the non-deficit schizophrenia group (NDS) contributed to the hypothesis that DS may be a distinct disorder (7,8). However, despite this evidence for deficit schizophrenia, it was not included as a subtype or a

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distinct psychotic disorder in the Fifth Diagnostic and Statistical Manual of Mental Disorders (9).

Although there is a neurohormonal effect in mental illnesses, it is difficult to confirm this role, especially in chronic diseases such as schizophrenia, since it is difficult to conduct hormonal studies that exclude the effect of drug use, the number of psychotic exacerbations, and the duration of the illness. In studies conducted patients with schizophrenia, abnormalities in the thyroid system such as decreased activity of the hypothalamo-pituitary-thyroid axis, increase in thyroid autoantibodies and decrease in T3 levels have been shown. (10). It has been shown that fT3 and fT4 levels are low and TSH is high in the chronic phase of schizophrenia (11). Although abnormalities in the thyroid system have been reported, there are not enough studies investigating abnormalities in the thyroid system in DS patients.

Less is known about the role of thyroid hormones in the pathophysiology of schizophrenia compared with the aforementioned endocrine disorders. It has been reported that clinically significant hyperthyroidism may occur in individuals with psychotic symptoms, and hypothyroidism may cause mood problems that resemble the negative symptoms of schizophrenia (12-14). Despite the association between thyroid hormones and symptoms has been reported, no studies investigate thyroid function in DS patients.

This study aims to investigate the clinical features and thyroid function in DS patients and compare them with NDS patients and healthy controls.

METHOD

Sample and study design

In this study, the patients in the patient group were selected from patients diagnosed with schizophrenia who presented to Aydin State Hospital Community Mental Health Center (CMHC) between December 2022 and April 2022. Patients with schizophrenia were categorized as DS and NDS using the Schedule for the Deficit Syndrome by the same psychiatrist. Two diagnostic methods are used for DS. 'Proxy for Deficit Syndrome' created using the Brief Psychiatric Rating Scale and the Positive and Negative Syndrome Scale and the 'Schedule for the Deficit Syndrome' (SDS) (15,16). The SDS was preferred in this study because it has inter-rater reliability, a high degree of stability with good test-retest reliability and it is the gold standard for the diagnosis of DS (17). The study included 33 individuals from DS, 35 from NDS, and 35 of similar age and gender as a healthy control group. Inclusion criteria for the patient groups were that they were between 18 and 65 years of age, had been in clinical remission for at least 3 months, had been taking a stable dose of antipsychotics for at least 12 months, and were clinically compatible with the scales to be used. Exclusion criteria for the patient and the healthy control groups were an additional diagnosis of a psychiatric disorder, chronic inflammatory disease, cancer or autoimmune disease that might affect thyroid function, mental retardation or cognitive impairment, and alcohol or drug use disorders.

Thyroid function data for the patient groups were obtained from routine CMHC applications. Sociodemographic data and scales were collected from patients when routine examinations were requested. Thyroid function data for the healthy control group were obtained from the examination results of individuals registered for screening at the internal medicine outpatient clinic of Aydin Adnan Menders University Faculty of Medicine Hospital. This study was conducted under the 1964 Declaration of Helsinki and its subsequent amendments. Ethical approval for the study was obtained from the Clinical Research Ethics Committee of the Aydin Adnan Menders University (Project number: E.278543).

Data Collection Tools

Sociodemographic Data Form: A questionnaire prepared by the authors was used to obtain information on patients' sociodemographic data, medications taken, duration and course of the disease.

Schedule for the Deficit Syndrome: It is a chart developed to detect deficiency syndrome. In the

first part, negative symptoms, consisting of limited affect, decreased emotional range, poor speech, lack of interest, a decreased sense of purpose, and decreased social drive, are scored between 0-4. For deficit syndrome, at least two symptoms must score 2 or higher. The second part assesses whether the negative symptoms from the first part have persisted within the past year. The third part assesses whether or not the negative symptoms are primary. The Turkish validity and reliability study was conducted by Çıtak et al. (18).

Positive Symptoms Evaluation Scale (SAPS): The scale consists of 34 items and 4 subscales: Hallucinations, Delusions, Strange Behavior, and Formal Thought Disorders. The severity of each item varies between 0-5. The Turkish validity and reliability study was conducted by Erkoç et al. (19).

Negative Symptoms Evaluation Scale (SANS): The scale consists of 25 items and 5 subscales: emotional blunted, alogia, decreased energy and desire, lack of pleasure, and social withdrawal and attention. The severity of each item varies between 0-5. Erkoç et al. investigated its Turkish validity and reliability (20).

Calgary Depression Scale in Schizophrenia (CDSS): It is a scale that assesses depressive symptoms in patients with schizophrenia independently of negative, positive symptoms and extrapyramidal side effects. It consists of 9 items, and the severity of each item varies between 0-3. Aydemir et al. (21) conducted Turkish validity and reliability studies. The cutoff score was reported as 11/12. In this study, it was taken as 11.

Statistical Analysis

The values of Skewness and kurtosis were checked for the normality test. Normal distribution was assumed if the values of kurtosis and Skewness were between -1.5 and +1.5. The t-test was used to compare the numerical values in the two groups, and the one-way ANOVA test was used to compare the numerical values in the three groups. The chi-square test was used to compare categorical data. Pearson correlation analysis was used for correlation analysis.

RESULTS

The DS group included 25 (75.8%) men and 8 (24.2%) women. The NDS group consisted of 23 (65.7%) men and 12 (34.3%) women, and the healthy control group consisted of 22 (62%, 9) men and 13 (37.1%) women. The mean age was 51.88±11.29 years in the DS group, 46.61±11.53 years in the NDS group, and 46.23±13.18 years in the healthy control group. There was no significant difference between the groups regarding gender and age (p=46.23±13.18 and p=0.104, respectively). 100% of the DS group were unemployed, 77.1% of the NDS group were not employed, and the percentage of unemployed was significantly higher in the DS group (p=0.005). The duration of illness was 25.73±12.57 years in the DS group and 20.14±10.42 years in the NDS group. The number of psychotic exacerbations was 5.42±3.51 in the DS group and 3.88±2.28 in the NDS group, with no significant difference between groups (p=0.05 and p=0.067, respectively). There were 14 (42.4%) suicide attempts in the DS group and 11 (31.4%) in the NDS group, and there was no significant difference between the groups. (p=0.347). (Table 1.)

When comparing the mean scale scores of the patients with schizopfrenia group's DS and NDS, the total and subscale scores of SANS (Assessment of Negative Symptoms) in the areas of emotional blunting, alogia, apathy, anhedonia, attention deficit at the significance level $p < 0.001$, the SAPS (Assessment of Positive Symptoms) subscale disorganized behavior blunted at the significance level p=0.018, and the CDSS blunted at the significance level p=0.017 was higher in the DS group. (Table 2.)

When comparing the thyroid functions of DS, NDS and the healthy control groups in terms of free T4 (fT4), free T3 (fT3) and TSH, there was no significant difference between the groups (p=0.093, p=0.398, p=0.647, respectively). (Table 3.)

There was no significant correlation between TSH, fT3, fT4 and total score SANS, total SAPS and CDSS score. There was a positive (r=0.284, p=0.019) significant correlation between SAPS total score and the SANS total score. There was a

Table 1. General characteristics of the participants

	Deficit	Non-deficit	Healthy control	P
Variable				
Age, mean–SD	51.88–11.29	46.61–11.53	46.23–13.18	0.104
Education (year), Mean–SD	7.58–3.77	9.14–3.95		0.1
Gender, Number (%)				
Men	25 (75.8)	23 (65.7)	22 (62,9)	0.491
Women	8 (24.2)	12 (34.3)	13 (37,1)	
Marital status, Number (%)				
Married	12 (36.4)	8 (22.9)		0.446
Single	15 (45.5)	18 (51.4)		
Divorced	6 (18.2)	9 (25.7)		
Working status, Number (%)				
Employed	0 (0)	8 (22.9)		0.005
Unemployed	33 (100)	27 (77.1)		
Durations of illness (year), Mean–SD	25.73–12.57	20.14–10.42		0.05
Psychotic exacerbations, Mean–SD	5.42–3.51	3.88–2.28		0.067
Suicide attempts, Number (%)				
Having attempted suicide	14 (42.4)	11 (31.4)		0.347
No suicide attempt	19 (57.6)	24 (68.6)		
Typical AP using, Number (%)				
Using	10 (30.3)	6 (17.1)		0.201
Not using	23 (69.7)	29 (82.9)		
Atypical AP using, Number (%)				
Using	28 (84.8)	33 (94.3)		0.252
Not using	5 (15.2)	2 (5.7)		
MD using, Number (%)				
Using	5 (15.2)	9 (25.7)		0.282
Not using	28 (84.8)	26 (74.3)		
AD using, Number (%)				
Using	11 (33.3)	16 (45.7)		0.297
Not using	22 (66.7)	19 (54.3)		
Smoking, Number (%)				
Smoker	18 (54.5)	24 (68.6)		0.234
Non smoker	15 (45.5)	11 (31.4)		

SD: Standard deviation, AP: Antipsychotic, MD: Mood stabilizer, AD: Antidepressant

positive correlation between the CDSS score ($r=0.498$ $p < 0.001$) and a positive correlation between the SANS total score and the CDSS score ($r=0.267$, $p=0.028$). (Table 4.)

DISCUSSION

This study assessed thyroid function in DS and NDS patients. There was no difference between the two groups and the healthy control group regarding TSH, fT3, and fT4. Moreover, it was found that these levels were not associated with negative, positive and depressive symptoms.

Although there are studies investigating thyroid functions in patients with schizophrenia, there are no studies investigating DS patients. In our study, thyroid function was assessed as TSH, fT3, and fT4 between the group's DS, NDS and the control group, and no significant difference was found between the groups. In a study conducted in our country, no significant difference was found in peripheral thyroid hormone levels (fT3, fT4) in schizophrenia with positive symptoms and schizophrenia with negative symptoms under the criteria reported by Andreasen and Olson (22,23). While positive and negative schizophrenia criteria were used in this study, we used SDS in our study. SDS is the gold standard for diagnosis of DS. For DS/NDS classification with SDS, it is recommended that patients be in periods of clinical stability (17). The patients in our study were also in clinical remission. Although other methods are used in terms of group (their groups: positive and negative schizophrenia, our groups: DS and NDS) formation, the results of our study are consistent with this study conducted in our country. However, the fact that our sample size was larger than this study and in our study there was no significant difference between the groups in terms of age, gender, type of drug used, number of psychotic exacerbations, and duration of illness makes our study stand out. The results of studies comparing patients with schizophrenia with the control group are inconsistent. Some studies found no difference in TSH (24,25), no difference in TSH and fT4 (26), no difference in TSH and fT3 (11) no difference in TSH

Table 2. Comparison of scale scores between groups

	Deficit Mean–SD	Non-deficit Mean–SD	P
Variable			
SAPS- hallucinations	3.00–4.76	1.86–3.45	0.260
SAPS-delusions	9.30–6.70	7.00–5.61	0.265
SAPS- disorganized behavior	4.97–2.05	3.69–2.28	0.018
SAPS- formal thought disorders	2.24–2.68	1.97–3.12	0.703
SAPS-total score	19.52–12.05	14.51–10.90	0.077
SANS-emotional blunting	11.27–4.27	2.63–2.22	<0.001
SANS-alogia	6.24–2.79	1.25–1.59	<0.001
SANS-apathy	9.12–1.85	5.49–1.36	<0.001
SANS-anhedonia	13.70–3.37	8.97–3.19	<0.001
SANS-attention deficit	6.64–1.59	5.03–1.54	<0.001
SANS-total score	46.97–10.28	23.37–4.99	<0.001
CDSS total score	3.73–2.15	2.49–2.01	0.017
	n (%)	n (%)	
Depression (CDSS cut off for 11)	0 (0)	0 (0)	

SAPS: Positive symptoms evaluation scale, SANS: Negative symptoms evaluation scale
CDSS: Calgary depression scale in schizophrenia

and fT3, high fT4 in schizophrenia (27), and high fT4 in schizophrenia (28). One of these studies was conducted in patients with psychotic exacerbations (27), one in patients who did not have a psychotic exacerbation for one year (11) and the other in patients who had a first episode (26). Other studies did not specify whether patients were in a psychotic exacerbation. Our study consisted of patients without psychotic exacerbation for at least 3 months. Obtaining different results in the studies may have depended on whether the patients were in a psychotic exacerbation period or not. Moreover these differences could be due to the ratio of men and women in the samples, use of psychotropic drugs, history of seizures and obesity (29).

In our study, TSH, fT3, and fT4 levels were not associated with negative, positive, or depressive symptoms. A previous study found no association between TSH level and positive symptoms, however, a negative association was found between negative symptoms (30). In contrast to this study, another study found a positive correlation between TSH levels and negative symptoms (28). This variability in the results, including our study, could be due to the different duration of the disease and the degree of remission of disease symptoms in the patient groups.

The results of our study show that DS patients are not employed at all, whereas the employment rate in the NDS group is very low. This finding indicates that employment and occupational functioning are more impaired when primary deficiency symptoms occur and persist and develop into a deficit syndrome, consistent with previous studies (31,32). As emphasized in previous studies, this can lead to withdrawal from social life, inability to achieve professionally, lower self-esteem, and increased psychopathological symptoms (33).

In our study, no significant difference was found between DS and NDS in suicide attempts, but there was a significant rate of suicide attempts in both groups. Previous studies found that DS was associated with a low risk of suicide, and suicide attempts were more common in NDS (34,35). Delusions are associated with more suicidality in patients with schizophrenia (36). The fact that our patients continue to attend CMHC regularly and receive regular treatment so that positive symptoms subside may explain the lack of difference in suicide rates between the DS and NDS groups in our study. Nonetheless, the presence of high suicide rates in both groups requires the continuation of regular

Table 3. Thyroid hormone levels of the groups

	fT3 (ng/L)	fT4 (ng/dL)	TSH (mIU/L
Normal range	2.3-4.2	0.89-1.76	0.35-5.5
Deficit	3.46–0.56	1.17–0.17	1.67–0.99
Nondeficit	3.43–0.6	1.27–0.37	1.87–1.32
Healthy control	3.17–0.67	1.20–0.33	1.95–1.08
P	0.093	0.398	0.647
	Abnormal fT3, n (%)	Abnormal fT4, n (%)	Abnormal TSH, n (%)
Deficit	3 (9,1)	1 (3)	1 (3)
Nondeficit	3 (8,6)	1 (2.9)	3 (8.6)
Scizophrenia	6 (8,8)	2 (2.9)	4 (5.9)
Healthy control	0 (0)	0 (0)	0 (0)

fT3: free T3, fT4: free T4, TSH: Thyroid stimulating hormone

Table 4. Relationship between thyroid hormone levels and symptoms

		TSH	fT3	fT4	SANS total score	CDSS
fT3	r	-0.033				
	P	0.743				
fT4	r	-0.028	-0.081			
	P	0.776	0.416			
SANS total score	r	-0.092	-0.023	-0.222		
	P	0.455	0.852	0.069		
CDSS	r	-0.095	0.016	0.027	0.267*	
	p	0.439	0.899	0.825	0.028	
SAPS total score	r	-0.063	-0.144	0.048	0.284*	0.498**
	P	0.608	0.242	0.695	0.019	<0,001

fT3: free T3, fT4: free T4, TSH: Thyroid stimulating hormone, SAPS: Positive symptoms evaluation scale, SANS: Negative symptoms evaluation scale CDSS: Calgary depression scale in schizophrenia, *Correlation is significant at the 0.01 level (2-tailed), ** Correlation is significant at the 0.01 level (2-tailed).

treatment.

The limitations of our study can be accepted since it was a single-center study, cross-sectional, there was no long-term follow-up, and psychotropic treatment was continued. In addition, patients diagnosed with mental retardation were not included in the study. Since the participants were followed-up patients from the clinic, additional IQ tests were not applied to the patients.

Consequently, there was no difference in thyroid functions of DS patients compared with NDS and healthy controls. There was no association between positive, negative and depressive symptoms and TSH, fT3, fT4. In future studies, it may be useful to conduct longitudinal studies with larger samples that also consider variables such as psychotic exacerbation period, remission period, and disease duration.

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The level of knowledge about autism spectrum disorders among a university hospital healthcare professionals in Turkey

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SUMMARY

Objective: Autism Spectrum Disorder (ASD) is a mental disorder with an increasing prevalence in recent years. In this study, the autism knowledge level of healthcare professionals from different occupational groups and the factors affecting the knowledge level were evaluated.

Method: A total of three hundred and seventeen (317) healthcare professionals working in tertiary health institutions in Turkey were included in the study. Participants completed both the "Health Workers Information Form" and the "Knowledge about Childhood Autism Among Health Workers" (KCAHW) questionnaire. Knowledge about childhood autism (KCA) as measured by scores in the KCAHW questionnaire.

Results: The total mean score of participated healthcare professionals on KCAHW questionnaire was 12.62 ± 2.80. Physicians' KCAHW test scores were significantly higher than other healthcare professionals ($p<0.001$). KCA was significantly associated with the age of healthcare professionals, had a higher mean score with increasing age ($r=0.139$, $p=0.013$). As the education level of the healthcare professionals and the time spent in the profession increased, the KCA also increased (respectively, $p=0.002$, $p=0.043$). KCA of doctors who were residency students were statistically significantly lower than those of specialist doctors ($p=0.008$). KCA was found to be significantly higher in healthcare professionals who had training on autism ($p=0.001$) and those who worked with a child with autism ($p=0.009$).

Discussion: In this study, it was found that healthcare professionals' knowledge about ASD is poor. Although physicians were more aware of the diagnostic criteria, their awareness of autism and its associated disorders was low, as were other healthcare professionals. Healthcare professionals should receive regular training. Specially, it should be targeted from physicians to residents and non-physician healthcare professionals.

Key Words: Autism , Autism knowledge level, Physicians, Nurses, Physical therapists

INTRODUCTION

Autism Spectrum Disorder (ASD) is a serious mental disorder with an increasing prevalence in recent years. The Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) defines ASD as the emergence of permanent impairment in social communication and interaction, the presence of restricted interests, and repetitive behavior patterns (1). According to data from the United States Centers for Disease Control and Prevention, the prevalence of autism was reported to be 1 in 150 children at the beginning of the millennium, while it was reported to be 1 in 36 children in 2020. Although the increase in prevalence is mostly explained by the change in the definition of ASD and the increase in awareness and ease of access to health services, some of the reasons still cannot be explained (2).

With the increase in prevalence, a rapidly growing field of research has emerged on the life experiences of individuals with ASD. It is observed that one of these areas is the health problems that indi-

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viduals diagnosed with ASD may encounter and the quality of the health service received. It has been reported that individuals with ASD have a higher probability of having mental disorders than the general population (3,4). In addition, it is stated that they also have a higher rate of physical health problems compared to the general population (5). For example, autistic adults are reported to be more likely to be diagnosed with epilepsy, cardiovascular disease, and diabetes compared to non-autistic adults (3). In a study conducted in Sweden, it was reported that for all categories of diseases except infectious diseases, autistic individuals were at a higher risk of death compared to the general population (6).

Considering these findings, it can be predicted that the need for access to health services individuals will be higher in individuals with ASD than in the general population. The studies conducted on this issue have reported that individuals with ASD admit to emergency services and outpatient services more frequently than the general population (7,8). Besides, another study reported that individuals with ASD reported lower satisfaction with the health service they received and had higher unmet healthcare needs than those without ASD (9).

In a recent review, it has been reported that healthcare workers have a moderate level of knowledge about ASD and they lacked education about ASD. It has been stated that one of the impediments to the access of individuals with ASD to health care is caused by the inadequate expertise and self-efficacy of health workers in interacting with autistic individuals (10). To better provide the medical treatments needed by those with ASD, it is important to comprehend the diversity of symptoms connected to the autism and the comorbid medical disorders. The multidimensional assessment required by the autistic individuals can be made easier by enhancing the health workers knowledge and experience of ASD. Communication deficiencies and sensory sensitivities, which are the main symptoms of ASD can also complicate medical diagnosis and management. So, healthcare workers may have difficulties in providing health services to autistic individuals (11). In order to provide care at high standards, regarding the needs of individuals with ASD, it is necessary for health professionals to have sufficient knowledge about the basic features of ASD and how the symptoms occur (12). In the literature, it is seen that knowledge and awareness are variable among health workers in different occupations and cultures for ASD (10).

In our study, we aimed to evaluate the knowledge level of ASD in healthcare workers from different occupational groups and the factors affecting the level of knowledge. Our study's hypothesis is that healthcare workers with low educational levels and limited expertise in ASD will have poor knowledge about ASD.

METHOD

This study was carried out in Afyonkarahisar Health Sciences University Hospital between April 2022 and May 2022. We formed the sample of our study from a hospital that provides tertiary healthcare services to which individuals with ASD frequently admit with various health problems. The participants were professionals such as physicians, nurses and physiotherapists. Children and adolescent mental health specialists and adult psychiatrists, who have a primary role in diagnosing ASD and following up individuals with ASD, were excluded in the study. The sample size was not calculated in the study because it was tried to reach the entire universe. Ethical approval for the study was obtained from the Afyonkarahisar Health Sciences University Ethics Committee on 01.04.2022 (2022/182).

In our study, the "Knowledge about childhood autism among health workers" (KCAHW) in collecting the data that will be used to evaluate the ASD knowledge and awareness level of health workers and the "Health Workers Information Form" in which we questioned the sociodemographic data and the experiences of the health workers on ASD. The total number of the distributed questionnaires is 350. Of these, 317 were evaluated with a response rate of 90.5%.

The KCAHW used in our study was developed by Bakare et al. (13). It measures the knowledge level about autism with 19 items in four areas. The first

domain, which consists of eight items, is focused on the social interaction deficit seen in autistic children. The second domain only has one item, the communication and language development symptom. The third domain, which has four items, describes the repetitive, stereotyped, and compulsive behaviors seen in autism. The fourth domain consists of six items and questions whether or not autism is a neurodevelopmental disorder, examines possible comorbid conditions, and explores the ages at which it emerges.

The possible total score that can be obtained from the questionnaire is between 0 and 19. Each item is answered as "yes", "no" or "don't know". Correct answers are calculated as 1 point and other answers as 0 points. The Turkish validity and reliability of the scale were performed by Özgür et al. in 2019 and it was reported that it was reliable in terms of test-retest and internal consistency, and its construct validity was satisfactory according to confirmatory factor analysis (comparative fit index= 0.79) (14).

Statistical analysis

A statistical program (SPPS for Windows, v21.) was used for data analysis. The normal distribution of the data was evaluated with the Kolmogrov-Smirnov test, histogram, and Skewness-Kurtosis coefficients. Nominal and ordinal variables were compared with the Pearson chi-square test. These data are given with numbers and percentages. KCAHW scores measuring the knowledge level of autism and the relationships between different parameters were analyzed using the Spearman correlation test, Student's t-test, and ANOVA test where appropriate. The independent effects of different predictors on KCAHW were examined by using a multivariate linear regression model. The model of fit was examined using the required residual and fit statistics. A value of $p<0.05$ was accepted as statistically significant.

RESULTS

Sociodemographic information

As the targeted participants, 90.5% agreed to participate in the study by completing the questionnaires, of whom 61.5% (n=195) were women. The mean age of the participants was 29.4±6.1 years. The youngest participant was 18 years old and the oldest was 51 years old. Of the participants, 35.3%

Table 1. Comparison of the sociodemographic features and KCAHW score of the participants

Sociodemographic characteristics (n=317)	n (%)	KCAHW total score	
		Mean – SD	p
Age groups (years)*			
18-25	87 (27.5)	11.90 – 2.91	
26-35	180 (56.7)	12.69 – 2.76	0.008
36 ≥	50 (15.8)	13.42 – 2.85	
Gender **			
Male	122 (38.5)	12.05 – 3.06	
Female	195 (61.5)	12.92 – 2.66	0.008
Education level **			
High-school/Undergraduate	89 (28.1)	11.85 – 2.74	
Graduate /Postgraduate	228 (71.9)	12.87 – 2.84	0.004
Occupation **			
Physician	112 (35.3)	13.54 – 2.35	
Other healthcare workers (Nurse, Physiotherapist)	205 (64.7)	12.06 – 2.90	0.000
Work experience*			
0-1 year	69 (21.8)	12.51 – 3.00	
1-5 years	119 (37.5)	12.09 – 2.71	
5-10 years	66 (20.8)	13.27 – 2.76	0.043
>10 years	63 (19.9)	12.88 – 2.90	
Worked experience with ASD**			
Yes	153 (48.3)	13.01 – 2.55	
No	164 (51.7)	12.19 – 3.06	0.009
Got training on ASD**			
Yes	158 (49.8)	13.12 – 2.63	
No	159 (50.2)	12.05 – 2.97	0.001
Having children with ASD **			
Yes	41 (12.9)	13.22 – 2.58	
No	276 (87.1)	12.49 – 2.88	0.127

KCAHW: Knowledge about childhood autism among health workers questionnaire. Significicant differences were shown in bold in the tables.
*ANOVA test, **t test.

Table 2: Percentage of correct answers to the information survey about childhood autism among health workers (n=317).

	Physician (n=112)	Nurse (n=168)	Physiotherapist (n=37)
	% (n)	% (n)	% (n)
Domain 1- Reciprocal social interactions			
Apparent deterioration in some non -verbal actions such as eye -to-eye contact, facial expressions, body posture and hand -arm movement during social interaction?	94.6 (106)	92.9 (156)	86.5 (32)
Inability to develop a friendship appropriate for the age of development?	97.3 (109)	85.7 (144)	94.6 (35)
Absence of willingness to share spontaneous liking, interest or activities?	85.7 (96)	77.4 (130)	86.5 (32)
Lack of social and emotional reciprocity?	84.8 (95)	85.7 (144)	81.1 (30)
Staring into space for long time and not being able to concentrate on a certain thing?	84.8 (95)	81.5 (137)	91.9 (34)
The child may appear as deaf or mute?	74.1 (83)	62.5 (105)	78.4 (29)
Loss of interest in around and people?	93.8 (105)	82.1 (138)	86.5 (32)
Social smile is usually not found in a child with autism?	53.6 (60)	44.4 (74)	70.3 (26)
Domain 2- Impairment in communication			
Delay in speech or not development or speech?	78.6 (88)	75.6 (127)	73.0 (27)
Domain 3- Restricted repetitive interests and behaviours			
Stereotyped and repetitive movement (such as flapping wings or flexing hand or fingers)?	76.8 (86)	79.8 (134)	81.1 (30)
Could be related with abnormal eating habits?	39.3 (44)	36.3 (61)	37.8 (14)
Being preoccupied with parts of objects?	81.3 (91)	74.4 (130)	75.7 (28)
Interest in regular routine activities?	46.4 (52)	45.2 (76)	45.9 (17)
Domain 4- Common associations			
Autism is childhood schizophrenia?	76.8 (86)	57.7 (97)	43.2 (16)
Autism is an autoimmune condition?	67.9 (76)	35.7 (60)	40.5 (15)
Autism is a neurodevelopmental disorder?	70.5 (79)	80.4 (135)	67.6 (25)
Mental retardation may be co-diagnosed in autism?	50.9 (57)	36.3 (61)	54.1 (20)
Autism may be co-diagnosed with epilepsy?	48.2 (54)	21.4 (36)	29.7 (11)
Autism usually starts in this era: Newborn/ Infancy/ Childhood	49.1 (55)	42.9 (72)	40.5 (15)

were doctors and 64.7% were other health workers (nurses and physiotherapists). When their professional experience was evaluated, there were 63 (19.9%) people with 10 or more years of experience, while 69 (21.8%) had less than 1 year of experience. The demographic characteristics of the participants are shown in Table 1.

Autism knowledge level

The ASD knowledge level of the participants was evaluated with KCAHW. The mean KCAHW score of all participants was 12.62/19 (SD=2.807). The knowledge level was related to the deterioration in social interaction and communication at the highest level (77.7%) (percentage of correct answers by participants in areas 1 and 2). The lowest level of information was the correct answer rate (50.8%) in field 4, which questioned ASD-related comorbidities. Only 31.8% (n=101) of the participants were aware that ASD could be associated with epilepsy, and 43.5% (n=138) knew that autism could be associated with mental retardation. It was also determined that the knowledge about limited interest and repetitive behaviors, which were symptoms of ASD, were also low (59.7%) (area 3 correct answer percentage). Of the participants, 37.5% (n=119) were aware that ASD could cause atypical eating habits, and 45.7% (n=145) were aware that ASD may have an interest in routine daily activities. The percentage of correct answers to the questions evaluating the knowledge and awareness level about ASD of the participants is given in Table 2 according to the occupational groups.

Table 3. KCAHW total scores by doctors' specialties

Specialties of doctors (n=112)	KCAHW total score	
	Mean – SD	Min-Max
Urology (12)	14.8 – 2.1	9-18
Obstetrics (12)	12.5 – 2.0	9-16
Brain surgery specialist (4)	13.0 – 5.3	7-18
Otolaryngologist (3)	12.3 – 2.0	10-14
Cardiovascular surgeon (1)	10.0	10
General surgery (10)	13.5 – 2.0	10-17
Orthopedic specialist (1)	15.0	15
Plastic surgery (3)	14.0– 1.7	12-15
Anesthesia (17)	12.8 – 2.4	8-16
Emergency specialist (4)	13.2 – 2.2	10-15
Internal medicine specialist (8)	13.8 –2.8	10-17
Family physician specialist (5)	15.0 – 1.2	14-17
Physical therapy and rehabilitation specialist (16)	13.9 – 2.1	10-18
Infectious disease specialist (2)	12.5 – 2.1	11-14
Pathology specialist (4)	15.5 – 1.7	14-18
Neurology specialist (5)	14.8 – 2.4	11-18
Pediatrics (5)	14.0 – 1.5	12-16

S.D.: Standard deviation; KCAHW: Knowledge about childhood autism among health workers questionnaire.

Physicians' KCAHW test scores were statistically significantly higher than other healthcare professionals (df=2, F=11.3, p<0.001) (Table 1). When the doctors' knowledge level of autism according to their residencies was compared with the univariate ANOVA analysis, no significant difference was found in the ASD knowledge level between the residencies (df=16, F=0.972, p= 0.493). KCAHW's total scores of doctors according to their residencies are given in Table 3. Doctors were divided into two groups as residency students and specialists,

Table 4. Comparison of KCAHW total scores of assistant and specialist physicians

	KCAHW total score	
Physician (n=112)	Mean – SD	p*
Assistant doctor (88)	13.2 – 2.2	
Specialist doctor (24)	14.6 – 2.3	0.008

S.D.: Standard deviation; KCAHW: Knowledge about childhood autism among health workers questionnaire. *t test.

and KCAHW scores were compared. KCAHW total scores of doctors who were residency students were statistically significantly lower than those of specialist doctors (p=0.008) (Table 4). The comparison of variables such as gender and education level according to the occupations of the participants is given in Table 5. The education level of doctors was higher than that of other health workers and there was more ASD-oriented education in their education (Table 5).

When the effect of the sociodemographic characteristics of the participants on the knowledge level of ASD was evaluated, it was determined that female health workers had a higher ASD knowledge level than men (p=0.008) and that there was a positive and significant correlation between age and ASD knowledge level (r=0.139, p=0.013). It was found that the level of knowledge about ASD was higher in healthcare professionals who had a higher education level and received training on ASD. The KCAHW scores of the participants according to the groups and variables are given in Table 1.

Multiple linear regression analyses (with the enter method) were used to evaluate the predictors of the participants' ASD knowledge level. Age, gender, occupation, education level, professional experience, training for ASD, working with an individual with ASD, and having a friend with ASD were used as predictors. The model was statistically significant (F =7.06, p=0.000) and could explain 13.3% of the variance in KCAHW scores without significant auto-correlation problems (Durbin–Watson=1.9). No multi-colinearity problems were detected in the model (VIF between 1.0 and 2.4) (Table 6). In linear regression analyses, it was determined that the variables of participants' gender, occupation, and having trained for ASD were significant predictors of KCAHW scores. It was determined that the gender of the healthcare worker increases the standard deviation of 0.22 units in the KCAHW score, being a doctor in profession increases the KCAHW score by 0.26 units, and being trained for ASD increases by 0.11 units.

Finally, the participants were asked, "Which department would you refer a patient with suspected ASD to?" question has been asked and 59% of the participants answered that they would refer them to a child psychiatrist, 30% to a child neurologist, 8.2% to a psychiatrist and 2.8% to a psychiatrist.

DISCUSSION

Although the incidence of ASD in the population is increasing day by day, it has been reported in studies that health professionals have limited knowledge about ASD and that the unmet healthcare needs of individuals with ASD are higher than the general population (2,10). This study, it was aimed to examine the knowledge levels of healthcare pro-

Table 5. The relationship of the participants occupation with the variables

	Physician (n=112)	Other healthcare workers (Nurse,Physiotherapist) (n=205)	p
Age*	30.8–6.0	28.7–6.0	0.516
	n (%)	n (%)	
Gender**			
Male	64 (57.1)	58 (28.2)	0.000
Female	48 (42.9)	148 (71.8)	
Education level**			
High-school/Undergraduate	0 (0.0)	88 (42.9)	0.000
Graduate /Postgraduate	112 (100.0)	117 (57.1)	
Got training on ASD**			
Yes	71 (63.3)	87 (42.4)	0.001
No	41 (36.7)	118 (57.6)	
Worked experience with ASD**			
Yes	59 (52.6)	94 (45.8)	0.242
No	53 (47.4)	111 (54.2)	
Having children with ASD**			
Yes	12 (10.7)	28 (13.6)	0.393
No	100 (89.3)	177 (86.4)	

Significicant differences were shown in bold in the tables.
** Pearson chi-square test, *t test.

Table 6. Significant predictors of autism knowledge level scores obtained by KCAHW.

	Beta	p	95% Confdence Interval	VIF
Age	0.1	0.12	-0.01 to 0.13	2.4
Gender	0.2	*0.00*	0.6 to 1.9	1.1
Occupation	0.2	*0.00*	-2.3 to -0.8	1.4
Education level	0.01	0.95	-0.7 to 0.7	1.3
Work experience	0.05	0.52	-1.4 to 0.7	2.3
Worked experience with ASD	0.08	0.10	-0.09 to 1.1	1.0
Got training on ASD	0.1	*0.04*	0.009 to 1.2	1.1
Having children with ASD	0.07	0.17	-0.2 to 1.5	1.0

Italic values indiacte $p < 0.05$

Beta standardized regression coefcient, VIF variance nfation factor, linear regression with enter method (only signifcant predictors shown)

fessionals about ASD, who were working in a hospital that provides tertiary health care.

In a recent review, it was reported that mean KCAHW scores ranged from 9.01 to 13.5 in studies evaluating the level of ASD knowledge in healthcare professionals using KCAHW. In that review, it was stated that most of the healthcare professionals reported only moderate knowledge and self-efficacy in their practice and that they generally lacked ASD-specific training in their professional training (10). Similarly, in our study, the level of ASD knowledge in healthcare workers was evaluated using the KCAHW questionnaire. The mean KCAHW score of the healthcare professionals participating in our study was 12.62 ± 2.80. In a study examining the psychometric properties of the Turkish version of the KCAHW questionnaire, the mean KCAHW questionnaire score of healthcare professionals was reported as 13.83 ± 2.55 (14). Unlike the aforementioned study, the knowledge level of the participants was measured in a university hospital providing tertiary health care, in our study. In the aforementioned study, it is seen that the level of ASD knowledge is evaluated in family physicians and family health workers in institutions providing primary health care services. In this study, it is seen that KCAHW scores are relatively high compared to our study. In another study in Turkey, that 278 nurses participated, the KCAHW total score used to measure the level of ASD knowledge was reported as 12.29 ± 3.19 (15). No study has been found in Turkey that compared the ASD knowledge level of nurses and doctors. Our study will also contribute to the literature in this respect. In one of the studies evaluating the ASD knowledge level of healthcare professionals in other countries, it was reported that the mean KCAHW total score was 9.80±3.44 among doctors from different specialties (16). In another study conducted with a study sample of pediatricians and psychiatrists, the KCAHW total score was found to be 12.4±4.4 (17). Although there were no psychiatrists in our study and pediatricians constituted 4.4% of the physicians, the KCAHW total score was found to be 12.62 ± 2.80.

In a recent systematic review, it was examined whether there was a change in knowledge, self-efficacy, and attitudes towards ASD in studies conducted before and after 2013, in which the diagnostic criteria of ASD were changed with the DSM-5 (1). Regarding the studies that measured the level of ASD knowledge using KCAHW, the mean score of KCAHW was 11.86 (min: 10.67, max: 12.56) from 1994 to 2013, while the average score was found to be 12.04 (min: 9.8, max: 13.5) from 2013 to present, and only small improvement was detected in the scores (10). Based on this review, it can be said that the ASD knowledge level of health professionals working in a center providing tertiary health services in Turkey has not increased significantly despite the increase in ASD incidence. However, in our study, we found that while 77.7% of healthcare professionals knew that inability to socially interact and communicate, which are the main symptoms of ASD, could be seen, 31.8% had true knowledge about ASD and its accompanying diseases. Considering that individuals with ASD often admit to the hospital providing tertiary health care due to comorbid medical and mental illnesses, we predict that this inadequate knowledge may cause difficulties in providing health services to individuals with ASD.

In our study, we created a regression model in which we evaluated the factors that could predict the level of ASD knowledge. According to this model, we found that being a female health worker, being a doctor, and having ASD -oriented training are factors that increase the level of ASD knowledge.

In our study, we found that 50.2% of health workers did not receive training on ASD. We found that the level of ASD knowledge was significantly hig-her in healthcare workers who received training. In the relevant literature, it is also observed that the majority of studies show a positive relationship between the completion of ASD-specific training or programs and ASD knowledge scores (10,18-20).

In the literature, among the studies investigating the relationship between ASD awareness and gender, it is mostly reported that there is no significant relationship between gender and knowledge level (10,17,21). In addition, it is seen that there are studies reporting that ASD awareness and positive attitudes toward individuals with ASD are higher in girls than in boys (22,23). Similar to these studies, we found that the level of ASD knowledge was higher in females in our study.

When the studies comparing the ASD knowledge level in different occupational groups are examined, it is seen that the autism knowledge level and awareness of doctors are higher in the majority of the studies. In a study conducted in this direction, the ASD knowledge level of senior medical students, nursing, and psychology students was compared and it was reported that the ASD knowledge level of medical students was higher than other students. This difference is explained by the absence of pediatric and psychiatry internships in the education of nursing and psychology students (24). In a similar study conducted in Turkey, it was reported that there is no difference in ASD awareness between medical students and nursing students (22). In a study examining whether the level of ASD knowledge changes with the residencies of doctors, it was stated that the level of ASD knowledge was higher in psychiatry, child psychiatry and neurology, and pediatric neurology physicians, which were considered as neuropsychiatric groups, compared to other branches (25). In another study evaluating the ASD knowledge level regarding the branches of physicians, it has been reported that psychiatrists had the highest ASD knowledge level, and general practitioners have the lowest level of knowledge (16). In our study, similar to previous studies, we also found that the ASD knowledge level of doctors was higher than that of other healthcare professionals. We observed that the education level of doctors was higher than that of other health workers and there was more autism-oriented education in their education. It can be said that this difference increases the knowledge of ASD. In addition, we found that there was no difference when the ASD knowledge level of the doctors was compared according to their specialty. However, we found that the ASD knowledge level of the doctors who were residency students was lower than the specialist doctors. These findings suggest that it would be useful to include teaching on autism into medical student training programs.

It is seen that there are conflicting results in previous studies evaluating the relationship between age and ASD knowledge level. In addition to a study reporting that the level of ASD knowledge increases with age (26) there are also studies (27,28) reporting that the level of ASD knowledge is higher in younger health workers. In our study, we found an increase in the scores on the scale evaluating the level of ASD knowledge with the increase in the age of the participants. The increase in professional experience with increasing age may explain this result. Because, we also found that with the increase in professional experience, the level of ASD knowledge also increased. In the literature, it is seen that the findings report that the level of knowledge and awareness about ASD increase with increasing experience is common (10). However, there are studies reporting that professional experience and ASD knowledge level are not related (10,29).

In our study, we found that knowing someone with autism did not affect the level of ASD knowledge. There are studies in the literature reporting that knowing someone with ASD is a factor that increases the level of ASD knowledge, contrary to our findings (19,29). The fact that this finding in our study does not agree with the literature can be explained to the small percentage of healthcare workers who are knowing someone with ASD.

In the literature, there are studies reporting that healthcare professionals who have experience with autistic individuals have higher ASD awareness compared to those who do not follow them (16,19).

In contradiction, there are studies reporting that the level of ASD knowledge is better in newly graduated health workers who do not have experience with individuals with ASD, or that there is no relationship between the level of ASD knowledge and the experience with individuals with ASD (27,29). In our study, the level of ASD knowledge was found to be higher among healthcare professionals who had experience with individuals with ASD.

With the national action plan for ASD in Turkey, health professionals working in primary health care services or community organizations were provided with training to increase the level of ASD knowledge and awareness. The fact that the level of ASD knowledge among health workers working in primary health care services or community organizations in Turkey is higher than in our study may be due to this national action plan (30). Considering that secondary and tertiary healthcare institution are centers that provide primary healthcare services for children with developmental disorders such as childhood autism, improving the ASD knowledge level of healthcare professionals in these centers will increase the quality of healthcare services. In this direction, it is necessary to provide training on ASD to health workers in secondary and tertiary health institutions and to develop policies to increase the quality of health services. Based on the findings of our study, it may be beneficial to plan training primarily for non-physician healthcare professionals in secondary and tertiary healthcare institutions and to update the information deficiencies.

Limitations

The strength of our study is that a standardized scale was used to evaluate the level of ASD knowledge. Since this scale is a self-reporting scale, it was applied under the supervision of a practitioner, considering that there was a risk of not reflecting the real data of the participants. Another strength is the large sample size compared to previous studies. The most important limitation of our study is that although the general knowledge level of the participants about the basic symptoms of ASD was measured, their knowledge of the conditions that occur with ASD or their knowledge in the context of the health care system could not be evaluated.

Childhood autism and other neurodevelopmental disorders require a multidisciplinary approach due to their nature. Apparently, there is a need for a special health service system to cover the current unmet needs of these children and their parents. Considering that the secondary and tertiary health institutions are the centers that provide primary health services for children with ASD, improving the ASD knowledge level of health workers in these centers will increase the quality of the health service provided. However, in order to achieve this, it is necessary to constitute policies and plan for the needs. There is a need for basic epidemiological data and studies that will provide these data that will guide the policies and planning to be constituted in this regard. These studies should focus on identifying the unmet needs of children with ASD in the current healthcare system and evaluating the current intervention and education facilities.

Ethical approval and consent to participate: This study was approved by the Afyonkarahisar Health Sciences University Ethics Committee (2011-KAEK-2, 2022/182). All methods were carried out in accordance with relevant guidelines and regulations of Helsinki declaration. Written informed consent was obtained from the participants parents or legal guardian included in the study.

Consent for pubilcation: Not applicable.

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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The impacts of adult separation anxiety disorder on nomophobia

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SUMMARY

Objective: Based on the idea that there may be a link between smartphone addiction and adult separation anxiety disorder (ASAD), our aim was to examine the impacts of ASAD symptoms on nomophobia and whether they predict nomophobia among ASAD patients.

Method: We randomly recruited 50 patients diagnosed with ASAD and 50 control subjects satisfying the inclusion criteria. We collected the data using a sociodemographic information form, the Adult Separation Anxiety Questionnaire (ASA-27), the Nomophobia Questionnaire (NMP-Q), the Beck Depression Inventory (BDI), and the Beck Anxiety Inventory (BAI).

Results: Fifty-four percent of the patients had moderate, and 46% showed mild nomophobia symptoms. The results revealed that, compared to healthy controls, the patients had significantly higher scores on the ASA-27, the BDI, the BAI, the NMP-Q (total), the NMP-Q not being able to access information, the NMP-Q giving up convenience, the NMP-Q not being able to communicate, and the NMP-Q losing connectedness ($p=0.006$ for the NMP-Q giving up convenience; $p<0.001$ for others). Moreover, the results yielded significant positive relationships between ASAD and the participants' nomophobia total and subscale scores (except for losing connectedness) ($p<0.05$). Finally, ASAD scores significantly predicted nomophobia, not being able to access information, giving up convenience, and not being able to communicate.

Discussion: To the best of our knowledge, our study is the first to report nomophobia levels among patients diagnosed with ASAD. The increased severity of separation anxiety symptoms contributed to the severity of nomophobia in the patients, which, in turn, significantly boosted the severity of their depression and anxiety.

Key Words: Anxiety, separation anxiety, nomophobia, smartphones

INTRODUCTION

Adult separation anxiety disorder (ASAD) is a prevalent mental disorder characterized by excessive anxiety about separation from an attachment figure (1). The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) has removed the age criterion for ASAD and reports that it may also give primary onset in adulthood (1). More prevalent among females, the lifetime prevalence of ASAD was previously found to be high, with an average of 4.8%, 43.1% of which is often reported after the age of 18 (2). In the National Comorbidity Survey Replication (NCS-R), 77.5% of adults were diagnosed with lifelong ASAD, and 75.2% had their first onset in adulthood (3). While the majority of adult-onset ASAD cases are encountered in the late teens and early twenties, childhood-onset cases are prevalent in middle childhood (4). Lifetime ASAD shows high comorbidity with anxiety and related disorders and depressive disorder (3).

Attachment theory has a critical place in the etio-

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logy of ASAD. Emotional attachment develops in the form of secure or insecure attachment in early childhood and affects one's whole life. Considering ASAD through the concept of attachment, ASAD was previously reported at higher rates among those with insecure and anxious attachment figures in childhood (4). The insecure attachment in childhood is a phenomenon that one maintains throughout their life (5).

Even though separation anxiety mainly arises when an infant is separated from the attached figure (usually their mother), it may also occur in adulthood, originating from the detachment with a materially tangible object. The individual finds a way to represent their own character through their attachment object (6). Today, smartphones, which are indispensable intruders of our lives, may easily become attachment objects. Therefore, nomophobia can be discussed on the basis of separation anxiety. Nomophobia, which has not yet found an official place in the DSM-5, is denoted as a phobia leading to many physical, emotional, and behavioral problems when away from smartphones (1). Although scholars have used different terms related to nomophobia, such as "smartphone addiction," the most recent term explaining smartphone separation anxiety is "nomophobia" (7).

Previous papers investigated attachment styles in the etiology of nomophobia, and the findings interestingly showed similarities with those in ASAD (8, 9). Some studies suggested that individuals with an anxious attachment style demonstrate more nomophobic characteristics (10, 11) and that such individuals tend to be more attached to their smartphones (12). Moreover, it was postulated that there is a link between smartphone addiction and ASAD (13). Attachment to smartphones appears to involve similar emotional responses in parent-infant attachment. Hence, ASAD and nomophobia, showing overlapping mechanisms regarding attachment styles, are seen as two subjects worth exploring.

So far, the research interest of nomophobia has been on the general population rather than clinical subjects. Besides, to the best of our knowledge, nomophobia levels have not been reported among patients with ASAD. Therefore, we believe that separation anxiety disorder - a disorder that may be ignored in adult populations - deserves to be explored considering this concept. In other words, we wonder about the relationship between ASAD and nomophobia and whether ASAD predicts nomophobia. Ultimately, our aim in the present study was to explore the impacts of the symptoms and severity of ASAD on nomophobia. We suggest that in patients diagnosed with ASAD, there may be high levels of nomofobia in parallel with clinics, and that ASAD can predict nomophobia. We think that the findings may contribute to clinical insights into nomophobia and ASAD. The findings may also emphasize the need to consider the anamnesis of patients with ASAD from a broader perspective and shed new light on its treatment protocols.

METHOD

Power analysis: The power analysis performed on the G*Power 3.1 program revealed that a sample size of 52 patients should be included in the study to reach 95% power at a significance level of 0.05 in the 95% confidence interval. The thesis titled "An Investigation of Relationship Between Separation Anxiety and Parasocial Breakup Comparison with Relationship of Attachment Style and Parasocial Interaction in Adults" was taken as a reference for the power analysis. However, we could reach 50 people in our study (participation rate: 96.2%).

Sample

Patient group: We randomly recruited 50 patients applying to the Elazığ Fethi Sekin City Hospital Psychiatry Clinic, treated as either inpatient or outpatient, diagnosed with ASAD according to the DSM-5 diagnostic criteria, and satisfying the inclusion criteria.

Control group: The control group consisted of 50 healthy volunteers applying to the Elazığ Fethi Sekin City Hospital Psychiatry Clinic, without any psychopathology according to DSM-5 criteria and a history of psychiatric disorders. These people were made up of healthy people who applied to the psychiatry outpatient clinic for a health report and patient relatives.

Procedure: We carried out the study in accordance with the Declaration of Helsinki after obtaining ethical approval and local permissions. After explaining the purpose and procedure of the study to all participants, we obtained their written consent. Then, the participants were administered a sociodemographic information form, the Adult Separation Anxiety Questionnaire (ASA), the Nomophobia Questionnaire (NMP-Q), the Beck Depression Inventory (BDI), and the Beck Anxiety Inventory (BAI). We explored comorbid psychiatric disorders in patients based on the DSM-5 criteria. The data collection procedure lasted 30-40 minutes per participant.

Inclusion criteria for the patient group; Being aged 18-65 years, the ASAD diagnosis according to the DSM-5 criteria (American Psychiatric Association, 2013), no other comorbid mental disorders (except for anxiety and associated disorders and depressive disorder), no significant somatic pathology or any neurological disorders that would affect the distribution of existing psychiatric symptoms, no history of alcohol or substance abuse disorder in the last six months, providing a signed written informed consent form.

Exclusion criteria for the patient group; Not being aged 18-65 years, no ASAD diagnosis according to the DSM-5 criteria, other comorbid mental disorders (except for anxiety and associated disorders and depressive disorder), significant somatic pathology or any neurological disorders that would affect the distribution of existing psychiatric symptoms, history of alcohol or substance abuse disorder in the last six months, not providing a signed written informed consent form

Statistical Analysis

We analyzed the data using SPSS 22.0 (Statistical Package for Social Sciences; SPSS Inc., Chicago, IL). While categorical data were shown as numbers (n) and percentages (%), we presented continuous data as mean±standard deviation (M±SD), median-interquartile range (25th-75th percentiles). We performed a Chi-square test (Pearson's Chi-square) to compare the categorical variables between the groups. Then, we ran the Kolmogorov-Smirnov test to check whether the continuous data showed a normal distribution. Since the data did not normally distribute, while performing a Mann-Whitney U-test to compare the groups, we used Spearman's correlation test to examine the relationships between the variables. Finally, Multiple Linear Regression analysis was utilized to determine whether adult separation anxiety significantly predicts nomophobia. While creating the model, those with significant correlations in correlation tests were included in the model. In all analyses, we accepted a p-value < 0.05 as statistically significant.

Data collection tools

Sociodemographic Information Form: We generated the form to obtain participants' age, sex, height-weight, employment status, marital status, educational attainment, occupation, place of residence, income level, psychiatric treatment status, family history of psychiatric disorders, and physical health status.

Adult Separation Anxiety Questionnaire (ASA-27): Manicavasagar et al. (14) developed the 27-item four-point Likert-type scale (0= This has never happened; 3= This happens very often) to measure the symptoms of separation anxiety appearing not only in childhood but also early adulthood. The scale was previously adapted to Turkish (15). The higher total score on the scale indicates intensified adult separation anxiety. The Turkish adaptation study revealed the cut-off point as 25 and above (22 in the original study) and calculated the internal consistency coefficient of the scale to be .93 (15).

Nomophobia Questionnaire (NMP-Q): It was developed by Yıldırım and Correira (16) to measure smartphone addiction among individuals. The 7-point Likert-type scale consists of 20 items within four subscales: not being able to communicate, losing connectedness, not being able to access information, and giving up convenience. Total score indicates the severity of nomophobia: none (NMP-Q Score = 20), mild (21 ≤ NMP-Q Score < 60), moderate (60 ≤ NMP-Q Score < 100), and extreme (100 ≤ NMP-Q Score ≤ 140). Yıldırım et al. (17) carried out its Turkish validity and reliability study and calculated Cronbach's alpha coeffi-

cient to be .94.

Beck Anxiety Inventory (BAI): The 4-point Likert-type inventory was developed by Beck. It consists of 21 items, and the total score ranges from 0 to 63. The high total score refers to one's high level of anxiety. Ulusoy et al. (18) adapted the tool into Turkish and found Cronbach's alpha coefficient to be 0.93.

Beck Depression Inventory (BDI): Developed by Beck, the inventory is a four-point Likert-type scale consisting of 21 items. The total score varies between 0-63. Hisli (19) carried out its Turkish validity and reliability study and calculated Cronbach's alpha coefficient to be 0.74 (19).

RESULTS

We carried out the study with a total of 100 participants, 50 patients and 50 controls. While the median age of the patient group was 29.5 (24.0 - 35.0), it was 28.0 (25.0 - 33.0) in the control group. There was no significant difference between the groups by age (p=0.355). Moreover, 76% and 78% of the groups were females, respectively, and we did not find a significant difference between the groups by sex (p=0.812). Besides, there were no significant differences between the groups by marital status (p=0.410), educational attainment (p=0.891), place of residence (p=0.673), income level (p=0.592), employment status (p=0.687), organic disease (p=1,000), and medication (p=0.779) (Table 1).

The incidence of comorbid psychiatric disorders (generalized anxiety disorder, panic disorder, agoraphobia, specific phobia, social phobia, depressive disorder) in the patient group (42%) was found to be significantly higher than that in the control group (0%) (p<0.001). Furthermore, we discovered that the patient group (46%) had a more prevalent history of psychiatric treatment than the control group (22%) (p=0.011). Similarly, the patient group significantly used alcohol/substance (20%) significantly more than the patient group (0%) (p=0.001). It was found that having married parents was significantly more common in the control group (78%) than in the patient group (32%) (p<0.001). Likewise, the rate of those living with their parents in the patient group (22%) was significantly lower than that in the control group (44%) (p=0.014). About one-fourth (24%) of the patients used their smartphones at home, 12% in outdoor spaces, 10% at work, and 54% in multiple places (home-work-outdoor), whereas 20% of those in the control group used them at home, 54% in outdoor spaces, and 26% at work. Accordingly, the groups significantly differed by where they spent the most time with their smartphones (p<0.001). The results also revealed that the patient group had significantly more daily smartphone usage time than the control group (p<0.001).

Yet, the groups did not significantly differ by family history of psychiatric disorders (p=0.061), smoking (p=0.529), and duration of smartphone ownership

Table 1. Sociodemographic characteristics of the patient and control groups

		Patient group		Control group		p*
		n	%	n	%	
Age, median (IQR)		29.5 (24.0-35.0)		28.0 (25.0-33.0)		0.355**
Sex	Female	38	76.0	39	78.0	0.812
	Male	12	24.0	11	22.0	
Marital status	Single	22	44.0	25	50.0	0.410
	Married	18	36.0	12	24.0	
	Widowed/Divorced	10	20.0	13	26.0	
Educational attainment	Middle school and below	15	30.0	15	30.0	0.891
	High school	17	34.0	15	30.0	
	University	18	36.0	20	40.0	
Place of residence	District	18	36.0	16	32.0	0.673
	City	32	64.0	34	68.0	
Income level	Low	10	20.0	14	28.0	0.592
	Middle	23	46.0	19	38.0	
	High	17	34.0	17	34.0	
Employment status	Employed	27	54.0	29	58.0	0.687
	Unemployed	23	46.0	21	42.0	

*Chi-square analysis, **Mann Whitney-U test.
IQR: Inter Quantile Range

Tablo 2. Comparison of disease characteristics of groups

		Patient group		Control group		p*
		n	%	n	%	
Organic disease	Yes	9	18.0	9	18.0	1.000
	No	41	82.0	41	82.0	
Medication	Yes	8	16.0	7	14.0	0.779
	No	42	84.0	43	86.0	
Comorbid psychiatric disorder	Yes	21	42.0	0	.0	<0.001
	No	29	58.0	50	100.0	
History of psychiatric treatment	Yes	23	46.0	11	22.0	0.011
	No	27	54.0	39	78.0	
Family history of psychiatric disorders	Yes	16	32.0	8	16.0	0.061
	No	34	68.0	42	84.0	
Smoking	Yes	16	32.0	19	38.0	0.529
	No	34	68.0	31	62.0	
Alcohol/substance use	Yes	10	20.0	0	.0	0.001
	No	40	80.0	50	100.0	
Parental relationship	Married	16	32.0	39	78.0	<0.001
	Officially divorced	12	24.0	0	.0	
	Mother deceased	11	22.0	6	12.0	
	Father deceased	11	22.0	5	10.0	
Cohabitant	Parents	11	22.0	22	44.0	0.014
	Mother or father	4	8.0	0	.0	
	Alone	19	38.0	18	36.0	
	Spouse	12	24.0	10	20.0	
	Other	4	8.0	0	.0	

*Chi-square analysis

(p=1.000) (Table 2,3).

While more than half of the patients (54%) exhibited moderate nomophobia, 46% showed mild nomophobia.

The results revealed that, compared to healthy controls, the patients had significantly higher scores on the ASA-27, the BDI, the BAI, the NMP-Q (total), the NMP-Q not being able to access information, the NMP-Q giving up convenience, the NMP-Q not being able to communicate, and the NMP-Q losing connectedness (p=0.006 for the NMP-Q not being able to access information; p<0.001 for others) (Table 3).

There were significant positive correlations between daily smartphone usage time and the participants' anxiety, depression, and nomophobia total and subscale scores (except for losing connectedness) (Table 4).

The results yielded significant positive relationships between adult separation anxiety disorder and the participants' depression, anxiety, and nomophobia total and subscale scores (except for losing connectedness). We also found that participants' depression scores showed significant positive correlations with their anxiety and nomophobia total and subscale scores (except for losing connectedness). Finally, the participants' anxiety scores had significant positive relationships with their nomophobia total and subscale scores (except for losing connectedness) (Table 5).

Considering nomophobia by smartphone ownership, we could not find a significant difference between the patients owning a smartphone for more than five years and those using a smartphone for less than five years (p=0.970).

The results of the multiple regression analysis suggested that participants' scores on the ASA-27 significantly predicted their scores on the NMP-Q (total) (β=0.648, p<0.001), the NMP-Q not being able to access information (β=0.070, p=0.034), the NMP-Q giving up convenience (β=0.071,

Tablo 3. Comparison of smartphone-related features of groups

		Patient group		Control group		p*
		n	%	n	%	
Duration of smartphone ownership	Less than 5 years	3	6.0	3	6.0	1.000
	More than 5 years	47	94.0	47	94.0	
Place where the most time spent with the smartphone	Home	12	24.0	10	20.0	<0.001
	Outdoor space	6	12.0	27	54.0	
	Workplace	5	10.0	13	26.0	
	Multiple spaces	27	54.0	0	.0	
Daily smartphone usage time Median (IQR)		5.5 (5-7)		3 (2-4)		<0.001**

*Chi-square analysis, **Mann Whitney-U test.
IQR: Inter Quantile Range

Table 4. Participants scores on the scales

	Patient group	Control group	p
	Median (IQR)	Median (IQR)	
ASA-27	42.0 (28.0-49.0)	3.0 (2.0-8.0)	<0.001
BDI	10.0 (6.0-15.0)	2.0 (.0-3.0)	<0.001
BAI	15.5 (10.0-25.0)	2.0 (.0-3.0)	<0.001
NMP-Q not being able to access information	10.0 (8.0-12.0)	7.0 (6.0-9.0)	<0.001
NMP-Q giving up convenience	9.5 (8.0-13.0)	8.0 (7.0-10.0)	0.006
NMP-Q not being able to communicate	30.5 (14.0-36.0)	8.0 (7.0-9.0)	<0.001
NMP-Q losing connectedness	11.0 (7.0-14.0)	7.0 (6.0-8.0)	<0.001
NMP-Q total	62.0 (41.0-72.0)	31.0 (28.0-34.0)	<0.001

*Mann Whitney-U

ASA-27: Adult Separation Anxiety Questionnaire, NMP-Q: Nomophobia Questionnaire, BDI: Beck Depression Inventory, BAI: Beck Anxiety Inventory

p=0.047), and the NMP-Q not being able to communicate (β=0.451, p<0.001). In addition, the scores on the BAI were found to significantly predict the scores on the NMP-Q not being able to access information (β=0.120, p=0.042). Overall, we concluded that the variables discussed as the predictors of nomophobia explained about 50.7% of the patients' nomophobia levels (Table 6).

DISCUSSION

The most noteworthy result of our study was that patients with ASAD exhibited significantly more nomophobic behavior compared to healthy controls. Accordingly, we may assert that patients do not want to lose online connection through their smartphones, avoid being away from communi cation, desire to access information at any time, and always prefer the convenience provided by their smartphones. The patients were found to have moderate nomophobia with a mean NMP-Q score of 62. Intensified separation anxiety symptoms lead patients to exhibit significantly increased nomophobic tendency (except for losing connectedness).

What encouraged us to design such a study was the common ground in previous research on the etiology of ASAD and nomophobia. Hopefully, our findings supported our consideration that there may be a relationship between ASAD and nomophobia. We know that ASAD is also explained through attachment styles. Attachment, acquired in early childhood and maintained throughout life, affects one's interpersonal relationships and behavior. While it is well-documented that people with ASAD may have anxious or insecure attachment characteristics (5), the previous research reported that people with anxious attachment can easily develop smartphone or Internet addiction (10,11).

We did not examine the patients' attachment styles. Yet, in nomophobia, one clinically experiences excessive anxiety when separated from their smartphone, just as when an ASAD patient leaves their attachment figure. Similarly, as in ASAD where

Table 5. Correlations of the participants daily smartphone usage time and their scale scores

		Daily smartphone usage time	ASA-27	BDI	BAI	NMP-Q not being able to access information	NMP-Q giving up convenience	NMP-Q not being able to communicate	NMP-Q losing connectedness
ASA-27	r	.216							
	p	.132							
BDI	r	.540	.302						
	p	.000	.033						
BAI	r	.463	.298	.848					
	p	.001	.035	.000					
NMP-Q not being able to access information	r	.419	.438	.402	.424				
	p	.002	.001	.004	.002				
NMP-Q giving up convenience	r	.361	.338	.397	.404	.320			
	p	.010	.016	.004	.004	.023			
NMP-Q not being able to communicate	r	.616	.572	.519	.468	.622	.549		
	p	.000	.000	.000	.001	.000	.000		
NMP-Q losing connectedness	r	.199	.185	.173	.081	-.081	.228	.300	
	p	.166	.198	.231	.576	.574	.111	.035	
NMP-Q Total	r	.610	.589	.563	.508	.636	.673	.946	.448
	p	.000	.000	.000	.000	.000	.000	.000	.001

ASA-27: Adult Separation Anxiety Questionnaire, NMP-Q: Nomophobia Questionnaire, BDI: Beck Depression Inventory, BAI: Beck Anxiety Inventory

Table 6. The results of multiple regression analysis for factors associated with nomophobia

	Beta	SE	Standard Beta	t	p
NMP-Q Total (R^2=0.507)					
ASA-27	0.648	0.162	0.461	4.007	<0.001
BDI	0.672	0.422	0.260	1.595	0.118
BAI	0.249	0.287	0.140	0.867	0.390
NMP-Q not being able to access information (R^2=0.315)					
ASA-27	0.070	0.032	0.297	2.188	0.034
BDI	-0.014	0.084	-0.031	-.163	0.871
BAI	0.120	0.057	0.398	2.095	0.042
NMP-Q giving up convenience (R^2=0.265)					
ASA-27	0.071	0.035	0.287	2.043	0.047
BDI	0.084	0.090	0.185	0.932	0.356
BAI	0.049	0.061	0.156	0.793	0.432
NMP-Q not being able to communicate (R^2=0.468)					
ASA-27	0.451	0.116	0.464	3.878	<0.000
BDI	0.385	0.303	0.215	1.271	0.210
BAI	0.180	0.206	0.146	0.870	0.389
NMP-Q losing connectedness (R^2=0.105)					
ASA-27	0.056	0.051	0.172	1.112	0.272
BDI	0.217	0.132	0.361	1.648	0.106
BAI	-0.099	0.090	-0.239	-1.100	0.277

ASA-27: Adult Separation Anxiety Questionnaire, NMP-Q: Nomophobia Questionnaire, BDI: Beck Depression Inventory, BAI: Beck Anxiety Inventory, SE: standard error

one needs to control and reach their attachment figure and tries to keep it close all the time, a nomophobic person shows a phone proximity-seeking tendency toward their smartphone (12). In addition, one's emotional dependence on their attachment figures may predict their tendency to show more fear and anxiety when away from their smartphone (8). People may tend to use smartphones to fulfill their need for attachment, so they may consider their smartphones attachment objects. From this point of view, it may not be surprising that those with ASAD may show nomophobia more than ordinary people. In this study, more than half of the patients were found to be moderately nomophobic, which might be because, on the other hand, ASAD patients have a strong desire to access their attachment figures when feeling depressed or anxious and/or they see their smartphones as attachment figures. Since patients cannot communicate with their attachment figures and lose their online connection, they may demonstrate nomophobic behavior. An ASAD patient may tend to use their smartphones more when away from their attachment figures. Also, these individuals may experience anxiety when not noticing the notifications and calls on their phones. Being away from their smartphones may probably trigger some stereotypical thoughts of ASAD patients, like losing family, relatives and/or friends or being left alone in a bad situation. Although our findings support the above-mentioned views, we cannot understand the underlying mechanisms of such findings due to the case-control design of the present study. We also recognize that our data are not comprehensive enough to evaluate nomophobia, which is still considered a phobia, on the basis of separation anxiety.

Another remarkable finding of our study was that separation anxiety significantly predicted nomophobia. Therefore, we may confidently postulate that ASAD patients' anxiety and stress are predictive of nomophobia development in smartphone deprivation. Similarly, Han et al. (20) reported that staying away from smartphones may trigger separation anxiety among today's people (20).

In our study, we found that 42% of the patients had comorbid psychiatric disorders (generalized anxiety disorder, panic disorder, agoraphobia, specific phobia, social phobia, and depressive disorder). Indeed, it was an expected finding considering the high rates of psychiatric comorbidities, especially anxiety and depressive disorders, in ASAD (3). In addition, while the patients exhibited mild depressive and anxiety symptoms, they had moderate separation anxiety symptoms with a mean score of 42 (cut-off point = 25). A study in 2017 reported a link between smartphone addiction and ASAD, moderated by depression (13). This finding seems to overlap previous research suggesting that smartphone addiction and depression coexist (21). Similarly, it was found that insecurely attached students choose their smartphones as self-objects to alleviate their depressive feelings (22). The author stated that the

smartphone is an alternative to one's insecure attachment. While evaluating our findings, it would be better to consider comorbidities among the patients.

In this study, we could not find a significant association between the duration of smartphone ownership (more/less than five years) and nomophobia. In a study, the participants using a smartphone for more than two years had a significantly higher mean nomophobia score than those having a smartphone for less than two years (17). Another study showed such a difference between those using a smartphone for more than five years and people owning a smartphone for less than a year (23). Considering the relationship between nomophobia and time spent with a smartphone in a day, it was previously found that the students using their smartphones for more than five hours a day showed more nomophobic behavior than their peers spending less than three hours with their devices (24). Another study revealed that an increased duration of smartphone use may elevate one's nomophobia (16). In line with previous findings, we concluded that the severity of nomophobia increased among our patients as they spent more time with their smartphones. In addition, the patient group had significantly more daily smartphone usage time than the control group.

The major strength of our study is that we explored nomophobia among ASAD patients, a group that can often be overlooked. It is also the first study to report nomophobia levels in patients diagnosed with ASAD.

Regarding limitations, we did not examine the attachment styles of the sample, which should be kept in mind when evaluating our results. In addition, our patients had comorbid psychiatric diseases with a rate of 42%. Finally, it may not be appropriate to generalize the finding since we designed the present research as a case-control study.

To the best of our knowledge, our study is the first to report nomophobia levels among patients diagnosed with ASAD. While more than half of the patients (54%) exhibited moderate nomophobia, 46% showed mild nomophobia. The increased severity of separation anxiety symptoms contributed to the severity of nomophobia among the patients, which, in turn, significantly boosted the severity of their depression and anxiety. Moreover, the patients' separation anxiety predicted their nomophobia, except for losing connectedness. Overall, our findings may shed light on interventions for patients with both ASAD and nomophobia. Besides, the results emphasize that smartphone use needs to be further investigated among ASAD patients. Perhaps, further experimental and longitudinal research may include nomophobia therapy in a psychoeducational program for ASAD patients. Although nomophobia is a subject that has attracted research attention in recent years, the literature still hosts limited research on it. We think that our findings may open room for further and comprehensive research on this subject.

Ethical Considerations: The Ethics Committee of Firat University for Non-Interventional Research granted the relevant approval to our study (Date: 11/04/2021, No: 2021/11-15). We carried out all procedures in the study in accordance with the Declaration of Helsinki. All patients provided written informed consent after adequate information on the purpose of the study was given.

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Conflict of interest: None to declare.

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Intimate partner violence and sexual dysfunction in women admitted to psychiatry outpatient clinic

Does culture affect outcomes?

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SUMMARY

Objective: Intimate partner violence (IPV) not only affects women's physical and mental health, but also affects their sexual health and causes various sexual dysfunctions. It was aimed to reveal the relationship between possible IPV and mental and sexual health in Turkish and Arabic women.

Method: The study was designed as cross-sectional and observational. The study included 105 (50 Arabic and 55 Turkish) women between the ages of 18-50 years old. Domestic Violence Against Women Scale, Golombok- Rust Inventory of Sexual Satisfaction Scale, Beck Depression and Anxiety Inventory were applied.

Results: All women participating in the study were exposed to at least one of the subtypes of violence. A significant positive correlation was observed between Golombok-Rust total score and physical ($p=0.003$), emotional ($p=0.006$), verbal ($p=0.027$), sexual violence ($p<0.001$), and the total violence score ($p=0.001$). A significant positive correlation was observed between the total violence score and the infrequency ($p=0.004$), non-communication ($p=0.024$), avoidance ($p=0.003$), non-sensuality ($p<0.001$) scores. The scores of sexual communication, satisfaction, and anorgasmia were significantly higher and the score of sexual avoidance, non-sensuality and vaginismus was significantly lower in the Arabic women than in the Turkish women.

Discussion: IPV and cultural differences are related to sexual functions. The possibility of IPV exposure should be considered and questioned in women applying to psychiatric outpatient clinics, taking into account the effects of different cultures.

Key Words: Culture, domestic violence, intimate partner violence, sexual dysfunctions, women's mental health

INTRODUCTION

A major global health issue is violence against women. Violence against women is one of the most important global health problems. Worldwide, 35% of women have been subjected to physical or sexual violence at the hands of an intimate partner (1). Intimate partner violence (IPV) has an impact on the sexual, reproductive, emotional and physical health of women. Compared to non-victims of violence, victims endure more health issues, spend much higher health care costs, visit doctors and hospitals more frequently, and stay in hospitals for longer periods of time (1).

In Turkey, 38% of women have been exposed to physical and/or sexual violence at some point in their lives (2). Almost half of married women reported that their husbands or partners had been emotionally abusive to them in the form of intimidation, threats, verbal abuse, insults and humiliation (2). In Turkey, 70.1% of the women who applied to the psychiatry outpatient clinic stated that they had experienced verbal violence in their

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marriage and 49.0% of the women reported that they had experienced physical violence. The most common complaints were depressive symptoms. The level of women's psychiatric symptoms who were exposed to physical and verbal violence was found to be significantly higher than those of the women who were not exposed to violence (3).

IPV not only affects women's physical and mental health, but also affects their sexual health and causes various sexual dysfunctions. Multiaxial problem-oriented systems, including partner's physical abuse and severe marital stress, have also been proposed in the past to classify sexual dysfunction (4). The deterioration of the romantic relationship due to violence, and as a result, the addition of depressive and anxious symptoms at various intensities is among the causes of women's sexual dysfunction. Studies have shown that there is a relationship between violence and the sexual functions of women (5). Women who have been exposed to domestic violence are 6.95 times more likely to experience sexual dysfunction than those who have not been exposed to domestic violence (6). According to the results of the other study, there is a statistically significant difference between non-abused and abused women in terms of various categories of sexual function. These categories include desire, arousal, lubrication, orgasm, sexual satisfaction and pain experienced during sexual activity (7). According to a study from Iran, women who had been sexually assaulted felt less sexually aroused than the non-assaulted group. There was a statistically significant difference between the groups exposed to violence and those not exposed to violence in terms of sexual orgasm (8). Women who suffered from sexual violence, often had painful intercourse (9).

Intimate partner violence affects especially women from different ethnic groups and immigrants. Studies have shown that IPV leads to more suicide attempts and causes more depression, posttraumatic stress disorder (PTSD), and sexual dysfunction in African - American, Latino, American Indian / Alaska Native, and South Asian immigrant women (10). African-American women experience 35% more spousal violence than white women, this inequality is greatly reduced when economic and neighborhood factors are controlled (11). The geographical location is one of the many factors that affects the IPV experience for victims. It has been reported that the rate of exposure to IPV among women in small rural towns is higher than that of women living in metropolitan areas (12).

Studies of the prevalence of sexual dysfunction and IPV have been conducted in many different countries and cultures, but there are also some differences based on cultural and social circumstances (13). Despite having comparable characteristics in countries that are geographically adjacent to one another, sexual difficulties vary depending on various social, cultural, religious, and political aspects. Today, there is a migration from the east to the west so it is crucial to introduce customs and behaviors of various civilizations to the new area. When people start to live in a new society, the cultural diffe-rences in that society can play a significant role in the development of health issues as a result of difficulty adjusting. Contrary to men, women are more impacted by social and cultural pressure. Both women's mental health and sexual health may be impacted by this factor.

Sexuality and intimate partner violence are two intimate topics for women. In Turkey, especially in the peripheral regions, the violence and sexual dysfunction that women are exposed to is ignored. Our aim is to help make these problems visible. Asking about these issues in the outpatient clinic can be difficult for healthcare professionals in different cultures. In this study, we tried to determine the frequency of possible intimate partner violence in women primarily admitted to the psychiatric outpatient clinic and to evaluate its relationship with culture. Secondly, the possible relationship between this exposure and the effect of culture on sexual function was investigated. We hypothesized that IPV causes different sexual function problems in Turkish and Arab women.

METHODS

This is a cross-sectional, observational study. The research was carried out in Istanbul Sancaktepe Training and Research Hospital and Sanliurfa Akcakale State Hospital. A hundred and five women between the ages of 18-50 years old, 50

from Sanliurfa and 55 from Istanbul, participated in the study.

While Istanbul is Turkey's most inhabited metropolitan area, Akcakale is a small city located on the Syrian border in Sanliurfa (Urfa) and it is inhabited by Turkish citizens of Arab ethnicity. This is the region with the highest fertility rate in Turkey, and it is a small city where the influence of Arabic culture is observed in every area, including family life and women's traditional clothing. Although polygamy is illegal in Turkey, this situation is seen in Akcakale. According to the data of the Turkish Statistical Institute (TUIK), the literacy rate reached 97.42% in 2020. Sanliurfa was the second province with the lowest literacy rate with 93.42%. In the report, which evaluates the socioeconomic development of the districts in Turkey, it is seen that Istanbul-Sancaktepe ranks 95th among the districts, with an index score of 1.275, and is in the second level. On the other hand, Sanliurfa - Akcakale is considered to be in the 964th rank among the districts, with an index score of -1.258 and in the sixth level. Although all of this puts the cultural difference between the two cities, the participants were asked about their ethnicity and those living in Akcakale defined themselves as "Arab" and those living in Sancaktepe defined themselves as "Turkish". These two cities were chosen considering that the direct effect of cultural difference on violence against women and sexual functions can be noticed.

Participants and Procedure

The participants in the study were women who presented to the psychiatric outpatient clinics of the two hospitals with any psychiatric complaint. Among these women, those who presented for the first time and who received a diagnosis other than 'depressive disorder' or 'anxiety disorder' after psychiatric assessment were not included in the study. The inclusion criteria were: being aged between 18-50, being married or having a partner (having active sexual life), apply in psychiatry outpatient clinics, and having signed the informed consent form. The exclusion criteria were: having any psychotic symptoms after the examination by a psychiatrist, not having a regular partner relationship. Individuals were evaluated according to Diagnostic and Statistical Manual of Mental Disorders 5 (DSM diagnostic criteria by conducting a psychiatric interview. All participants - including Arab women - spoke Turkish.

The scales were given to the women who agreed to take part in the study. They were asked to complete them after the examination. All scales are also in Turkish. The Arab women participating in the study are Turkish citizens, not immigrants. Those who were educated went to school in Turkey. The first psychiatric admission was evaluated according to the women's statements. Women who stated that they had previously taken psychiatric medication were excluded from the study at the onset. The women participating in the study were not using any psychotropic medication. The study was conducted between October 2019 and December 2019. It was not possible to perform a power analysis to determine the number of participants. The sociodemographic data form prepared by the researcher was given to the eligible patients to be included in the study. Then, the patients were given to fill in on their own or with the researcher the Beck Depression, Beck Anxiety, Golombok-Rust Sexual Satisfaction Scale and Psychological Maltreatment of Women Inventory Short Form.

The self-report scales were asked to be completed by the women themselves, except for women who were not be able to read or write. These women were completed by the researcher at the outpatient clinic and outside working hours, with the researcher reading the scales. Women who reported experiencing violence were informed of their rights and those who needed support were referred to the appropriate services. None of the women asked for help. The fact that the self-scales were filled together with the researcher in Sanliurfa, because the women can not be able to read, may have caused the problems to be minimized.

All subjects participating in the study were given an informed consent form approved by the Maltepe University Clinical Research Ethics Committee (number: 2019/900/54 and date: 18/09/2019). Before the clinical interview and application, detailed information about the study was given, and

then the signed consent of all participants was obtained.

Instruments

Sociodemographic Data Form: It is an 18-item form prepared to obtain information about the demographic characteristics of the participants. Questions were asked about the participants' level of education, their spouse's level of education, their parents' level of education, the number of children they had, and the place or people they would seek help from if they were subjected to intimate partner violence.

Psychological Maltreatment of Women Inventory Short Form (PMWI) - Turkish adaptation: It was developed by Tolman (14). The Turkish validity-reliability was made by Ersoy, Hünler, and Namer in 2017 (15). PMWI has Restriction/Blaming/Threat, Emotional/Verbal Violence and Responsibility subscales. It consists of a total of 18 items in the short form. Higher scores indicate higher exposure to psychological violence and the inventory does not have a cut-off point. Internal consistency coefficient (Cronbach-Alpha) was found to be .93; split half reliability was found to be .90 and .87 for the first and second halves, respectively, and the correlation between the two halves were found to be .71. The Cronbach-Alpha value of the current study is 0.83.

Golombok-Rust Inventory of Sexual Satisfaction (GRISS): It is a measurement tool for evaluating the quality of sexuality and sexual dysfunctions. There are two separate forms prepared for men and women, each consisting of 28 items. In female and male forms, there are 7 sub-dimensions, 5 of which are common (avoidance, satisfaction, communication, sensuality and frequency of intercourse). In addition, there are vaginismus and orgasmic disorder (anorgasmia) in the female form, and premature ejaculation and impotence (erectile dysfunction) in the male form (16). The Turkish adaptation of the inventory was made by Tuğrul et al. and evidence regarding its validity and reliability was obtained (17). The Cronbach alpha internal consistency coefficient of Golombok-Rust Sexual Satisfaction Scale was calculated as 0.83 for men and 0.94 for women. According to the data obtained from this sample, Cronbach's alpha values for all sub-dimensions were found to vary between 0.59 and 0.88 in the female form and between 0.42 and 0.85 in the male form. The Cronbach-Alpha value of the current study is 0.88.

Domestic Violence Against Women Scale: The reliability study of the scale, which was developed by Betul Ciler Kilic was conducted, and the total score gives the score for the level of violence against women (18). The reliability study of the scale, which was developed by Betul Ciler Kilic was conducted, and the total score gives the score for the level of violence against women (17). In the first stage, the scale created by the researcher was submitted to an expert opinion for concept validity and necessary corrections were made. In the second stage, item analysis was carried out to determine the reliability of the items in the scale. This procedure checked the correlations between the item scores and determined whether each item measured the variable it was intended to measure. In the third step, the Kuder-Richardson coefficient of 20 was determined for internal consistency. The reliability coefficients of the total scores of the items determine the relationship between the variance of each item and the variance of the total score. The r values for the Domestic Violence Against Women Scale vary between 0.25 and 0.77. The r value for all questions was greater than 0.20 and was considered significant. In this analysis, which examined the internal consistency and homogeneity of the scale, the alpha values for the Domestic Violence Against Women Scale and its sub-groups ranged from 0.73 to 0.94. The Cronbach-Alpha value of the current study is 0.84. The scale, which consists of 50 items in total, has 5 subgroups: physical violence, emotional violence, verbal violence, economic violence and sexual violence. In a 3-point Likert-type scale, the "never" response is scored as 1, the "sometimes" response as 2, and the "always" response as 3, and the score range is between 50 and 150 points. High scores indicate higher levels of violence.

The Physical Violence subgroup measures the level of physical violence such as beating, slapping and similar physical violence done to the woman by the partner. The Emotional Violence subgroup mea-

sures the level of emotional violence such as whether the woman is loved; her family and friends are humiliated by her partner and frightened by her partner. The Verbal Violence subgroup measures the level of verbal violence such as insults and threats addresses to the woman by her partner. The Economic Violence subgroup measures situations such as whether a woman restricts her work because of her partner who controls her expenditures. The Sexual Violence subgroup evaluates situations such as whether the woman is forced to have sexual intercourse against her will and her partner mocks her about her sexual desire or avoidance.

Beck Depression Inventory (BDI): Developed by Beck et al. (19) and adapted into Turkish by Hisli (20). It was determined that the scale had sufficient reliability and validity. Two-half test correlation was r=.74 and internal consistency coefficient (Cronbach Alpha) reported as .80. The Cronbach-Alpha value of the current study is 0.78.

Beck Anxiety Inventory (BAI): Developed by Beck et al.(21) and adapted to Turkish by Ulusoy, Sahin, and Erkmen (22). It was determined that the scale had sufficient reliability and validity. As a result of the validity and reliability study of the Turkish version, the Cronbach alpha value was found to be 0.93. The Cronbach-Alpha value of the current study is 0.89.

Statistical Analysis

In the descriptive statistics of the data, mean, standard deviation, median minimum, maximum, frequency and ratio values were used. The distribution of variables was assessed with the Kolmogorov Smirnov test. The independent-sample t-test and Mann- Whitney U test were used in the analysis of quantitative independent data. Chi-square test was used in the analysis of qualitative independent data, and Fisher Test was used when the Chi-square test conditions were not met. Spearman correlation analysis was used in the correlation analysis. SPSS 28.0 program was used in the analysis. Subscales with a significant difference between the two groups were evaluated one by one in the linear regression model in which age, education period, number of children, marriage duration, BA and BD score were evaluated as predictors.

RESULTS

The mean age of the 105 women participating in the study was 33.7±7.3 years old, and a total of 25 participants were not be able to read or write (3 Turkish, 22 Arabic women). The sociodemographic characteristics including their marrige history of participants were given in Table 1.

No significant difference was found between the total score of the Domestic Violence Against Women Scale and the sub-scores of physical violence, emotional violence, verbal violence, economic violence, and sexual violence in the Turkish or Arabic groups ($p>0.05$). The comparison of domestic violence against women scores of Turkish or Arabic women is given in Table 2. 41.9% of women reported that they have not been exposed to physical violence, 3.8% have not been exposed to economic violence, and 2.8% have not been exposed to sexual violence when the scale score is under 10 in each sub-dimension. There was no significant difference between BDI score and BDI score distribution, BAI score and BAI score distribution among the Turkish and the Arabic women ($p >0.05$). The BDI and BAI scores were given in Table 2.

There was no significant difference between GRISS total score and sexual frequency scores in both groups ($p >0.05$). The scores of sexual communication, satisfaction, and anorgasmia were significantly higher in Arabic women than in Turkish women ($p<0.05$). In the Arabic women, the score of sexual avoidance, non-sensuality and vaginismus was significantly lower than in the Turkish women ($p<0.05$). The comparison of GRISS scores of Turkish and Arabic women is given in Table 2. Sexual dysfunction (GRISS>33) was found in 78% in Turkish women and in 68% in Arabic women. This rate corresponds to 73.3% of all participants.

No significant difference was found in both groups in terms of the Female Psychological Maltreatment Inventory Restriction/Blame/Threat, Emotional/Verbal Violence sub-scores and Total

Table-1: Comparison of sociodemographic characteristics of the Turkish and the Arabic women

	Turk Mean – SD / %	Arab Mean – SD / %	p	t / Z
Age (years)	34.8 – 9.6	31.5 – 6.1	0.037* t	2.121
Number of siblings	4.0 – 1.7	7.2 – 2.9	<0.001* *m	-6.055
Educational Level (years)	8.9–3.8	4.2 –3.6	<0.001** t	6.458
Partner s Educational Level (years)	9.6 –3.6	7.6 –3.7	0.007* t	2.740
Mother s Educational Level (years)	4.8–3.2	1.4–1.3	<0.001** t	72.207
Father s Educational Level (years)	7.4–3.2	4.1–2.3	<0.001** t	98.346
Working Status				
Working	18.2%	30.0%	0.156 x†	2.016
Not working	81.8%	70.0%		
Family income level				
Low	25.5%	68.0%	<0.001** x2	19.107
Middle	47.3%	20.0%		
High	27.3%	12.0%		
Duration of Marriage (years)	13.3–9.0	13.1–7.1	0.956 m	-.055
Partner s Age (years)	40.5–9.0	38.9–9.9	0.364 t	.913
Number of Children	1.9–1.0	4.2–2.2	<0.001** m	-5.672
Way of forming marriage				
Arranged and non-consensual	29.1%	76.0%	<0.001* x2	23.079
Consensual	58.2%	20.0%		
Arranged and consensual	12.7%	4.0%		
Who Do You Ask for Help If Your Partner Treats You Badly?				
Friends	21.8%	8.0%	<0.001* x2	38.616
Police	25.5%	0.0%		
Family	43.6%	32.0%		
Relatives	9.1%	38.0%		
No one	0.0%	22.0%		
Does Your Partner Have Another Partner?				
No	100%	76.0%	<0.001* x2	14.903
Yes	0	24.0%		

t: Independent-sample t-test, m : Mann-Whitney U test, x^2 : Chi-square test, **: p<0.01, *: p<0.05

Score (p>0.05). The Female Psychological Maltreatment Inventory Responsibility score in the Arabic group was found to be significantly lower than the Turkish group (p<0.05). The comparison of PMWI scores of Turkish and Arabic women is given in Table 2.

Correlations of GRISS Total Score and Violence Scores (with sub-scores) were shown in Table 3. Correlations of Violence Total Score and GRISS Scores (with subscrores) were shown in Table 4. Correlations were shown for both total participants and groups separately.

Table-2: Comparisons of domestic violence against women scale, Golombok-Rust inventory of sexual satisfaction, psychological maltreatment of women inventory short form, Beck Depression, and Beck Anxiety Inventory between Turkish and Arabic women

Scale	Sub-scales	Turk Mean – SD	Median	Arab Mean – SD	Median	p	t / Z
Domestic Violence Against Women Scale	Physical Violence	11.2– 1.5	11.0	11.7–2.2	11.0	0.576 m	.559
	Emotional Violence	17.2–2.6	17.0	17.8–2.7	17.0	0.713 m	-.368
	Verbal Violence	16.2 –2.6	16.0	16.7–4.4	15.0	0.504 t	-.687
	Economic Violence	15.4 –2.6	16.0	15.6–2.9	16.0	0.818 t	-.230
	Sexual Violence	14.1 –2.4	14.0	13.9–2.6	14.0	0.667 t	.431
	Total Violence Score	74.2 –7.8	74.0	75.7–12.7	72.0	0.865 m	-.170
GRISS	Frequency	3.7–1.6	4.0	3.9–2.2	4.0	0.514 m	.653
	Communication	3.5–1.6	3.0	5.8–2.6	7.0	<0.001** m	4.549
	Satisfaction	6.4–3.7	7.0	9.4–5.5	11.0	0.001* m	3.435
	Avoidance	5.6–3.8	6.0	4.0–3.9	3.0	0.034* t	2.144
	Sensuality	6.3–2.9	7.0	4.9–4.2	4.0	0.012* m	-2.501
	Anorgasmia	5.7–2.6	5.0	8.2–4.8	7.0	0.001* t	-3.418
	Vaginismus	6.0–2.9	7.0	4.3–2.7	4.0	0.002* t	3.101
	Golombok Total Score	45.2–14.5	48.0	46.2–22.8	50.0	0.626 m	.488
PMWI	Restriction/Blaming/Threat	18.3–5.6	19.0	17.5–7.0	18.0	0.483 t	.704
	Emotional/Verbal Violence	17.1–4.8	17.0	18.4–6.8	18.0	0.304 m	1.029
	Responsibility	10.3–3.5	11.0	9.3–3.4	8.5	0.046* m	-1.996
	Total PMWI Score	45.7–10.7	48.0	45.2–15.3	45.0	0.829 t	.217
BD Score		21.5–9.9	21.0	23.4–11.8	22.5	0.378 t	-.885
BA Score		22.3–7.7	22.0	22.9–9.6	23.0	0.729 t	-.347

t: Independent-sample t-test, m: Mann-Whitney U test, **: p<0.01, *: p<0.05, BD: Beck depression, BA: Beck Anxiety, PMWI: Psychological Maltreatment of Women Inventory Short Form, GRISS: Golombok-Rust Inventory of Sexual Satisfaction

Table-3: Correlations of GRISS Total Score and Violence Scores

		Physical Violence	Emotional Violence	Verbal Violence	Economical Violence	Sexual Violence	Total Violence Score
All Participants GRISS	r	0.286	0.266	0.215	0.168	0.339	0.328
Total Score	p	0.003*	0.006*	0.027*	0.087	<0.001**	0.001**
Turkish GRISS Total	r	0.080	0.320	0.246	0.163	0.450	0.381
Score	p	0.562	0.017*	0.071	0.234	0.001**	0.004*
Arabic GRISS Total	r	0.446	0.287	0.268	0.254	0.315	0.341
Score	p	0.001**	0.043*	0.060	0.075	0.026*	0.015*

*: p<0.05, **: p?0.001, Spearman Correlation, GRISS: Golombok-Rust Inventory of Sexual Satisfaction

Subscales with a significant difference between the two groups were evaluated one by one in the linear regression model in which age, education period, number of children, marriage duration, BA and BD score were evaluated as predictors. For sexual communication, which is the sucscale of GRISS; It was observed that BA score (B = 0.093, β = 0.328, t = 3.539, p = 0.001) and ethnicity (B = 1.831, β = 0.378, t = 3.221, p = 0.002) had a significant effect. For sexual satisfaction, significant effects of BA score (B = 0.131, β = 0.233, t = 2.292, p = 0.024) and ethnicity (B = 2.730, β = 0.282, t = 2.201, p = 0.030) were found. For sexual avoidance; a significant effect of BD score (B = 0.105, β = 0.290, t = 2.722, p = 0.008) was observed, but no significant effect of ethnicity was detected. For sexual sensuality; Significant effects of BD score (B = 0.094, β = 0.281, t = 2.688, p = 0.008) and ethnicity (B =-2.227, β =-0.309, t =-2.307, p = 0.023) were observed. For anorgasmia, only the number of children (B = 0.673, β = 0.269, t = 2.496, p = 0.014) had a significant effect. For vaginismus, only ethnic origin (B =-2.376, β = 0.408, t =-3.012, p = 0.003) was found to be significant. In the Responsibility subscale of PMWI, only the effect of age (B =-0.170, β =-0.407, t =-2.651, p = 009) was found to be significant.

DISCUSSION

In this study, we concluded that sexual functions are affected by intimate partner violence. Additionally, this impact may differ across cultures. The Arabic women whose father, mother and husband have lower education level, have significantly lower education level and more children than the Turkish women. The fact that arranged marriages are more common among in Arabic women and 22% of these women do not even think of going to any authority, when they are subjected to violence, can be seen as a reflection of the culture they live in.

It is understood that all women participating in the study were exposed to at least one of the subtypes of violence. However, there is no difference between these two groups about IPV. In a study investigating physical and sexual intimate partner violence in 15 countries, the lifetime prevalence of violence was reported as 15% to 71%. It was reported that drastic variations in the prevalence of IPV were observed across different geographic regions (23). According to this study, we can interpret that the geographical difference has no effect on IPV. This may be related to the mental state of women. Although there is no difference the severity of depression and anxiety scores between the two groups, violence may have been definable more in women seeking treatment. According to one study, women who suffer from mental disorders such as post-traumatic stress disorder, anxiety or depression are more likely to be exposed to violent behaviour (24).

The Turkish and Arabic groups did not differ significantly on the Golombok-Rust total score or sexual frequency score. Sexual avoidance, non-sensuality and vaginismus severity scores were significantly lower in the Arab group than in the Turkish group, although sexual non-communication, dissatisfaction and anorgasmia severity scores were significantly higher in the Arab group than in the Turkish

Table-4: Correlations of Violence Total Score and GRISS Scores

GRISS		Infrequency	Non-communication	Dissatisfaction	Avoidance	Non-sensuality	Vaginismus	Anorgasmia
All Participants	r	0.279	0.220	0.496	0.283	0.335	0.113	0.121
TVS	p	0.004*	0.024*	<0.001**	0.003*	<0.001**	0.251	0.220
Turkish TVS	r	0.322	0.069	0.503	0.214	0.342	0.129	0.117
	p	0.017*	0.619	<0.001**	0.118	0.011*	0.350	0.396
Arabic TVS	r	0.294	0.275	0.496	0.317	0.390	0.124	0.107
	p	0.039*	0.053	<0.001**	0.025*	0.019*	0.390	0.460

*: p<0.05, **: p<0.001, Spearman Correlation, GRISS. Golombok-Rust Inventory of Sexual Satisfaction, TVS: Total Violence Score

group. Compared to white women, African American women engaged in more sexual activity, but Hispanic women reported less physical pleasure and arousal. Japanese and Chinese women, with arousal being the only notable exception, reported lower levels of arousal and desire than white women (25). We can say that in societies where cultural oppression is experienced less, women try to experience their sexuality more. In conservative societies, however, this seems to be difficult. There are significant differences in the prevalence of specific sexual disorders between white, African American and Asian American women, so health professionals should be cautious about generalising about the sexual concerns of women from different ethnic backgrounds (26).

According to the data of sociodemographic variables in China, women of non-Han or ethnic minorities reported sexual dysfunction less frequently than women of Han ethnicity. Ethnic minorities have a reduced likelihood of sexual dysfunction than people of Han ethnicity. In terms of regional variance, female sexual dysfunction was less common in the southern provinces than in the northern provinces. The regional variation and the regional variation in economic development did not correlate. This finding may be due to a cultural difference in Chinese people's reluctance to acknowledge their sexual troubles or seek treatment for sexual dysfunction (27). There is a similar situation in the current study. However, Istanbul is the biggest city in Turkey in all areas escpecially socioeconomic area, the Turkish women have reported more sexual dysfunctions than the Arabic women. This difference may be related to the expectation from sexuality. The empowerment of women in the socio-cultural field also increases their power to take responsibility for their sexuality.

To compare 10% of women in Turkey and 6.7% of women in Greece, 40% of Iranian women never talk about sexual issues with their partners, according to the survey of women's sexual problems in different countries (13). The assumption that women are prevented by social and religious norms from expressing themselves unless their partner does so may explain why this problem is more prevalent in Iran. The 'good girl' model is used in cultures where women are expected to play a traditional sexual role and adhere to the notion that they must 'control all kinds of emotional and behavioural issues, limit sexuality to responding to their partner, and control all kinds of negative emotions and behaviours'. Differently from Turkey and Iran, where there are religious restrictions on sexuality and where sexuality is considered forbidden, it can be argued that religion contributes to the greater sexual freedom of Greek women (13). The effort of being a "good girl" and pleasing her husband due to cultural pressure; women continue to have sexual intercourse even if they have been subjected to violence. All these lead to problems in the mental health of women. Especially in depressed and anxious women, possible intimate partner violence and sexual functions should be questioned. The way of questioning may be different in different ethnicities.

Similar to other women, the majority of Muslim women suffer arousal, desire, and orgasmic disorders linked to physiological and psychologic variables. Given the prevalence of unconsummated marriage in this demographic, sexual pain disorders may be more common there. Maintaining virginity and protecting the hymen before marriage are special issues (28). In our study, the concern of polygamy, especially among the Arabic women, draws attention as a problem specific to this culture. Possible risk factors for female sexual dysfunctions among Beijing women included unhappiness with the partner's sexual ability, low marital affection, the partner's sexual issues, displeasure with the marriage, and rural lifestyle (29). Considering that IPV can affect marital happiness and satisfaction between partners, similar results seem to be achieved.

Significant relationships have been found between sexual dysfunction and IPV, particularly physical and sexual violence (30). The authors commented that in Iranian women, sexuality is based on pleasing the partner. In our study sexual communication, satisfaction, and anorgasmia severity scores were significantly higher in the Arabic group than in the Turkish group. This difference may be due to cultural influences, partner relationships, mood disorders or different perceptions of sexuality. Similar to the aforementioned study, a relationship

was found between Golombok total score and physical, verbal, sexual and emotional violence in the current study. In particular, women's sexual health is affected by emotional and verbal abuse as well as sexual and physical abuse. A woman who has experienced IPV is expected to be less responsive to her partner's sexual demands and desires.

One study found that physical and psychological IPV were present in 56.7% and 10% of cases respectively. Sexual dysfunction, sexual communication and lifetime physical and psychological IPV were all significantly associated with sexual dissatisfaction (31). The perception of the spouse as too directive or too independent, non-violent issues in the marital relationship, may be associated with sexual dysfunction in addition to the identified violence (32). Similar results were reached in the current study. Violence in a relationship is a sign of relationship dysfunction, and it is difficult to have healthy sexuality in a dysfunctional relationship. Sexual miscommunication will cause sexual dysfunctions, including sexual dissatisfaction in women who need more verbal stimuli for arousal. Regardless of culture, IPV is likely to lead to sexual dysfunction.

There was no significant difference in the Restraint/Blame/Threat, Emotional/Verbal Violence and the Total Scores of the Psychological Maltreatment of Women Inventory Short Form in the Turkish and Arabic women. The Responsibility score of the Form was significantly lower in the Arabic women than in the Turkish women. This difference can be explained by the fact that the Arabic women have low expectations from their partners about responsibility with housework. The fact that the items loaded on other factors in the original form of the scale and related to taking responsibility for common life were gathered under a single factor is thought to indicate a difference in Turkish culture. Obtaining a three-factor structure in the Turkish application study of the long form of the scale also supports this explanation (15).

The first limitation was that only women who applied to the psychiatry outpatient clinic and sought help for mental health were included in the study. The inclusion of individuals with psychiatric disorder is insufficient in terms of reflecting the structure of the general society. The lack of a structured interview to diagnose depression or anxiety is also a limiting factor. An important limitation is that sexual functioning was assessed only with a self-report scale. As the diagnosis of sexual dysfunction was not made by psychiatric examination, the data may have been insufficiently analyzed. The fact that the violence scale has only been tested for validity and reliability in Turkey and it is a local scale and not an internationally valid scale may also have reduced its reliability. We think that the questions of the test are effective in revealing violence. There are also statistical limitations due to the use of only univariate analysis.

This is the first study to assess the relationship between IPV and sexual functioning in Turkey. We suggest that the results of the study may be particularly useful for clinicians or health professionals working in the urban areas to understand the women living there. We can suggest that the probability of any subtype of IPV will be very high in women who apply to the psychiatry outpatient clinic. Psychiatrists or mental health professionals should ask about each subtype of violence in women. Again, it seems important to question sexual functions in these women. Sexual dysfunction is strongly associated with violence experienced by women. The fact that there was no difference in intimate partner violence between two different cultures may be related to women's mental health. The fact that the Arabic women had lower avoidance scores due to the threat of polygamy may be the result of cultural influence. It is clear that the treatment of women's mental and sexual health will begin with their protection from partner violence. Strengthening the mental health of women who apply to the psychiatry outpatient clinic is about educating them about their rights and informing them of reliable addresses they can reach when they are exposed to partner violence. As a result, it is suggested that health services may benefit from staff taking a holistic approach to patient care, including women's religious and socio-cultural components before assessing IPV and sexuality issues and offering appropriate coping techniques. For health professionals to have more systematic and standardized access to the cultural information of the society they serve, transcultural models of

care need to be used. In future studies, intimate partner violence should be evaluated in groups without psychiatric disorders. In addition, women who report having been exposed to violence should be interviewed about post-traumatic stress disorder. A psychiatric interview is also recommended for the diagnosis of sexual dysfunction.

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Informed consent was obtained from all individual participants included in the study.

All data generated or analysed during this study are included in this published article

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Evaluation of early maladaptive schemas and domains in social anxiety disorder specifiers and non-clinical samples

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SUMMARY

Objective: Regarding symptoms, Social Anxiety Disorder (SAD) is a heterogeneous disorder, and DSM-V defines it with a performance-only specifier. This study aimed to examine early maladaptive schema, the differences in SAD specifiers with the non-clinical samples, and the prediction of early maladaptive schema domains on SAD specifiers' symptom severity.

Method: Our sample included 59 patients with performance-only SAD (P-SAD), 61 with unspecified SAD (U-SAD), and 155 individuals in non-clinical samples. We used the Young Schema Questionnaire-Short Form 3 and the Liebowitz Social Anxiety Scale to assess the samples.

Results: Our results were remarkable differences in early maladaptive schemas between individuals of SAD's specifiers and non-clinical samples; we also found that although U-SAD's social anxiety severity related to all early maladaptive schema domains, P-SAD's social anxiety severity associated with Disconnection and Rejection and Impaired Autonomy & Performance schema domains. Our clinical findings suggest that the Disconnection and Rejection schema domain is positive, the Excessive Responsibility and Standards schema domain is negatively predicted for P-SAD's social anxiety severity, and the Impaired Autonomy & Performance schema domain is positively predicted for U-SAD's social anxiety severity.

Discussion: Early maladaptive schema domains have essential impacts on social anxiety symptoms. Understanding the various early maladaptive schema differences among SAD specifiers and a non-clinical sample and predicting these specifiers' social anxiety symptoms with early maladaptive schema domains might help explain different social anxiety disorders' clinical symptomatology.

Key Words: Early maladaptive schemas, social anxiety disorder, specifier.

INTRODUCTION

Social anxiety disorder (SAD) is characterized by overwhelming fear and anxiety in social situations and includes avoidance behaviors that interfere with occupational, social, and academic functioning (1). SAD is a psychopathology that is challenging to explain using categorical diagnosis systems since every individual with SAD is in different clinical presentations. According to research, SAD can be divided into various subtypes, and the "generalized" subtype was added and expanded in the DSM-IV (1). Several studies have shown that as social fears increase, impairment linearly increases with no identifiable threshold (2) or subthreshold (3). There is some debate about the differences between broad social fears and performance-specific fears. Some evidence suggests that there is no subtype or specifier for SAD and that the conceptualization of the disorder is based on the number of social fears (4). However, patients with broad social fears are more likely to be female, younger, have lower income, and have an earlier onset than those with performance-only fears (5). So, research

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appears contradictory regarding the contextualization of SAD as a disorder with subtypes (6) or as a dimensional rather than categorical disorder (7-9). In the DSM-V, the generalized subtype has been replaced by a performance-only specifier to provide more concrete distinctions between intense social anxiety and other types of anxiety (1).

Research on the etiology of social anxiety focuses on cognitive models, which propose that cognitive and attentional biases play a role in the onset and maintenance of SAD (10-13). Contrary to studies determining surface-level cognitions' role in SAD, some authors have examined more stable and deeper levels of cognitions known as schemas (14). Although cognitive behavioral therapy (CBT) is considered the most effective therapy for individuals with social fears or SAD, some researchers have found that some individuals do not improve or drop out, typically ranging from 10-20% of treatment (15, 16). One possible explanation for this may be that certain individuals have persistent maladaptive schemas, which may not be adequately addressed during time-limited sessions of CBT. Young et al. (2003) proposed schema theory, an extended version of Beck's cognitive schemas, which identifies early maladaptive schemas that are asserted to underlie various psychopathologies. Early maladaptive schemas are described as pervasive, broad, and dysfunctional beliefs comprising emotions, cognitions, bodily sensations, and memories about oneself and relationships with others (17). These develop in childhood and adolescence, are elaborated upon throughout one's lifetime, and centralize Beck's cognitive schemas as a cognitive processing component (18) but focus on early development and thematic contents (19, 20). Once established, early schemas are kept stable during one's lifetime to ensure cognitive consistency. However, early schemas can also become maladaptive, and early maladaptive schemas (EMSs) conduct self-destructive emotions, cognitions, and behaviors. EMSs are theoretically assumed to operate on the deepest level of cognition (21). Young et al. (2003) classified five core emotional needs unmet by family or peers that can lead to EMSs: secure attachment, autonomy, competence, sense of identity, freedom to express valid needs and emotions, spontaneity and play, realistic limits, and self-control. These five schema domains or broad categories are the Disconnection & Rejection (D&R), Impaired Autonomy & Performance (IAP), Impaired Limits (IL), Other-directedness (OD), Overvigilance and Inhibition (O&I) domains (17). A recent analysis has validated the presence of 18 schemas and provided support for a new four-domain model, the latent structure of schemas, which is considered more suitable than a model comprising five domains (22). So, these domains were organized into four groups based on empirical support and theory: the names of the three are the same: D&R, IAP, IL, and lastly, Excessive Responsibility and Standards (E&S) (23-25) (see Table 1).

Young assumed that EMSs play a significant causative role in developing psychopathologies. Several studies have investigated the role of EMSs

Table 1: Brief descriptions of schema domains.

Young and colleagues s (2003) schema domain classification	
Disconnection & Rejection (D&R) domain	Abandonment, Mistrust/abuse, Emotional deprivation, Defectiveness/shame, and Social isolation/alienation
Impaired Autonomy & Performance (IAP) domain	Dependence/incompetence, Vulnerability to harm or illness, Enmeshment/undeveloped self, and Failure to achieve
Overvigilance and Inhibition (O&I) domain	Negativity/pessimism, Emotional inhibition, Unrelenting standards/hypercriticalness, and Punitiveness
Other-directedness (OD) domain	Subjugation, Self-sacrifice, and Approval seeking/recognition seeking
Impaired Limits (IL) domain	Entitlement/grandiosity and Insufficient self-control/self-discipline.
Bach and Bernstein s (2019) schema domain classification	
Disconnection & Rejection (D&R) domain	Emotional deprivation , Social isolation/alienation, Emotional inhibition, Defectiveness/shame, Mistrust/abused, Pessimism/negativity
Impaired Autonomy & Performance (IAP) domain	Dependence/incompetence, Failure to achieve, Subjugation, Abandonment/instability, Enmeshment, Vulnerability to harm
Excessive Responsibility and Standards (E&S) domain	Self-sacrifice, Unrelenting standards, Self-punitiveness
Impaired Limits (IL) domain	Entitlement, Approval/admiration-seeking, Insufficient self-control

in various psychopathologies such as depression and anxiety (19, 26-28), eating disorders (29, 30), personality disorders (31, 32), and personality and character traits (33, 34). But, previous evidence has not demonstrated specific EMSs that lead to different emotional disorders (35, 36). Also, Calvete et al. (2005) pointed out that measurement differences could be related to these inconsistent findings (37). According to this, some authors proposed that it could be helpful to investigate via schema domains instead of EMSs (38). So, it could enable some transdiagnostic approaches like self-criticism and experiential avoidance that are part of schema therapy with great emphasis on experience and emotional responses, as trying to suppress or avoid emotions can often perpetuate or worsen, and psychotherapies which are by learning how to regulate emotions more adaptively, could be considered rather than classical cognitive psychotherapies (39, 40). Because, studies have shown that some transdiagnostic factors such as high self-criticism and dependency are strong predictors (41), and self-compassion related to fear of negative and positive evaluation (42), perfectionism and unrealistic social standards are high in socially anxious indivi-duals (43). Operating on these factors including via schema therapy before other cognitive therapies may lead to earlier results in SAD psychotherapy process.

Research has shown a significant relationship between schema domain and anxiety in the literature. It has been found that individuals exhibiting higher levels of anxiety symptoms are prone to obtaining higher scores across all schema domains in comparison to healthy control groups (44). Studies have reported stronger associations between general anxiety symptoms and schema domains related to D&R, IAP, and OD schemas in clinical samples (36, 44). Similar results have been determined in a sample of young adults who were university students, where IAP schemas were found to predict an increase in anxiety symptoms (45). Several studies have also investigated the relationship between SAD and EMSs. Pinto-Gouveia et al. (2006) found that individuals with higher EMS scores, particularly on D&R, IAP, and OD schema domains, were more likely to have social anxiety symptoms. In the same study, in a clinical sample, individuals with social phobia had higher EMS scores on the D&R schema domain than those with mixed anxiety groups (including panic disorder and obsessive-compulsive disorder) (46). Calvete and Orue (2008) found that higher scores on the D&R and IAP schemas were associated with more severe social anxiety symptoms in a non-clinical sample (47). However, these studies were limited in that they could only measure three of the five schema domains, so the predictive roles of IL and O&I on social anxiety could not be examined. Hinrichsen et al. (2004) found that abandonment and emotional inhibition schemas accounted for 25.9% of the variance in social anxiety, agoraphobia, and female gender in patients with an eating disorder (29). Some research has also examined the relationships between EMSs and SAD symptom severity via mediation analysis. For example, Carlucci et al. (2018) found that D&R and IAP schemas mediated the relationship between anxiety and co-rumination (defined as excessive rumination about personal problems between same-sex friends) (48). Difficulty in emotion regulation was also found to mediate the relationship between D&R, IAP, IL schema domains, and social phobia symptoms in university students (49). Calvete et al. (2013) found that EMSs predicted automatic thoughts of anticipatory failure and strengthened the IAP schema domains by mediating the OD schema domain in non-clinical adolescents, similar to other Calvete studies in three schema domains (27). It has been found that the D&R domain directly predicted depression symptoms, whereas schemas in the OD domain predicted social anxiety symptoms via the brooding component of rumination (50). Individuals with SAD indicate a cognitive processing bias, a social looming mediate between OD and social anxiety over time (51).

There was limited study related to differences according to different categorical classifications of SAD in literature. Studies according to some categorical classifications have revealed that there may be heterogeneous cognitive structures in SAD. Several theorists have suggested that performance anxiety (PA) and interaction anxiety (IA) are the dimensions underlying and correspondence between specific social phobia (SSP) and generalized social phobia (GSP), respectively (5, 8). It has been shown that PA/SSP is related to panic and other disorders and acute anxiety reactions (5, 8),

but IA/GSP is more closely associated with depression than PA/SSP (8, 52). According to these classifications, GSP rises before the development of metacognitive processes and before age 10 (53); however, SSP rises after the outcome of metacognitive processes and close to age 16 (54). It is also congruent with SSP, was involved in acute anxiety reactions via specific triggers that necessitate metacognition, and GSP has involved a disturbed self-image (5). Similarly, it has shown SAD's different patterns of appraisal processes; in a study, PA was conceptualized with a fear of negative evaluation of others, but IA was conceptualized with a self-image disturbance (55). Furthermore, understanding maladaptive self-deficiency issues or core fears is crucial in developing and maintaining SAD, mainly since subtypes or specifiers reflect fundamental dimensions and processes. But, in the literature, the utilization of subtypes was inconsistent and different theorists proposed multiple types of attentional biases in SAD. Some studies used the subtype concept rather than specifiers (5, 56, 57).

In summary, SAD is a psychiatric disorder with different specifiers or subtypes. Beyond emotions and beliefs, early schemas represent deeply ingrained, dysfunctional beliefs about oneself and relationships with others that are highly resistant to change. When maladaptive, they may hinder treatment progress in SAD. Not much research has been conducted lately concerning social anxiety and schemas, nor on the specifier of SAD according to DSM-V. This study aimed to examine the possible differences in EMSs between individuals with performance-only SAD (P-SAD), unspecified SAD (U-SAD), and a non-clinical sample, and the predictive power of schema domains on social anxiety symptom severity when comparing U-SAD with P-SAD.

Our hypotheses of the study are,

• There would be individuals with P-SAD with higher EMSs and schema domain scores than the non-clinical healthy group (NCG), and U-SAD has higher EMSs and schema domain scores than the P-SAD sample.

• There would be individuals with U-SAD's symptom severity scores more correlated to EMSs and, D&R and IAP schema domains' scores than P-SAD's symptom severity scores.

• All schema domains would predict individuals with U-SAD's symptom severity and only D&R and IAP schema domains would predict individuals with P-SAD's symptom severity.

METHODS

Participants and procedure

Patients aged 18-65 with the diagnosis of SAD were recruited from routine outpatient visits for three months in 2021 and were excluded if they met DSM-V criteria for mental retardation, personality disorder, autism spectrum disorder, bipolar or psychotic disorders, addiction disorders, and neurocognitive disorders. Patients who received a primary diagnosis of SAD during their routine outpatient admission were referred to one of the authors for further assessment. Patients were diagnosed using the Structured Clinical Interview for DSM-V (SCID 5-CV) and assessed for performance only specifier and others addressed as unspecified (58). The study continued until 65 people were recruited for both P-SAD and U-SAD, considering what could be excluded from the study to exceed the minimum sample size in each group. Then, six people from the P-SAD group were excluded for various reasons: three provided random responses on the measurement tools, three withdrew from the study, and four patients from the U-SAD group were excluded due to providing random responses on the questionnaire. There was 59 participant in the P-SAD group and 61 in the U-SAD group from a hospital's psychiatry outpatient clinic within one month. One hundred sixty-one individuals were recruited from hospital personnel who had no current psychiatric complaints, as determined by anamnesis and mental examination and did not meet the criteria for psychiatric disorders. Six individuals were excluded due to random responses on the measurement tools. A total of 155 participants were finally included in the non-clinical group. All participants completed a sociodemographic questionnaire and an EMSs scale, and individuals with SAD also completed a social phobia severity scale.

Detailed information about the study procedures was provided to participants, and their informed consent was obtained before their participation. The local ethical committee approved the study procedures (numbered 2021.12.09.02/04) and conducted under the ethical standards specified in the 2013 Helsinki Declaration.

Measurements

Sociodemographic data form: This form was created by the research team to determine the age, gender, and education level of the participants.

Young Schema Questionnaire - Short Form 3 (YSQSF-3): The YSQ-SF3 was developed by Young et al. (2003) to assess early maladaptive schemas. It consists of 90 items that assess 18 EMSs and five domains. The distribution of EMSs for the Disconnection & Rejection domain is Abandonment, Mistrust/abuse, Emotional deprivation, Defectiveness/shame, and Social isolation/alienation; the Impaired Autonomy & Performance domain is Dependence/incompetence, Vulnerability to harm or illness, Enmeshment/undeveloped self, and Failure to achieve; the Overvigilance and Inhibition domain is Negativity/pessimism, Emotional inhibition, Unrelenting standards/hypercriticalness, and Punitiveness; the Other-directedness domain is Subjugation, Self-sacrifice, and Approval seeking/recognition seeking; the Impaired Limits domain is Entitlement/grandiosity and Insufficient self-control/self-discipline. Higher scores on the scale indicate higher levels of maladaptive schemas. It was translated and adapted into Turkish by Soygüt and colleagues (59, 60). The reliability and validity of the Turkish version of the YSQSF-3 were assessed with university students, and the findings revealed a factorial solution comprising five schema domains and 14 early maladaptive schemas (60). The distribution of item numbers for each schema subscale in this study differed from that of the original research. The internal consistency coefficients for the EMSs ranged from 0.63 to 0.80, while those for the schema domains ranged from 0.53 to 0.81, respectively. The test-retest reliability correlations for the EMSs were between 0.66 and 0.82, and for the schema domains, they were between 0.66 and 0.83, respectively. However, Bach and Bernstein (2019) has focused on 18 EMSs and four schema domains: D&R, IAP, E&S, and IL (25) due to related studies, which is considered more suitable than a model comprising five domains (22, 61). In the present study, YSQSF-3 revealed 18 schema dimensions and four domains. This was consistent with Bach and Bernstein's (2019) research. Cronbach alpha coefficients were 0.90 for D&R, 0.89 for IAP, 0.72 for E&S, and 0.71 for IL subscales for the present study.

Liebowitz Social Anxiety Scale (LSAS): The LSAS was developed by Liebowitz (62) to assess the fear and avoidance of social situations among people with SAD. LSAS is a 24-item, 4-point Likert-type scale comprising two subscales: social interaction and performance. Each item on the LSAS is rated separately for anxiety and avoidance. The LSAS has been adapted into Turkish by Soykan et al. (2003), and the original LSAS has comparable psychometric properties in the Turkish sample, including Cronbach alpha coefficients of 0.95 for avoidance and 0.96 for anxiety subscales (63). Cronbach alpha coefficients were 0.94 for avoidance and 0.75 for anxiety subscales for the present study.

Data analysis

All statistical analyses were performed with IBM SPSS 21. Descriptive statistics and normality were assessed. Pearson correlation analysis was used to determine the correlation between specifiers of SAD severity and schema domains was determined with Pearson correlation analysis. One-way analyses of variance (ANOVA) and post-hoc Tukey were used to compare three groups: P-SAD, U-SAD, and non-clinical samples with the LSAS scores, the dependent variable. Hierarchical regression analyses were used to evaluate the predictive factors of LSAS scores, the dependent variable. The data did not show multicollinearity, which is the presence of strong correlations among variables, and the correlations among the variables were not too high (<.80). A p-value of less than .05 was considered statistically significant in all analyses.

We used an online calculation tool based on Soper's work to determine the sample size for their study. This tool requires input on anticipated effect size, desired statistical power level, number of predictors in each model, and probability level (64). We received the expected effect size as 0.3 (expert opinion was considered due to lack of similar study, and the medium effect size was expected), the desired power was 0.80, the number of predictors was each model 2 (age and gender), and 4 (YSQSF-3 schema domain scores-D&R, IAP, E&S, IL), and the alpha was 0.05. Accordingly, the required sample size for our study in each group should be at least 47. After conducting the research and performing post-hoc analyses, the power of study was calculated to be in the range of 0.90-0.91 (64).

RESULTS

The study sample included 120 adults diagnosed with SAD, 59 with the performance-only specifier, 61 with the unspecified specifier, and 155 in the non-clinical group. The SAD group was 61.7% female (N=74) with an age range of 18-64 (mean=31.54±10.12), and the control group was 63.9% female (N=99) with an age range of 18-64 (mean=30.53±2.45). The SAD group had a mean of 14.21±2.70 years of education, while the non-clinical group had a mean of 20.60±2.59 years. There were no significant differences between the SAD and control groups in terms of age (p=0.286) or gender (p=0.707), but there was a significant difference in years of education (p=0.000).

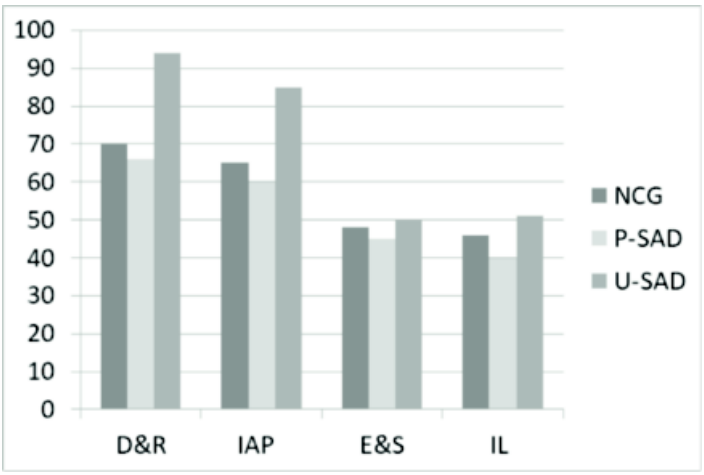
The differences in early maladaptive schemas between the groups (P-SAD, U-SAD, and NCG) were examined using ANOVAs and post-hoc Tukey corrections. (see Table 2). Our results show differences among the three groups in the IL domain scores. The U-SAD group had a higher schema domain score than the P-SAD group, and the P-SAD group had a higher schema domain score than the NCG group. Our findings determine differences between the U-SAD and P-SAD groups in the D&R and IAP schema domain scores. The U-SAD group had higher schema domain and EMS scores than P-SAD except for Unrelenting Standards, Entitlement, and Approval/Admiration-seeking schemas, which were higher in P-SAD than the U-SAD group. There were no significant differences between the U-SAD and P-SAD groups in the E&S domain, except for self-sacrifice and self-punitiveness. There were no significant differences

Table 2: EMS means and standart deviations in P-SAD, U-SAD and non-clinical samples.

	Non-clinical group (NCG) (N=155)		P-SAD (N=60)		U-SAD (N=60)		p	Post-hoc (Tukey)
Measures of EMSs and EMSs domains severity	M	SD	M	SD	M	SD		
Emotional inhibition	8.80	4.06	9.37	5.39	13.26	6.99	<0.001*	U-SAD>NCG=P-SAD
Abandonment/Instability	11.85	3.78	10.86	4.77	15.09	6.43	<0.001*	U-SAD>NCG=P-SAD
Mistrust/Abuse	12.46	4.43	12.74	6.05	16.24	6.73	<0.001*	U-SAD>NCG=P-SAD
Social isolation/Alienation	12.05	4.27	11.69	6.38	15.98	7.41	<0.001*	U-SAD>NCG=P-SAD
Defectiveness/Shame	8.84	4.07	9.66	5.65	14.52	7.61	<0.001*	U-SAD>NCG=P-SAD
Failure to achieve	9.48	4.10	8.89	5.07	14.09	7.60	<0.001*	U-SAD>NCG=P-SAD
Dependence/Incompetence	8.81	3.38	8.01	3.59	11.68	6.29	<0.001*	U-SAD>NCG=P-SAD
Vulnerability to harm	11.83	4.37	11.32	5.60	16.03	7.03	<0.001*	U-SAD>NCG=P-SAD
Enmeshment	11.35	3.96	11.37	4.40	13.26	5.45	0.013*	U-SAD>NCG=P-SAD; U-SAD=P-SAD>NCG
Subjugation	11.21	4.28	9.54	4.55	14.72	6.40	<0.001*	U-SAD>NCG=P-SAD
Self-sacrifice	16.50	5.08	15.49	6.34	17.78	6.45	0.087	-
Emotional deprivation	11.33	4.68	10.18	4.84	15.96	7.06	<0.001*	U-SAD>NCG=P-SAD
Unrelenting standards	17.62	4.36	14.88	5.93	17.50	6.31	0.002*	P-SAD>NCG=U-SAD
Entitlement	15.82	4.26	13.54	4.95	16.08	5.86	0.004*	P-SAD>NCG=U-SAD
Insufficient self-control	14.24	4.12	12.49	4.87	17.24	5.94	<0.001*	U-SAD>P-SAD>NCG
Approval/Admiration-seeking	16.13	4.78	13.61	6.33	17.85	6.79	<0.001*	P-SAD>NCG=U-SAD
Pessimisim/Negativity	13.94	4.94	13.28	5.90	18.52	6.75	<0.001*	U-SAD>NCG=P-SAD
Self-punitiveness	14.05	4.16	13.61	6.24	14.93	5.65	0.329	-
D&R	69.98	24.07	66.77	26.10	94.50	35.14	<0.001*	U-SAD>NCG=P-SAD
IAP	64.81	20.16	60.01	20.70	84.90	32.04	<0.001*	U-SAD>NCG=P-SAD
E&S	48.23	10.86	44.91	18.44	50.22	14.97	0.101	-
IL	46.45	10.34	39.64	13.48	51.18	15.74	<0.001*	U-SAD>P-SAD>NCG

D&R: Disconnection and rejection, IAP: Impaired Autonomy and Performance, E&S: Excessive Responsibility and Standards, IL: Inpaired Limits, one-way ANOVA and post-Tukey analyses. *: p<0.05

Figure 1: Mean ratings of EMS domains for the three groups (Non-clinical group, performance-only SAD, and unspecified SAD).



D&R: Disconnection and Rejection; IAP: Impaired Autonomy & Performance; E&S: Excessive Responsibility and Standards; IL: Impaired Limits; NCG: non-clinical group; P-SAD; Performance only social anxiety disorder; U-SAD: unspecified social anxiety disorder.

between the U-SAD and NCG groups in the EMS scores of Emotional Inhibition, Abandonment/Instability, Mistrust/Abuse, Social isolation/Alienation, Defectiveness/Shame, Failure to achieve, Dependence/Incompetence, Vulnerability to harm, Subjugation, Emotional Deprivation, Insufficient self-control, and Pessimism/Negativity. There were also no significant differences between the U-SAD and NCG groups in the Unrelenting Standards, Entitlement, and Approval/Admiration-seeking schema domains. (see Table 2 and Figure 1)

Table 3 shows the significant correlations between EMSs and schema domains and the symptom severity of individuals with either P-SAD or U-SAD. The relationships between each patient group and the independent variables vary, further supporting the heterogeneity of SAD. The symptom severity of patients with U-SAD was significantly correlated with all EMSs and schema domains. However, the symptom severity of patients with P-SAD was only significantly associated with Emotional Inhibition, Abandonment/Instability, Mistrust/Abuse, Social isolation/Alienation, Defectiveness/Shame, Failure to achieve, Dependence/Incompetence, Subjugation, Emotional Deprivation,

Table 3: Correlations between EMSs and schema domains scores and P-SAD s and U-SAD s LSAS scores.

Measures of EMSs and schema domains severity	P-SAD (*N*= 60)	U-SAD (*N*= 60)
Emotional inhibition	.498**	.502**
Abandonment/Instability	.354**	.634**
Mistrust/Abuse	.342**	.529**
Socialisolation/Alienation	.475**	.673**
Defectiveness/Shame	.304*	.638**
Failure to achieve	.362**	.684**
Dependence/Incompetence	.381**	.559**
Vulnerability to harm	.251	.606**
Enmeshment	.226	.594**
Subjugation	.477**	.697**
Self sacrifice	.097	.524**
Emotional deprivation	.280*	.545**
Unrelenting standards	-.010	.450**
Entitlement	.076	.423**
Insufficient self-control	.269	.662**
Approval/Admiration-seeking	.175	.557**
Pessimisim/Negativity	.348**	.622**
Self-punitiveness	.179	.393**
D&R	.489**	.710**
IAP	.458**	.773**
E&S	.068	.564**
IL	.207	.648**

D&R: disconnection and rejection, IAP: impaired autonomy and performance, IL: impaired limits, E&S: excessive responsibility and standards, LSAS: Liebowitz Social Anxiety Scale.
**: p<0.05, **: p<0.01*, Pearson correlation test

Table 4: Summary of the regression equations predicting the U-SAD s and P-SAD s LSAS scores.

Predictors	Adj. R Square	B	SE	Beta	CI (LL/UL)
U-SAD s LSAS					
	.235**				
Age		-1.322	.341	-.458**	(-2.006/-.639)
Gender		-5.171	7.316	-.084	(-19.816/9.474)
	.650**				
D&R		.177	.141	.216	(.459/.710)
IAP		.491	.139	.544**	(.769/.773)
E&S		.216	.249	.112	(.716/.564)
IL		-.144	.291	-.078	(.439/.648)
P-SAD s LSAS					
	.031				
Age		.388	.306	.168	(-.225/1.000)
Gender		.1773	6.153	.038	(-10.554/14.099)
	.475**				
D&R		.724	.180	.810**	(.363/1.806)
IAP		.215	.200	.191	(-.187/.617)
E&S		-.619	.212	-.489**	(-1.044/-.193)
IL		-.108	.267	-.062	(-.644/.427)

note: D&R: disconnection and rejection, IAP: impaired autonomy and performance, IL: impaired limits, E&S:excessive responsibility and standards, LSAS: Liebowitz Social Anxiety Scale.
SE: standard error, CI: Confidence Interval, LL: Lower Level, UL: Upper Level.
**: p<0.05, **: p<0.01*, hierarchical regression analyses

Pessimism/Negativity schemas, as well as only the D&R and the IAP schema domains. According to our results, U-SAD symptom severity was found to be more correlated to all EMS and schema domains than P-SAD symptom severity.

We conducted a hierarchical regression analysis to examine the relationship between SAD severity and EMS domains in individuals with P-SAD and U-SAD samples. In the first step, we controlled for the effects of age and gender on SAD severity, and in the second step, we evaluated the impact of schema domains on SAD severity. For the U-SAD group, the first regression model was significant [$F(2, 58) = 8.907$, $p < 0.001$, adjusted R square = 0.235]. After controlling for age and gender, the second model was also significant [$F(6,54)=6.724$, $p<0.001$, adjusted R square=0.650] and determined that only the IAP domain had a positive predictive effect on SAD severity ($\beta = 0.544$, $p<0.001$). For the P-SAD group, the first model was not significant. Still, the second model was significant [$F(6,52)=7.826$, $p<0.001$, adjusted R square= 0.475] and determined that the D&R domain had a positive predictive effect ($\beta = 0.810$, $p<0.001$), and the E&S domain had a negative predictive effect ($\beta = -0.489$, $p=0.005$) on SAD severity (see Table 4).

DISCUSSION

SAD is a heterogeneous disorder; different schemas may be relevant for other specifiers. Fundamentally, we aimed to examine the possible differences between EMSs on P-SAD, U-SAD, and NCG, and also different symptom severity predictions and correlations in P-SAD and U-SAD groups with schema domains.

Our study found partial consistency with our hypothesis that U-SAD had higher EMS questionnaires than patients with P-SAD and NCG samples. Specifically, individuals with U-SAD had higher scores on schema domains the D&R and IAP except for Unrelenting Standards, Entitlement, and Approval/Admiration-seeking. These findings provide empirical support for a cognitive model of SAD, which posits that individuals with U-SAD have negative self-perceptions of being defective, socially incompetent, and undesirable (65). Our results are consistent with previous research showing that the D&R and IAP schema domains play a central role in the onset and maintenance of SAD (27, 46, 47). Difficulty in emotion regulation was found to mediate the relationship between D&R, IAP, IL schema domains, and social phobia symptoms in university students (49). When maladaptive schemas are activated in social situations, they can have a negative impact on clinical symptomatology because they are state-dependent and are not easily accessible when not activated (38). To cope with the negative consequences of schema activation, individuals may engage in avoidance, surrender, or overcompensatory strategies that reinforce schema-related behaviors and beliefs, hindering schema healing (17).

U-SAD had higher scores on the EMSs in the IL schema domain than P-SAD and the NCG, consistent with our hypothesis. In the schemas of Unrelenting Standards, Entitlement, and Approval/Admiration-seeking, P-SAD had higher scores on the EMSs than U-SAD. These findings

are consistent with previous results, which found that patients with SAD had higher scores on all 18 schemas than the general population, except the Unrelenting Standards schema (46). Approval/Admiration-seeking and unrelenting standards schema resemble perfectionism, a transdiagnostic trait. Some studies have reported that perfectionistic strivings and concerns positively correlated to social anxiety, and perfectionistic self-promotion scores demonstrated more interpersonal rumination related to social anxiety in students (66). Social anxiety has been conceptualized as doubt about attaining others' desired impressions (67).

Our study showed no significant differences between U-SAD and P-SAD in the E&S schema domain and self-sacrifice and self-punitiveness schemas, contrary to the literature (46). Self-sacrifice schemas, which belong to the OD schema domain, have significantly played the of a mediator in non-clinical adolescents (27). Also, other research has implicated the relationship between the OD schema domain and social anxiety (27, 68, 69). In these studies, OD consisted of self-sacrifice, subjugation, and approval for seeking, so different classifications of EMSs with our study could explain this discrepancy.

In our study, it was determined that the measurement scores of Emotional Inhibition, Abandonment/Instability, Mistrust/Abuse, Social isolation/Alienation, Defectiveness/Shame, Failure to achieve, Dependence/Incompetence, Vulnerability to harm, Subjugation, Emotional Deprivation, Insufficient self-control, Pessimism/Negativity, and Enmeshment schemas for P-SAD did not significantly differ from those of the NCG. It was found that performance anxiety was involved in fear of negative evaluation by others (55). According to Young et al. (2003), the D&R was engaged in a frequent struggle to develop fulfilling and secure bonds with others, and IAP consists of the expectations regarding oneself and others that will hinder an individual's perceived ability for successful performance and independent function (17). Our study results might be explained with P-SAD being more associated with others' evaluations than self-evaluations.

Our study also had no significant differences between the U-SAD and NCG groups in the Unrelenting Standards, Entitlement, and Approval/Admiration-seeking schema domains. These results are consistent with previous studies that found that clinical samples of young adolescents with psychiatric diagnoses scored considerably higher on 14 out of 18 EMSs than non-clinical samples of high school students, except for Enmeshment, Entitlement/Grandiosity, Insufficient Self-Control, and Approval-Seeking (70). There were also some studies about no significant differences in schemas between psychopathologies and undergraduate psychology students, community controls (71-73). These EMSs were Enmeshment, Entitlement/Grandiosity, Self-Sacrifice, and Unrelenting Standards. Moreover, in a non-clinical sample, all five schema domains were significant predictors of trait anxiety (74). This raises the question of whether there are transdiagnostic schemas related to social anxiety that are present in all people. Further research is needed to investigate this possibility using a dimensional approach. However, previous findings have not indicated specific EMSs that lead to different emotional disorders (35, 36). Also, Calvete et al. (2005) represented that measurement differences could be related to these inconsistent findings (37). According to this, some authors suggested that it could be helpful to investigate via schema domains instead of EMSs (38).

It was determined that patients with U-SAD's symptom severity were significantly correlated to all EMSs and schema domains. Patients with P-SAD's symptom severity was significantly correlated to Emotional inhibition, Abandonment/Instability, Mistrust/Abuse, Social isolation/Alienation, Defectiveness/Shame, Failure to achieve, Dependence/Incompetence, Subjugation, Emotional deprivation, Pessimism/Negativity schemas, and as well as only D&R and IAP schema domains, consistent with our hypothesis. It might be related to patients with SAD primarily fear of being rejected and negatively appraised by other people (75). The D&R and IAP schema domain form fundamentally negative perceptions of self like defectiveness, shame, invalid or unwanted, and failed or inadequate/incompetent (13, 43, 76, 77). These findings might suggest that U-SAD patients may have more generalized social anxiety, while P-SAD patients may have more specific fears related to negative self-perceptions and relationship dynamics.

Our regression analysis results indicate that D&R predicted positively, E&S predicted negatively in P-SAD's symptom severity, and IAP positively predicted U-SAD's symptom severity, supporting our hypothesis. Our results are consistent with studies about the distinction of PA from IA or GSP, the conceptualization of PA as a fear of negative evaluation of others; however, IA was conceptualized with a self-image disturbance (5, 55). Prediction with D&R finding is consistent with the nature of SAD, which includes a socially defective self, perfectionist standards, low support, and emotional intimacy (27, 46, 49). The finding revealed that abandonment and emotional inhibition schemas in the D&R domain explained 25.9% of the variance in social phobia with eating disorders (29). Besides, it was found that difficulty in emotion regulation played a mediating role in the relationship between early maladaptive schema domains of D&R, IAP, IL, and social phobia symptoms in university students (49). Evidence has determined that interpersonal schemas (D&R and OD) relate to depression via negative inferences about social stressors (78). Specifically, the D&R schema domain, which includes social isolation (79), defectiveness/shame and abandonment (80), mistrust/abuse, and emotional deprivation (81), is consistent with cognitions related to social anxiety, including beliefs about being defective and/or flawless and socially isolated, which may lead to the belief that significant others will leave them. However, our results are inconsistent with previous studies in the literature that IAP has mainly predicted SAD. This inconsistency of no prediction of P-SAD symptom severity could be related to measurement differences, our sample who had not activated IAP domains schemas, or the categorization of SAD specifiers. In this case, IAP and IL schema domains could be less salient in our P-SAD sample. It might also be related to the D&R schema domain, which encompasses expectations of the individuals' requirements for safety, love, acceptance, and stability, which would not be satisfied predictably, so mainly external evaluation could be essential in P-SAD, but; the IAP domain consists of the expectation regarding oneself and the environment, which will obstruct individuals' perceived skills for successful performance and independent function, so mainly inner and outer evaluation could be essential in U-SAD. The IAP domain includes maladaptive schemas of failure to achieve, practical incompetence/dependence, and subjugation which is consistent with the beliefs that social anxiety holds about less competent and capable than others (82). A study of non-clinical adolescents demonstrated that EMSs predict automatic thoughts of anticipatory failure and worsen IAP schema domains by acting as a mediator of the OD schema domain (27). Another study in a non-clinical sample determined that emotion regulation difficulty mediates between D&R, IAP, IL schema domains, and social phobia (49). Some studies have stated that the mediation by D&R and IAP schema domains was also implied between anxiety and co-rumination (48). Contrary to the literature, we did not find that the D&R schema domain predicted the severity of social anxiety in U-SAD. This discrepancy may be due to measurement differences, our SAD sample who had not activated the D&R schema domains EMSs, or the categorization of SAD. Consequently, these differences may be beneficial for explaining different social anxiety clinical symptomatologies so that it could lead the way of schema therapy. Further research is required to understand the relationship between schemas and SAD fully.

It is important to note that the negative predictive effect of the E&S schema on social anxiety symptom severity in the P-SAD group is difficult to interpret. Individuals who act based on the E&S schema may have fewer social anxiety symptoms due to behavioral learning. It is also possible that individuals with severe P-SAD may use cognitive, behavioral, or emotional avoidance as a coping strategy with the E&S schema, which could reduce self-reported scores on the LSAS. For instance, fear of being rejected by others leads to increasing multidimensional perfectionism, which includes self-oriented perfectionism (SOP), other-oriented perfectionism (OOP), and socially prescribed perfectionism (SPP) (83). Conroy et al. (2007) examine that only SSP, not SOP, was significantly related to beliefs about failure that resulted in aversive interpersonal consequences. When it corresponds to their standards, it could result in several avoidance strategies finally abandoning tasks entirely (84, 85). Besides, experiential avoidance eliminates uncomfortable internal experiences suppressed or controlled by avoiding cases that generate them (86). Some studies related to experiential avoidance partially mediate perfectionism and worry, which involves context about doubts and failure to actions and uncertainty to achievements regarding

personal goals (87). In this case, it could be said that individuals with SAD can already be given psychotherapy with high levels of perfectionism, self-critical perfectionism, and unrealistic social standards (88) with transdiagnostic approaches via schema therapy, but further research is necessitated.

One of the strengths of our study is that it is the first study to examine the DSM-V SAD with performance-only specifier and unspecified within the concept of EMS domains. We also examined the disorders using structured clinical interviews. The study has several limitations that should be considered when interpreting the results. The SAD sample is not homogeneous in terms of treatment duration and type, and the scales used in the study were self-reported, which may have influenced the accuracy of the results. Besides, the SAD sample had comorbidities with some psychiatric disorders; this study did not control for these comorbid disorders. The generalizability of our study's findings may be limited by factors such as the sample size, single-center design, and the study's cross-sectional nature. Finally, the study only evaluated the relationships between EMSs and SAD and did not consider the potential impact of other factors, such as personality traits or environmental factors. Therefore, further longitudinal and comprehensive studies are needed.

Our study found differences in EMSs between SAD and healthy people; we also found P-SAD and U-SAD related to different EMSs and schema domains. However, some schemas did not differentiate between healthy individuals and patients with SAD. It is worth noting that previous research has shown that people with multiple social fears, as opposed to performance-only fears, tend to have greater avoidance, negative evaluation fears, higher overall anxiety, more social deficits, higher comorbidity, and differences in heritability and treatment response (5, 53, 89-91). From a clinical perspective, it may be essential to consider that potential differences in schemas prediction of P-SAD or U-SAD may explain different clinical symptomatology. Our clinical findings suggest that D&R is positively and, E&S is negatively predicted to P-SAD, and IAP positively predicted to U-SAD. Therefore, people with SAD could be carefully evaluated, focusing on different EMSs, so it could lead the way to schema therapy, which may help reduce social anxiety symptoms with no-time loss (17). Identifying schema domains according to the specifiers of SAD may enable individuals to be treated and their symptoms to regress by applying transdiagnostic treatment techniques via schema therapy (92) (i.e., self-criticism and experiential avoidance). By adjusting their emotional regulation habits, individuals can diminish the intensity of emotional challenges and restore their emotions to a functional state (93). Operating on these transdiagnostic factors, including via schema therapy before other cognitive therapies, may lead to earlier results in the SAD psychotherapy process. This study proposes the significance of researching the effects of EMSs and schema domains on social anxiety symptoms in SAD by focusing on different schemas and schema domains in different SAD specifiers in future research.

Ethical considerations: The participants were informed in detail, and informed consent was obtained. Local ethics committee approval was received for this study (December 13th, 2021, numbered 2021.12.09.02/04) which was conducted per the ethical standards set out in the 2013 Helsinki declaration.

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Comparison of substance users under judicial supervision with controls in terms of attention deficit hyperactivity disorder and emotion regulation difficulties

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SUMMARY

Objective: Substance abuse and addiction are reported to be approximately 2 times more common in individuals diagnosed with Attention Deficit Hyperactivity Disorder (ADHD) compared to the general population. Adults with ADHD have been stated to have difficulties in emotion regulation as well as core symptoms of the disease. In this study, it was aimed to evaluate individuals who applied to a university hospital psychiatry clinic probation clinic in terms of attention deficit hyperactivity disorder and emotion regulation difficulties. The hypothesis of the study is that individuals who apply to the outpatient clinic will have higher ADHD symptoms and emotion regulation difficulties than healthy controls.

Method: The research was conducted between 18.06.22-30.10.22. 135 male patients diagnosed with substance use disorder and 141 healthy volunteers without any psychiatric disease were included in the study. Adult ADHD self-report scale (ASRS), Difficulty in Emotion Regulation Scale Short Form (DERS-16), and sociodemographic data form were administered to the participants.

Results: The probation group's ASRS total score, attention deficit and hyperactivity/impulsivity subscale scores were found to be statistically significantly higher than the control group (p=0.004, p=0.005, p=0.007, respectively). Also DERS-16 impulse and nonacceptance subscale scores of the probation group were statistically significantly higher than the control group (p=0.001, p=0.015, respectively).

Discussion: ADHD and accompanying emotion regulation difficulties may increase the risk of substance use in adults. Considering these clinical features in individuals applying to the probation outpatient clinic may make therapeutic interventions more effective.

Key Words: Probation outpatient clinic, attention deficit hyperactivity disorder, emotion regulation difficulties, substance abuse

INTRODUCTION

Substance-related and addiction disorders are increasingly significant public health problems in Turkey and across the world (1, 2). Probation practices (PP) are used to deal with drug use and related crimes in various countries worldwide. Before Turkey, PP was implemented in the United States and Europe (3, 4). PP was initiated in Turkey in 2005. Article 191 of the Turkish Penal Code No. 5237 defines the procedures for treating individuals sentenced to probation for offences related to "purchasing, accepting, or possessing drugs or stimulant substances for personal use, or using drugs or stimulant substances." Individuals referred to probation are required to visit a healthcare facility within 5 days following the instructions of the probation office. These individuals must visit the institution three times with a two-week interval between visits. During each visit, urine analysis for substance detection is conducted, and a psychiatric evaluation is carried out. If the test results are positive or the interviews confirm substance use, the probation is extended, and three more visits with a

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two-week interval are required. Based on clinical evaluations and repeated toxicological analyses, if it is determined that the individual is still using substances, they are referred to an addiction treatment center (5). It has been reported that PP has yielded effective results in treating individuals with substance use disorders in society (6).

Attention Deficit Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder that begins in childhood, can persist into adulthood, and is characterized by varying degrees of attention deficit, hyperactivity, and impulsivity (7). Epidemiological studies have shown that ADHD occurs in approximately 5% of children and adolescents and 2.5% of adults (8). It has been reported that some or all of the ADHD symptoms can persist in adulthood in about 50% of the cases (9). Untreated individuals with ADHD in adulthood can exhibit risky behaviors such as alcohol and substance abuse, self-injury, propensity for crime, and involvement in traffic accidents (10). Maladaptive behaviors in childhood (such as adjustment problems, impulsive behaviors, academic underachievement) can potentially lead to criminal behavior as individuals grow older (11). Individuals with ADHD and alcohol or substance dependence may engage in illegal activities to obtain alcohol or substances, thereby increasing their propensity for criminal behavior (12).

Adult ADHD manifests with a more heterogeneous clinical presentation and causes impaired functioning compared to its typical symptoms in childhood. It has been reported that most adults with ADHD have at least one psychiatric comorbidity, including anxiety and mood disorders, substance use disorders, and personality disorders (13). Substance use disorder, particularly alcohol and/or nicotine, cannabis, and cocaine, has been suggested as the most common comorbid condition accompanying ADHD (14). It has been stated that substance abuse or addiction is approximately twice as prevalent in individuals with ADHD compared to the general population (15). Ozen et al. showed that about one-third of individuals with substance use disorders met the diagnostic criteria for ADHD (16). Patients with both ADHD and substance use disorder as comorbidities exhibit more complex and chronic substance use patterns than those without ADHD comorbidity. Some of the factors associated with this condition include a higher prevalence of psychiatric comorbidity and multiple substance use, lower treatment adherence, and poorer prognosis (7, 17). Therefore, it is important to consider the possibility of ADHD comorbidity in the follow-up of patients with substance use disorders.

Emotion regulation can be defined as the ability of an individual to monitor, evaluate, control, and modify their emotional responses to achieve their goals. Parents play an important role in developing emotion regulation skills by showing appropriate sensitivity to their children's emotional reactions (18). Emotion regulation skills continue to develop from childhood to adolescence, from adolescence to adulthood, and with aging (19). Studies have evaluated difficulties in emotion regulation from similar perspectives and have made various definitions. Gratz and Roemer emphasized the necessity of flexibility in controlling behaviors toward desired goals. They stated that effective emotion regulation requires being aware of and understanding emotions, accepting emotions, controlling impulses and behaviors in line with the goal, and using appropriate strategies depending on the situation (20). Studies have shown that emotion regulation difficulties are associated with numerous psychiatric disorders such as ADHD, alcohol and substance use disorders, post-traumatic stress disorder, anxiety and mood disorders, and borderline personality disorder (21). It has been stated that adults with ADHD experience difficulties in emotion regulation as much as the core symptoms of the disorder, which disrupts their peer and social relationships and increases risky behaviors (22).

This study aimed to evaluate individuals with substance use disorder who were referred to the probation polyclinic of a university hospital, in terms of their clinical and socio-demographic characteristics, ADHD symptoms, and difficulties in emotion regulation. The study's hypothesis is as follows: Individuals with substance use disorder have higher ADHD symptoms and difficulties in emotion regulation compared to healthy controls. Our goal is to test this hypothesis and contribute to the literature in this regard.

METHODS

Study Sample

This study was conducted in the psychiatry clinic of a university hospital from June 18, 2022, to October 30, 2022. Approval was obtained from the University Clinical Research Ethics Committee (2022/27 - June 17, 2022) for conducting the study. The research included patients with substance use disorder referred to the probation clinic and healthy controls without a history of mental illness. Orum et al. found a difference of 15 in the ASRS mean scores of patients with substance use disorder and healthy controls (17). Based on this study, it was estimated that there would be a 5-point difference in the ASRS mean scores of probation and control groups, and a power analysis based on these data, with $\alpha = 0.05$ and power $(1-\beta) = 0.80$, showed that at least 51 subjects were required in each group to obtain a 5-point difference in the ASRS mean scores of the groups. The inclusion criteria for the study were as follows: agreeing to participate in the study, being between the ages of 18-65 years, being male, having a diagnosis of substance use disorder, and being literate. Since most individuals referring to the probation clinic were male, only male patients were included in the study.The exclusion criteria for the study were as follows: incomplete filling out of forms and scales. The control group was composed of healthcare workers who did not have a history of mental illness or psychiatric drug use and were matched to the probation group in terms of age and gender. A total of 151 patients with substance use disorder in the medical records of the probation clinic were collected for the study. However, 16 of them did not complete the necessary forms and scales for evaluation and were therefore not included in the study. Accordingly, a total of 135 patients were included in the study to form the probation group. To compare the data between the groups, 141 healthy individuals were included in the study. Structured psychiatric interviews for diagnosis were not conducted with those in the groups. Written informed consent was obtained from all participants. Then they were administered the Adult ADHD Self-Report Scale (ASRS), the Difficulties in Emotion Regulation Scale-16 item version (DERS-16), and a sociodemographic data form.

Psychiatric Assessment Scales

*Adult ADHD Self-Report Scale (ASRS):*The ASRS is a self-report scale developed by Ustun et al. in collaboration with the World Health Organization for screening ADHD in adults (23). It consists of two subscales, Attention Deficit and Hyperactivity/Impulsivity, each comprising 9 items. The items assess the frequency of each symptom occurring in the past 6 months. As the scale score increases, the severity of psychopathology also increases. The Turkish validity and reliability study of the scale was conducted by Doğan et al.(Cronbach's alpha = 0.88) (24).

Difficulties in Emotion Regulation Scale-16 item version (DERS-16): The DERS is a 36-item self-report scale developed by Gratz and Roemerto assess various dimensions of difficulties in emotion regulation (20). The 16-item short form of the scale was developed by Bjureberg et al. (25). It consists of five subscales: Non-acceptance, Clarity, Impulse, Strategies, and Goals. As the scale score increases, the severity of difficulties in emotion regulation increases. The validity and reliability study of the scale was conducted by Yiğit and Kuzey (Cronbach's alpha = 0.92) (26).

Socio-demographic Data Form: The authors prepared this form and includes questions about the participants' socio-demographics and clinical characteristics such as education level, age, marital status, duration, frequency, and type of substance use.

Statistical Analysis

SPSS Statistics version 22.0 was used for conducting statistical analysis in this study. Qualitative data were expressed as numbers and percentages. The suitability of the quantitative data in terms of normal distribution was evaluated with the Kolmogorov-Smirnov test. Data that did not show normal distribution were expressed as median (min-max), and data with normal distribution were expressed as mean±standard deviation. Qualitative and quantitative data were compared between probation and control groups. This evaluation was made using the Chi-square test for qualitative data and the Mann Whitney-U test for quan-

titative data. Correlation analysis between ASRS and DERS-16 scores was performed using Spearman's Ordered Correlation Test. A value of $p<0.005$ was considered statistically significant.

RESULTS

Clinical and Sociodemographic Data

A total of 135 patients with substance use disorder referred to the probation outpatient polyclinic of the university hospital were included in the probation group, and 141 healthy individuals were included in the control group. The mean age of those in the probation and control groups was 28 ± 6.37 and 26 ± 8.12 years, respectively. Both groups were similar to each other in terms of age. In addition, 123 (91.1%) of those in the probation group and 54 (38.3%) of those in the control group were smokers; and 88 (65.2%) of those in the probation group and 39 (27.7%) of those in the control group were alcohol uses. The number of participants who reported smoking and alcohol use was significantly higher in the probation group than in the control group ($p<0.001$ for both). Table 1 presents the groups' clinical and socio-demographic characteristics.

In the probation group, the age of first substance use experience was 19 (10-47) years, and the duration of substance use was 5 (1-26) years. The majority of them (59 individuals, 43.7%) had their first substance use experience in the age range of 16-20 years, and they most commonly used cannabis (63.7%), followed by methamphetamine (51.9%). Table 2 and Figure 1 present the substance use-related clinical characteristics of patients in the probation group.

Participants' Scale Scores

Patients in the probation group had statistically significantly higher ASRS total and subscales (attention deficit, hyperactivity/impulsivity) scores than individuals in control ($p=0.005$, $p=0.007$, $p=0.004$, respectively). In addition patients in the probation group had statistically significantly higher DERS-16 impulse and nonacceptance subscales scores than individuals in the control group ($p=0.001$, $p=0.015$, respectively). Although patients in the

Table 1: Comparison of the groups in terms of clinical and sociodemographic characteristics

	Probation	Control	p
	Mean–Sd		
Age	28–6.37	26–8.12	0.115
	n (%)		
Marital status			
Married	55 (40.7)	61	0.760
Single	80 (59.3)	(42.6)	
		80	
		(57.4)	
Education level			
High school or	116	21	**<0.001**
lower	(85.9)	(14.9)	
University	19 (14.1)	120	
		(85.1)	
Failed year			
Yes	60 (44.4)	26	**<0.001**
No	75 (55.6)	(18.4)	
		115	
		(81.6)	
Employment			
Yes	76 (56.3)	74	0.525
No	59 (43.7)	(52.5)	
		67	
		(47.5)	
Physical illness			
Yes	15 (11.1)	10 (7.1)	0.245
No	120	131	
	(88.9)	(92.9)	
Cigarette			
Yes	123	54	**<0.001**
No	(91.1)	(38.3)	
	12 (8.9)	87	
		(61.7)	
Alcohol			
Yes	47 (34.8)	102	**<0.001**
No	88 (65.2)	(72.3)	
		39	
		(27.7)	
Total	135	141	
	(100)	(100)	

Sd: Standard deviation. Chi-square test was used for the analysis of categorical data, and Mann Whitney U test was used for the analysis of numerical data. Bold font indicates statistical significance. p<0.005

Table 2: Descriptive statistical analyzes in the probation group

	Median (Min-Max)
Substance use duration	5 (1-26)
Substance first experienced age	19 (10-47)
	n(%)
Previous addiction treatment history	
Yes	50 (37.0)
No	85 (63.0)
Frequency of substance use	
Every day	34 (25.2)
Several times a week	31 (23.0)
Several times a month	20 (14.8)
Every few months	50 (37.0)
Cannabis	
Yes	86 (63.7)
No	49 (36.3)
Synthetic cannabinoid	
Yes	18 (13.3)
No	117 (86.7)
Heroin	
Yes	7 (5.2)
No	128 (94.8)
Methamphetamine	
Yes	70 (51.9)
No	65 (48.1)
Ecstasy	
Yes	20 (14.8)
No	115 (85.2)
Cocaine	
Yes	11 (8.1)
No	124 (91.9)
Benzodiazepine	
Yes	12 (8.9)
No	123 (91.1)
Biperiden	
Yes	5 (3.7)
No	130 (96.3)
Pregabalin	
Yes	44 (32.6)
No	91 (67.4)
Other	
Yes	3 (2.2)
No	132 (97.8)
Total	135 (100)

probation group had higher DERS-16 total scores than individuals in the control group, this difference was not statistically significant (p=0.097). Table 3 compares the groups' scale scores.

Evaluation of the Correlation between ASRS and DERS-16 Scores

There was a positive correlation between the groups' total and subscale scores for both scales (p<0.001 for all analyses). There was a high level of correlation between the groups' ASRS and DERS-16 total scores (p<0.001, r=0.731). Table 4 presents the correlation between the groups' ASRS and DERS-16 scores.

DISCUSSION

As one of the most important results of this study, patients in the probation group had significantly higher ASRS total and subscale scores than individuals in the control group. Orum et al. evaluated cognitive errors and ADHD symptoms in individuals diagnosed with substance use disorder in Turkey. They reported that the patient group had a significantly higher ASRS total score than the control group (17). Another study reported that individuals diagnosed with substance use disorder referred to the probation outpatient polyclinic showed higher ADHD symptoms than controls (27). ADHD is associated with an increased risk of developing substance use disorder later in life. Studies have reported high rates of comorbidity between ADHD and substance use disorder. A meta-analysis of 29 studies reported that 23.1% of individuals diagnosed with substance use disorder have ADHD (28). Studies have also shown that in patients with substance use disorder, ADHD is associated with an earlier onset of substance use, increased likelihood of hospitalization, increased risk of suicide attempts, multiple substance use, low treatment adherence, and lower abstinence (13).

Various theories have been proposed regarding the relationship between ADHD and substance use disorder, but the underlying mechanism has not been fully understood yet. It has been suggested that impulsivity, executive function impairments,

Table 3: Comparison of the groups in terms of scale scores

	Probation	Control	p
	Median (Min-Max)		
Clarity	4 (2-10)	4 (2-10)	0.074
Goals	7 (3-15)	8 (3-15)	0.419
Impulse	6 (3-15)	5 (3-13)	**0.001**
Strategies	10 (5-25)	9 (5-25)	0.064
Nonacceptance	6 (3-15)	6 (3-15)	**0.015**
DERS-16total	36 (16-79)	32 (16-76)	0.097
Attention deficit	13 (1-34)	10 (1-30)	**0.005**
Hyperactivity/Impulsivity	14 (1-35)	11 (1-30)	**0.007**
ASRS total	26 (2-69)	20 (2-57)	**0.004**

DERS-16: Difficulties in Emotion Regulation Scale-16 item version, ASRS: Adult ADHD Self-Report Scale. Mann Whitney U test was used for the analysis of numerical data.
Bold font indicates statistical significance. p<0.005

Table 4: Evaluation of the correlation between participants' ASRS and DERS-16 scores

Spearmans rho		CLAR	GOA	IMPUL	STRA	NONAC	DERS-16	ATT DE	HA/IMP	ASRS
CLAR	r	1	0.530	0.507	0.640	0.596	0.721	0.565	0.433	0.532
	p		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
	n	276	276	276	276	276	276	276	276	276
GOA	r	0.530	1	0.631	0.761	0.603	0.853	0.650	0.542	0.632
	p	<0.001		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
	n	276	276	276	276	276	276	276	276	276
IMPUL	r	0.507	0.631	1	0.750	0.617	0.822	0.557	0.577	0.607
	p	<0.001	<0.001		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
	n	276	276	276	276	276	276	276	276	276
STRA	r	0.640	0.761	0.750	1	0.759	0.947	0.670	0.619	0.684
	p	<0.001	<0.001	<0.001		<0.001	<0.001	<0.001	<0.001	<0.001
	n	276	276	276	276	276	276	276	276	276
NONAC	r	0.596	0.603	0.617	0.759	1	0.824	0.555	0.523	0.580
	p	<0.001	<0.001	<0.001	<0.001		<0.001	<0.001	<0.001	<0.001
	n	276	276	276	276	276	276	276	276	276
DERS-16	r	0.721	0.853	0.822	0.947	0.824	1	0.719	0.654	0.731
	p	<0.001	<0.001	<0.001	<0.001	<0.001		<0.001	<0.001	<0.001
	n	276	276	276	276	276	276	276	276	276
ATT DE	r	0.565	0.650	0.557	0.670	0.555	0.719	1	0.759	0.929
	p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001		<0.001	<0.001
	n	276	276	276	276	276	276	276	276	276
HA/IMP	r	0.433	0.542	0.577	0.619	0.523	0.654	0.759	1	0.941
	p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001		<0.001
	n	276	276	276	276	276	276	276	276	276
ASRS	r	0.532	0.632	0.607	0.684	0.580	0.731	0.929	0.941	1
	p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	
	n	276	276	276	276	276	276	276	276	276

CLAR: Clarity, GOA: Goals, IMPUL: Impulse, NONAC: Nonacceptance, DERS -16: Difficulties in Emotion Regulation Scale -16 item version, ATT DE: Attention Deficit, HA/IMP: Hyperactivity/Impulsivity, ASRS: Adult ADHD-Self Report Scale, p<0.050

and weakened judgment in ADHD contribute to the risk of developing substance use disorder. The central role of dopamine transmission in both ADHD and substance use disorder models has attracted researchers' attention, and it has been reported that individuals with ADHD have higher dopamine transporter density compared to those without ADHD. This may result in rapid clearance and lower synaptic dopamine levels. Substance use increases synaptic dopamine concentrations, primarily in the nucleus accumbens, the brain's reward center (29, 30). Stimulant drugs manage ADHD symptoms by increasing synaptic dopamine levels in the striatum, including the nucleus accumbens (31). Individuals with ADHD may use substances to increase synaptic dopamine concentrations for self-medication. A recent study has reported that individuals with ADHD who use cannabis mentioned acute beneficial effects of cannabis on many symptoms related to ADHD, improving most of the side effects of medication, such as anxiety and irritability (32).

As commonly reported by previous studies, the characteristics associated with ADHD in childhood are not equally sensitive in adulthood. The overlapping symptomatology between ADHD and anxiety disorders, mood disorders, or substance use disorders presents various challenges to clinicians in the diagnosis and treatment of ADHD. Studies have found that difficulties in emotion regulation are frequently observed in adults with ADHD, but these symptoms can be misdiagnosed as mood disorders (13). Similarly, substance use can mask ADHD symptoms (32). Clinicians are more familiar with mood and anxiety disorders in adults. All of these factors can lead to overlooking the diagnosis of ADHD in adults and delays in treatment. Multimodal treatment is necessary for individuals with ADHD and substance use disorders. Clinicians should be cautious about the risk of drug abuse in treating these patients (13).

The higher ASRS scores in the probation group compared to the control group in our study suggest that there may be more individuals with ADHD in the probation group than in the control group. Due to the design of our study, structured psychiatric interviews were not conducted with the participants, has prevented us from making a definitive conclusion about this suggestion. Participants were evaluated using scales, and the focus was on the level of symptoms. The fact that some participants in the probation group were accompanied by law enforcement and the need for evaluation in a short time were among the reasons we chose this

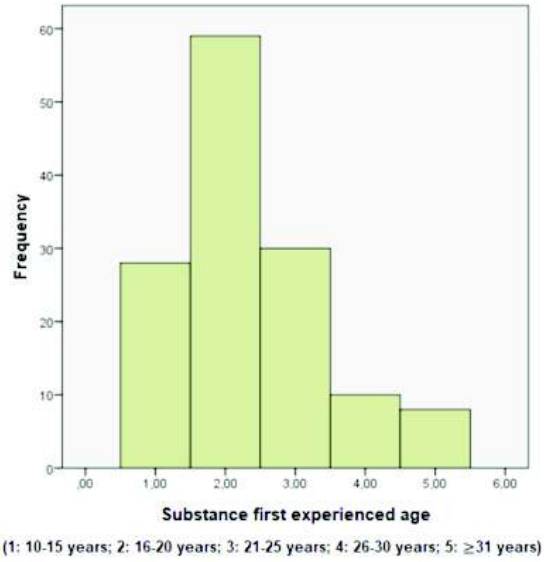

Figure 1: Substance first experienced age range of participants in the probation group

method. Therefore, this is a limitation of our study. The results of our study support previous studies in the literature. Our findings show the importance of considering when approaching the individual in probation polyclinics practice that this individual may have ADHD-based substance use. Clinical features such as the early onset of substance use, multiple substance use, low adherence to treatment, and more complex substance use patterns, including high psychiatric comorbidity, are remarkable in these individuals. The treatment and rehabilitation services considering these clinical features, will contribute to more effective outcomes for both individual and public health.

As another important result of our study, patients in the probation group had significantly higher DERS-16 impulse and non-acceptance subscales scores than individuals in the control group. Additionally, there was a high level of correlation between the groups' DERS-16 and ASRS total scores. Various studies have evaluated emotion regulation and emotion regulation difficulties in patients with substance use disorders (33, 34). The ability to effectively regulate emotions is associated with resilience to psychopathology. It has been reported that individuals with substance use disorders show less skill in regulating negative moods compared to healthy controls, suggesting a potential link to the development and maintenance of addiction behavior (34). Dingle et al.found that adults receiving substance use disorder treatment had more difficulties in emotion regulation than healthy ones (35). A meta-analysis by Stellam et al., including 22 studies, reported that individuals with substance use disorders had higher scores on all DERS subscales, especially strategies and impulse, compared to controls (34). A study compared individuals with cocaine addiction and healthy controls in terms of difficulties in emotion regulation and reported that addicted individuals had significantly higher difficulties in understanding, managing, and controlling emotions during the first week of treatment. Their difficulties in impulse control persisted at the end of treatment. The study also emphasized that there could be a high risk of relapse in the early period after cocaine addiction treatment due to exposure to stressors (36). Another study reported that having emotional distress after addiction treatment is the number one trigger for relapse (35).

To achieve success in addiction treatment, therapeutic interventions should be provided to help addictive individuals develop appropriate emotion regulation strategies when exposed to potential stressors (33). Improvements in emotion regulation difficulties play a mediating role in maintaining abstinence (37). A modified and abbreviated 6-session group program for substance users called "the Tobacco, Alcohol and Drug Dependence Treatment Program (SAMBA)", is implemented in probation polyclinics in Turkey. Ögel et al. evaluated the effectiveness of SAMBA programs implemented in probation polyclinics and reported that it increases treatment adherence in substance-using individuals (38). In addition to the SAMBA, additional therapeutic approaches aimed at improving emotion regulation skills in substance users can contribute to developing more comprehensive and effective treatment programs. They can help achieve more successful results in probation polyclinics. Our study found that patients in the probation group had significantly higher DERS-16 impulse and non-acceptance subscale scores than individuals in the control group. Therefore, patients in the probation group had weaker skills in accepting emotional reactions and more difficulties in impulse control during negative emotional experiences. Our results are consistent with those in the literature.

As another significant result of our study, there was a positive correlation between the participants' ASRS and DERS-16 total and subscales scores. Studies have indicated that adults with ADHD experience difficulties in emotion regulation as much as the disorder's core symptoms, causing them to have significant problems in their social live (22). However, it is impossible to solely attribute the difficulties in emotion regulation to ADHD based on our results. In the study, diagnostic psychiatric interviews were not conducted with the participants. Therefore, our result may also be attributed to other comorbid psychiatric disorders accompanying substance use disorder. Emotion regulation difficulties have been associated with numerous psychiatric disorders such as ADHD, alcohol and substance use disorders, mood and anxiety disorders, borderline personality disorder, and eating disorders (21).

In the present study, the mean age of patients in the probation group was 28±6.37, and the age of their first substance use was 19 (10-47) years. In addition, 43.7% of them had their first experience with substances between the ages of 16-20 years. Although substance use rates in Turkey are lower compared to Western countries, there has been a significant increase in substance use frequency in recent years, and the age of initial substance use has significantly decreased in Turkey (39). The prevalence and severity of substance use under the age of 25 years have been reported to be higher than in those over 25 years old (1). Bulut et al.examined the sociodemographic characteristics of individuals who received treatment in the alcohol and substance use disorder unit of a university hospital in Gaziantep, Turkey and emphasized the most common substance abuse as heroin, followed by cannabis. In their study, the age of first substance use among substance-using individuals was reported as 22.44±7.15 years, and the age of first alcohol and substance use ranged from 11 to 20 (40). Sehlikoğlu et al. also examined the clinical characteristics of individuals who received treatment in a probation polyclinic in Adıyaman, Turkey and reported the mean age of the participants as 27.21±6.77 years and the most common age range for first substance use as 16-20 years, with rare instances of substance use initiation after the age of 30. In their study, the most commonly used substance was reported to be cannabis (94.9%), followed by ecstasy (52.6%) (41). The results of our study are consistent with those in the literature. In our study, the most commonly used substance was cannabis (63.7%), followed by methamphetamine (51.9%). Based on our results, the type of substance used by substance users may vary over time and regionally. Our results, parallel to previous research results, indicate that adolescents constitute a significant risk group for substance use disorders. Therefore, it would be beneficial to add necessary lessons to the curriculum before high school to increase awareness about substance abuse and addiction at an early age.

In our study, patients in the probation group had significantly higher cigarette and alcohol use than individuals in the control group. This result can be explained by the presence of similar mechanisms in the etiopathogenesis of addiction (42). Based on our results, the participants in the probation group may carry a higher risk for cigarette and alcohol addiction than those in the control group. Due to the lack of diagnostic psychiatric interviews with the participants, further interpretations could not be made in this regard.

Our study has some strengths. Firstly, it is the first study in Turkey to evaluate the clinical characteristics of individuals referred to probation polyclinic, along with ADHD and difficulties in emotion regulation. In the literature, there are mainly retrospective studies about the sociodemographic and some clinical characteristics of individuals referring to probation polyclinics. Data loss is a significant problem in these types of studies. The prospective design of our study is important in minimizing data loss.

Our study also has some limitations. First, our study lacked diagnostic psychiatric interviews with the participants and focused on their symptoms using scales. Therefore, their scale scores may have been influenced by comorbid mental disorders. Second, although the content and design of the study were explained to the participants, those in the probation group may not have provided objective answers to the questions on the scale and sociodemographic data form as they were brought

to the clinic by law enforcement. Third, only male participants were included in the study. Therefore, a comparison between genders could not be made. Finally, the study's cross-sectional design and the small sample size are also among its limitations.

This study found significantly higher ASRS total and subscales scores and DERS-16 impulse and nonacceptance subscales scores for patients in the probation group compared to individuals in the control group. Our results are significant in bringing to mind clinical features such as substance use based on ADHD, a more complex substance use pattern, more emotion regulation difficulties, and a tendency to impulsive and risky behaviors in evaluating the individual who applied to the probation outpatient clinic. Therefore, providing them with proper treatment and rehabilitation services considering these clinical characteristics will contribute to achieving more effective outcomes for both individual and public health. In this regard, it seems necessary to expand PP and develop relevant fundamental health and safety policies. There is a need for multivariate and better-structured studies with larger sample sizes to evaluate the mechanisms of ADHD and difficulties in emotion regulation in individuals diagnosed with substance use disorder who are referred to probation polyclinics.

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Examination of post-traumatic growth, post-traumatic stress symptoms, and neurocognitive flexibility levels in individuals who have experienced a traffic accident

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SUMMARY

Objective: Pathological responses can occur in the aftermath of traumatic experiences, alongside positive changes in levels of functioning, such as Post-Traumatic Growth (PTG). Neurocognitive flexibility involves the adaptive restructuring of information in response to changing conditions. The aim of this study is to investigate the potential impact of neurocognitive flexibility on PTG. Post-Traumatic Stress Disorder (PTSD) and PTG are examined together.

Method: A total of 96 participants of had a traffic accident, consisting of 43 individuals with a diagnosis of PTSD and 53 without a diagnosis of PTSD, participated in the study. Structured Clinical Interview for DSM-5, Clinician-Administered PTSD Scale, Sociodemographic and Trauma-Related Characteristics Data Form, Life Events Checklist for DSM-5, PTSD Checklist for DSM-5, Depression Anxiety Stress Scale 42, Post-Traumatic Growth Inventory, Stroop Test, Trail Making Test, and Category Fluency Test were used as assessment tools.

Results: According to correlation analyses, weak significant relationships were found between the PTG inventory subdimension of changes in life philosophy and neurocognitive flexibility scores. Statistically significant relationships were found between PTSD and neurocognitive flexibility scores. However, no significant relationship was found between PTSD and PTG. Linear regression analyses revealed a trend between PTG inventory and Category Fluency scores.

Discussion: This study is the first in Turkey to examine the relationship between PTG and neurocognitive flexibility using neuropsychological tests. Including tests that measure neurocognitive flexibility in future studies with a larger sample size could yield more specific and robust findings. Investigating the impact of neurocognitive flexibility is theoretically important for understanding the cognitive variables that affect PTG and can help plan psychological interventions that encompass neurocognitive flexibility. This study was presented as a Poster Presentation at the 21st National Neuroscience Congress.

Key Words: Cognition, Post Traumatic Stress Disorder, Post Traumatic Growth, Psychological Trauma, Traffic Accident

INTRODUCTION

Trauma can be defined as a direct or witnessed exposure to an event that threatens an individual's psychological and physical well-being. It is expected that individuals who experience trauma will manifest emotional, behavioral, and cognitive responses. After trauma, individuals may either return to their previous level of functioning, respond with higher levels of functioning, or exhibit pathological responses resulting from maladaptive modulation of the stress response due to the trauma (1,2). Responses to trauma have been under scrutiny since the time of Herodotus. (3) It was not until after the Vietnam War that Post-Traumatic Stress Disorder (PTSD) was first formally defined in DSM-III, eventually reaching its current definitions in DSM-5 and ICD-11. (4, 5)Following a traumatic experience, disturbances in emotional state and cognitive functions, such as re-experiencing, avoidance of reminders, and physiological responses when confronted with reminders, as well as withdrawal from others, alienation, or other disintegrative reactions, including "depersonalization"

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and "derealization," can occur. These symptoms can disrupt a person's social, occupational, or other important areas of functioning (6). The examination of post-traumatic responses is crucial. It is known that PTSD increases the risk of suicide by 2.8% (7). Many studies have focused on the role of genetics in pathological responses to trauma, demonstrating genetic influences ranging from 30% to 72%, as well as exploring cortisol release, the Hypothalamus-Pituitary-Adrenal (HPA) axis, and the hypothalamus-pituitary-thyroid (HPT) axis (8) . Neurocognitive research has emphasized the modulation of the amygdala and hippocampus, as well as alterations in the ventromedial prefrontal cortex, dorsolateral prefrontal cortex, and anterior cingulate cortex in response to traumatic stress symptom severity. However, while approximately 41-86% of the population experiences at least one traumatic event in their lifetime, a significant portion of individuals can overcome these experiences without developing psychopathological disorders (9-11). To fully understand responses to trauma, it is essential to investigate why some individuals develop pathological responses while others do not, despite experiencing similar traumatic events. It is known that individuals attempt to make meaning of traumatic experiences and may exhibit positive responses such as Post-Traumatic Growth (PTG) during this process (12). PTG has been scientifically studied since the 1990s, primarily focusing on individuals with oncological diseases, war veterans, and survivors of traffic accidents. Studies on PTG have shown a U-shaped curve, indicating that the likelihood of PTG occurring increases within the first 24 months after a traumatic experience and then decreases after this period. PTG consists of five sub-dimensions: changes in self-perception, an increased sense of personal strength, improved interpersonal relationships, the identification of new opportunities, and changes in one's philosophy of life. These changes are believed to occur as individuals cope with the schema disruption caused by trauma (13). Similarly, according to the cognitive schema restructuring model, individuals construct new schemas as their previously held beliefs of a safe world and personal invulnerability are shattered (14). According to Schaefer and Moss' model, PTG develops as individuals actively cope with trauma. In the transformational coping model, individuals may experience both negative changes and the development of PTG (15). Examining the relationship between PTG and PTSD, it is possible for both to co-occur, and the development of PTG may be influenced by the severity of traumatic stress. Symptoms associated with PTSD, such as re-experiencing and rumination, can affect the development of PTG, while avoidance may have a negative impact on it. A meta-analysis of 42 studies showed that initially, PTSD symptom severity had a positive effect on PTG, but when it reached a critical level, the likelihood of PTG decreased (16).Nevertheless, it is essential to understand the relationship between PTG and PTSD completely. Thus, this study investigated whether there is a relationship between PTG levels and a diagnosis of PTSD among individuals who have experienced similar traumatic events. Numerous studies have examined responses to trauma from a neurocognitive perspective, with many of them focusing on neurocognitive flexibility, one of the subcategories of executive functions. Neurocognitive flexibility can be defined as the ability to restructure problem-solving strategies in response to the changing complexity of conditions, and it is evaluated across four main domains (17). Set-Shifting: The ability to redirect attention from one stimulus to another, when necessary, with a focus on dorsolateral prefrontal cortex and fronto-parietal regions. Cued Task Switching: The ability to adapt to changing rules depending on the task at hand, with an impact on the anterior cingulate cortex and putamen regions Cognitive Inhibition: The ability to suppress unwanted responses in line with the task's requirements, with evidence of reduced performance and slowing down indicating a weakness in this ability (18). Reversal Learning: The ability to adapt to the reversal of a previously learned pattern during a task, with a focus on the orbitofrontal cortex and prefrontal cortex (19). Neurocognitive flexibility has a positive relationship with psychological well-being and is negatively associated with various psychiatric disorders such as obsessive-compulsive disorder, anxiety disorders, depression, eating disorders, and schizophrenia (20-24). In trauma-focused studies, individuals with severe PTSD symptoms and low neurocognitive flexibility scores showed significant reductions in symptoms when undergoing neurocognitive therapy (25). However, despite the emphasis on cognitive restructuring in models explaining PTG, there is a

limited body of work that comprehensively examines PTG from a cognitive perspective. The hypothesis of this research is that neurocognitive flexibility may play a role in the formation of post-traumatic growth in trauma survivors and the probability of post-traumatic growth may increase as neurocognitive flexibility increases. Also, the side hypothesis of this research is that whether there is a statistically significant relationship between PTG and PTSD symptoms. Many studies have demonstrated the relationship between PTSD symptoms and neurocognitive flexibility, establishing the link between neurocognitive flexibility and PTG is crucial from a theoretical perspective to understand responses to trauma holistically and from a practical standpoint to design trauma interventions with a focus on enhancing neurocognitive flexibility.

METHOD

Between September 2019 and January 2020, a total of 96 individuals who had sought medical attention at Dokuz Eylül University Faculty of Medicine (DEUFM) Department of Forensic Medicine and DEUFM Psychiatry Outpatient Clinic due to a traffic accident were included in the study, while 9 individuals were excluded from the research. Inclusion criteria were as follows: having experienced a traffic accident, being 18 years of age or older, being literate, and providing informed consent through verbal and written informed consent forms. Exclusion criteria included diagnoses of Intellectual Disability or Autism Spectrum Disorder (ASD), cognitive impairment of a degree that would hinder continued participation in the study, visual or hearing impairment to a degree that would disrupt study participation, participation in any of the neuropsychological tests to be administered within the last 6 months, a major psychiatric diagnosis according to the DSM-5 (such as one of the diagnoses within the Schizophrenia Spectrum and Other Psychotic Disorders, Bipolar and Related Disorders), ongoing alcohol/substance use disorder or dependence as defined in the DSM-5.

For diagnosis, the Structured Clinical Interview for DSM-5 (SCID-5) was used. The "Socio-Demographic Information Form," prepared by the researchers to include variables that could be important for the study and containing comprehensive socio-economic and clinical questions about the research participants, was administered. The researchers completed the "Trauma-Related Characteristics" form to collect information on the details and severity of the traumatic event.

The Clinician-Administered PTSD Scale-5 (CAPS-5) was administered to confirm the diagnosis of PTSD. To gather detailed information about PTSD symptoms, severity, and variables that could affect the study, the DSM-5 PTSD Checklist, Depression Anxiety Stress Scale (DASS-42) were administered. To examine the relationship between Post-Traumatic Growth and Cognitive Flexibility, the Post-Traumatic Growth Inventory along with selected neuropsychological tests from the literature (Stroop Test, Trail Making Test Part A, Trail Making Test Part B, Category Fluency Test) were administered.

Socio-Demographic Information Form: This form, created by the authors based on the literature, aims to control for socio-demographic variables in the analyses. It includes information about the participant such as identification number, interview date, date of birth, gender, marital status, total years of education, per capita income in the household, employment status, and educational status.

Trauma-Related Characteristics Form: This form, created by the authors based on the literature, aims to control for variables related to the accident in the analyses. It includes variables related to the accident such as accident date, presence of loss in the accident, accident-related physical damage, type of vehicle involved in the accident, post-accident operation, post-accident intensive care unit treatment.

Clinical Interviews: Structured Clinical Interview for DSM-5 (SCID-5) Axis I Disorders Validation and reliability studies were conducted by Bayad et al (26) to ensure standardized application of diagnostic assessment.

Clinician-Administered PTSD Scale (CAPS-5) Validation and reliability studies, as well as adaptation to Turkish, were conducted by Boysan et al

(27). The English version was developed based on studies with Vietnam War veterans (28). It is a structured clinical interview form widely used to assess PTSD symptoms and their impact on the patient's social and occupational functionality.

DSM-5 PTSD Checklist (PCL-5): This is a self-report scale assessing PTSD symptoms, with each item scored on a scale from 0 to 4 (29). The validity and reliability study found composite reliability coefficients between 0.79-0.92 for re-experiencing symptoms, 0.73-0.91 for avoidance symptoms, 0.85-0.90 for negative alterations, and 0.81-0.88 for hyperarousal symptoms. The two-week test-retest intra-class correlation coefficients were determined as 0.70, 0.64, 0.78, and 0.76 respectively (29, 30).

Depression Anxiety Stress Scale-42 (DASS-42): DASS-42 is a self-report scale consisting of 42 questions with 4 multiple-choice options each, designed to measure depression, anxiety, and stress levels. Its Turkish validity and reliability were established in 2009, (31-33).

Post-Traumatic Growth Inventory (PTGI): PTGI is a psychological assessment tool that quantifies positive changes experienced by individuals following trauma or life challenges. Comprising 21 items, it evaluates posttraumatic growth across five domains: personal strength, new possibilities, relating to others, spiritual change, and appreciation of life. Participants rate items on a scale (often 0-5), with higher scores indicating greater growth. PTGI has applications in clinical therapy and research, shedding light on how individuals transform after adversity (34). Although the original test evaluates factors based on a 5-factor structure, for the Turkish validity and reliability study, a 3-factor structure was considered more appropriate (35).

Neuropsychological Assessment

Stroop Test: This test measures the ability to process attended and unattended stimuli in parallel, assessing processing speed, automatic process resistance, and the ability to resist the disruptive effects of automatic processes. The validity and reliability of the Turkish version of the Stroop Test have been established (36).

Trail Making Test Part A and B The standardized version of the Trail Making Test for Turkish was conducted by Cangöz et al(35).The test assesses different skills that require executive functions such as motor speed, visual-motor conceptual scanning, planning, numerical knowledge, abstract thinking, set shifting, resistance to response tendency generated by physical properties of the stimulus, concentration, and tolerance to inhibition (37).

Category Fluency Test Participants are asked to name as many animal names as they can within one minute. It evaluates language skills, executive functions, and semantic memory. The Category Fluency Test is evaluated based on total count, clustering, and switching between clusters (38).

Statistical analyses were conducted using IBM SPSS Statistics v. 22.0 software. Variable distributions were tested, and non-normal distributions were transformed using natural logarithm (LN). For binary variables, chi-square independence tests were used, and for parametric measurements testing for significance between (continuous)variables in independent groups, t-tests were applied. Logistic regression analyses were used to analyze changes in significance levels when a variable affecting an independent variable was modeled with other added variables.

Ethics: The University Ethics Committee approved research as number 654 on 08/12/2022.

RESULTS

Out of the participants, 30 (31.3%) were female, 66 (68.8%) were male, 54 (56.3%) were married, and 42 (43.8%) were single. Among them, 49 (51%) were employed and 47 (49%) were unemployed. Among the unemployed participants, 6 (6.3%) described their work environment as comfortable, 18 (18.8%) as normal, and 20 (20.8%) as stressful.

When examining sociodemographic variables between groups, no statistical differences were found regarding age, income, body mass index, and years of education. Among the participants, 43

Table 1. Sociodemographic characteristics of the groups

	PTSD		Control		X^2/df	P
	Mean	SD.	Mean	SD.		
Age(year)	35,68	12,83	34,97	12,27	94	0,675
Income (TL) *	1349,76	1104,44	2010,71	3136,32	94	0,115
Education(year)	10,2	4,5	11,22	4,05	94	0,259

N: Number, %: Percentile, *: minimum wage of this years is: 2020,90 and 2324,71 (Republic of Turkey Official Gazette Number: 30991), TL: Turkish Lira

(45%) received a diagnosis of PTSD, while 53 (55%) did not. The mean age of the participants with PTSD was 35.68, while that of the control group was 34.97. The average monthly per capita income in the PTSD group was 1350 TL, and in the control group, it was 2011 TL. The minimum wage between the study dates was 2021-2325 TL. The mean years of education were 10.2 years in the PTSD group and 11.22 years in the control group. The sociodemographic characteristics of the groups are presented in Table 1.

Twenty-five individuals (26%) had a chronic illness, while 71 (74%) did not have any chronic illness requiring regular medication. 9.4% (n=9) of the participants had a psychiatric disorder diagnosis other than PTSD before the study (1 Major Depressive Disorder, 2 panic disorder, 3 General Anxiety Disorder,2 non-specified), and 90.06% (n=86) did not have any psychiatric disorder diagnosis before the study. 32.3% (n=31) of the participants received expert help (Medication or Psychotherapy for treatment and full recovery before the accident) after the accident, while 67.7% (n=65) did not receive expert help after the accident. None of the participants were diagnosed with ASD or adjustment disorder. 11 (11.5%) participants received a diagnosis of major depressive disorder (MDD). MDD is not included as an exclusion criterion because of its prevalence in trauma. 89.6% (n=86) of the participants experienced invehicle accidents, while 10.4% (n=10) experienced out-of-vehicle accidents. 7 (7.3%) participants experienced loss in the accident. 85 (88.5%) participants sustained physical damage in the accident, while 11 (11.5%) did not sustain any physical damage. 45 (47%) participants underwent surgery after the accident, and 51 (53%) participants did not require any surgery after the accident. 82 (85.4%) participants were admitted to the intensive care unit after the accident. The distribution of Clinical Characteristics and Traumatic Event-Related Characteristics of the Participants is given in Table 2.

Table 2. Distribution of participants' clinical characteristics and characteristics related to the traumatic event

Chronic Illness			Psychiatric Illness			Specialist Support			Major Depressive Disorder		
	N	%		N	%		N	%		N	%
Presence	25	26	Presence	9	9,4	Presence	31	32,3	Presence	85	88,5
Absence	71	74	Absence	87	90,6	Absence	65	67,7	Absence	11	11,5
Sum:	96	100		96	100		96	100		96	100

N: Number, %: Percentile

Post-traumatic growth was analyzed in terms of total scores and changes in self-perception, philosophy of life, and relationships using the PTGI scoring system. No significant differences were found between groups in terms of post-traumatic growth total and subcategory scores (Table 3).

A moderate negative relationship was found between years of education and TMT Part A duration, TMT Part B duration. A moderate negative relationship was found between years of education and Stroop Test (interference duration). A moderate positive relationship was found between age and TMT Part A duration, Stroop Test (interference duration). A weak positive relationship was found between age and Trail Making Test Part B. A weak negative relationship was found between

Table 3. Analysis of PTG in relation to PTSD t-test

PTG PTSD Relation	PTSD N=43	Control N=53	2 (*df*) / t (*df*)	P
Mean Sum of PTGI (SD)	36,65(18,88)	35,69 (25,13)	-0,212/94	0,123
Mean of Self Perception (SD)	19,37(11,64)	19,75(13,86)	0,144/94	0,191
Mean of Life Philosophy (SD)	10,3(5,8)	9,11(7,38)	-0,861/94	0,141
Mean of Relationships with others (SD)	6,97(4,95)	6,83(6,49)	-0,122/94	0,156

SD: Standard Derivative, N: Number, PTGI: Post Traumatic Growth Inventory, PTG: Post Traumatic Growth, PTSD: Post Traumatic Stress Disorder.

Table 4. Correlation analysis of all participants(n=96) demographic characteristics and cognitive flexibility

		P	R	N
Education (Year)	TMT A	0,000	-0,555	96
	TMT B	0,000	-0,492	96
	Stroop Test (Interference Time)	0,000	-0,396	96
Age (Year)	TMT A	0,000	0,527	96
	TMT B	0,003	0,298	96
	Stroop Test (Interference Time)	0,000	0,482	96
Income per Person (TL)	TMT A	0,041	-0,209	96
	TMT B	0,011	-0,260	96

*Pearson s R: Correlation coefficient, N: Number, TL: (Turkish Lira)

monthly per capita income and TMT Part A duration, TMT Part B duration (Table 4).

A weak negative relationship was found between (PTGI)sub-scores of changes in philosophy of life and TMT Part A duration (r=-0.263; p=-0.01). A weak negative relationship was found between (PTGI)sub-scores of changes in philosophy of life and Stroop Test (interference duration) (r=249; p=0.014). A weak positive relationship was found between (PTGI) sub-score of change in philosophy of life and Category Fluency Test total scores (r=0.299; p=0.003) (Table 5).

Table 5. Correlation analysis of PTG inventory scores and cognitive flexibility

		P	R	N
PTGI Life Philosophy	Sum of Categorical fluency Score (Animal Count)	0,003	0,299	96
	TMT A	0,01	-0,263	96
	Stroop Test (Interference Time)	0,014	-0,249	96

*Pearson s R: Correlation coefficient, N: Number

In the logistic regression analysis of (PTGI) total scores for PTSD group, no significant relationship was found. In the first model, only (PTGI)scores were included, in the second model, logistic regression analysis was conducted by modeling (PTGI)scores with age, gender, years of education, and income level. In the third model, logistic regression analysis was conducted by modeling (PTGI)scores with age, gender, years of education, income level, and DASS scores. However, no significant results were obtained in the Total (PTGI), PTSD Logistic Regression Analysis. The same modeling was used for Linear Regression Analyses. No statistically significant relationship was found between total (PTGI)scores and neurocognitive flexibility test scores in Linear Regression Analysis.

In the linear regression analysis of (PTGI)total scores and Category Fluency total scores, no significant relationship was found. However, a trend tendency was observed between (PTGI)and Category Fluency total scores (Table 6) (p= 0.068). Also, PTGI life Philosopy scores and Stroop Interference Scores shows significant relationship. (Table 7) (p=0,015).

DISCUSSION

It is imperative to acknowledge the inherent limitations within this study. Firstly, the cross-sectional nature of the study design precludes the establishment of causality. Longitudinal research is necessitated to explore the temporal relationships between neurocognitive flexibility, trauma, and Post-Traumatic Growth (PTG) over an extended

Table 6. Linear regression analysis of ptgi score and total category fluency test scores.

Linear Regression Analysis	B	P	%95 CI
Model 1	0,758	0,068	-0,057/1,572
Model 2	0,835	0,080	-0,102/1,773
Model 3	0,829	0,085	-0,116/1,774

CI: Confidence Interval
Model 1: Sum of PTGI + Sum of Animal Naming Count
Model 2: Sum of PTGI + Sum of Animal Naming Count + Age + Sex + Education + Income
Model 3: Sum of PTGI + Sum of Animal Naming Count + Age + Sex + Education + Income + Sum of DASS-42 scores

Table 7. Linear regression analysis of PTGI score and stroop interference scores

Linear Regression Analysis	B	P	%95 CI
Model 1	-0,76	0,015	-0,137/-0,015

Dependent Variable: Sum of PTGI Life Philosopy Score
Model 1: Stroop Interference Score

period. Secondly, the study centered around a specific traumatic event (traffic accidents), potentially constraining the generalizability of findings to other traumatic contexts, and the study's small sample size limits the robustness of results. Further research encompassing diverse traumatic experiences is imperative to substantiate the association between neurocognitive flexibility and PTG across varied populations. Thirdly, the reliance on self-report measures may introduce response bias, potentially impacting data accuracy. In summary, this study aspires to contribute theoretically to the understanding of neurocognitive flexibility's role in comprehending post-traumatic growth and practically to clinical interventions by incorporating neurocognitive flexibility into trauma-focused treatments. The core hypothesis posited that individuals with higher levels of neurocognitive flexibility would exhibit higher levels of PTG. Additionally, all traumas experienced by participants prior to their enrollment were recorded, and potential relationships between trauma and neurocognitive flexibility were included in the analyses. Weak, statistically significant positive correlations were identified between neurocognitive flexibility levels and the change in the philosophy of life sub-dimension of PTG. Regression analyses further supported our hypothesis. Although this research is distinctive in its examination of neurocognitive flexibility and PTG in Turkey, the findings alone are not sufficient to establish that neurocognitive flexibility enhances PTG. The research outcomes suggest that increasing the sample size and revisiting the topic with different trauma types may demonstrate the impact of neurocognitive flexibility on PTG more clearly. A meta-analysis conducted in 2019 compared PTG across different trauma types and found that PTG was lowest in the group of individuals who had experienced traffic accidents. Given that all participants in this study had experienced traffic accidents, it is possible that this particular trauma type influenced PTG levels (39). Therefore, future studies could focus on a different type of trauma to address this issue. Another limitation is that neurocognitive flexibility was measured solely through tests like the Trail Making Test, categorical fluency, and Stroop tests. The inclusion of other neurocognitive flexibility measurement tools such as the Tower of London or the Wisconsin Card Sorting Test might yield more specific results. In this study, the relationship between PTSD symptoms and PTG levels was also investigated; however, no statistically significant relationship was found. One of the limitations here is that this research was cross-sectional. Future research with a longitudinal design, considering specific symptoms like avoidance and re-experiencing in separate analyses, may provide more precise insights into the relationship between PTSD and PTG and demonstrate a temporal relationship. Examining the clinical characteristics of the participants, it is worth noting that 11% of them received a diagnosis of Major Depressive Disorder (MDD) according to DSM-5 criteria. In the literature, the comorbidity rate of PTSD and MDD is approximately 25%, making it challenging to exclude individuals with MDD from trauma studies (40). The presence of MDD in 11% of the participants might have negatively affected their cognitive flexibility test performance due to symptoms such as psychomotor retardation and decreased motivation. However, including DASS-42 scores as a control variable in statistical modeling aimed to mitigate these limitations. The finding that neurocognitive flexibility levels positively correlate with changes in the philosophy of life sub-dimension of PTG is believed to be attributed to the fact that increased levels of neurocognitive flexibility lead to changes in one's philosophy of life, consistent with the literature (41). It is believed that similar associations may exist with other sub-dimensions in different types of traumas. Additionally, future research can explore the personalization of treatment and the incorporation of neurocognitive interventions in clinical settings, focusing on the impact of cognitive flexibility on traumatic stress symptoms and levels of PTG.

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Investigation of the relationship between adult attention deficit hyperactivity disorder and reinforcement sensitivity in substance use disorders?

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SUMMARY

Objective: It is known that adult ADHD coexistence is high in patients with substance use disorder (SUD). With the prediction that the Behavioral Activation System (BAS) and Behavioral Inhibition System (BIS), which Gray suggested to underlie motivated behavior, may be effective in these two psychopathological conditions, this study investigated the relationship between BIS/DAS dimensions and ADHD symptoms in substance abusers.

Method: The study included 91 male patients over the age of 18 diagnosed with substance use disorder according to DSM-5 who were admitted to the AMATEM outpatient clinic of Elazığ Mental Health and Diseases Hospital for outpatient treatment and 99 male healthy controls with similar sociodemographic characteristics. Participants were given a form in which sociodemographic and substance use questions were asked and Adult Attention Deficit Hyperactivity Disorder Self-Report Scale (ASRS), Wender-Utah Rating Scale (WURS), Behavioral Inhibition System/Behavioral Activation System Scale (BIS/BAS).

Results: In our study, the prevalence of adult ADHD among substance abusers was found to be 10.1%. When the groups were compared according to the scale scores, a statistically significant difference was found between the individuals with substance use disorder and the control group according to BIS-anxiety, FFFS-fear, WURS scale scores and total ASRS scores.

Discussion: Our findings suggest that in substance abusers, an inhibitory system such as DCDS-fear may not be activated as negative feedback, and they may impulsively turn to substances to cope with increased anxiety, and that substance use in individuals with ADHD may be effective on attention by increasing the sense of pleasure rather than hyperactivity that impulsivity may provide.

Key Words: ADHD, BIS/BAS, Substance use disorder

INTRODUCTION

Substances are chemicals that are taken into the body in various ways, cause changes in perception, mood, cognitive and other brain functions of the individual and may lead to abuse and addiction (1). Substance use disorder (SUD) is a set of behavioural, cognitive and physiological symptoms suggesting that the individual will continue to use one or more substances compulsorily (2). Psychological, sociological and economic dimensions of substance use are important (3,4). Today, the revised fifth version (DSM-5) of the DSM (Diagnostic and Statistical Manual of Mental Disorders) classification system is used. DSM-5 expanded the previously accepted concepts of "Substance Abuse and Dependence" and analysed them under the title of "Substance Use Disorders" (5).

It is reported that a personality predisposed to substance use is important in MDD (6). Gray's

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Reinforcement Sensitivity Theory (RST) is a biologically based personality theory that continues to be accepted today. According to this theory, there are two main motivation systems in the human brain, which Gray hypothesised as Behavioural Activation System (BAS) and Behavioural Inhibition System (BIS). BAS is a behavioural system that includes positive excitement, is sensitive to reward and controls approach behaviour, whereas BIS is a system that includes negative excitement, is sensitive to punishment and controls avoidance behaviour. It is predicted that anxiety and impulsive personality dimensions of RST are related to these two motivational systems. The systems are activated by stimuli that are sensitive to them and this activation is effective on avoidance and approach behaviour (7,8). In the last revision of the RST proposed by Gray, "freezing" sub-dimension was added to the Fight-Flee-Freeze System (FFS) and the Fight-Flee-Freeze System (FFFS) was organised (7). Anxiety is associated with BIS and fear is associated with FFFS. Sensitivity to punishment, which was previously associated with the BIS, was assigned to the FFFS in the revision.

In a study in which BIS/BAS scale scores of substance abusers, alcoholics and healthy control groups were compared, substance abusers had higher BAS scores compared to controls. This higher score was found to be prominent in the BAS impulse and BAS fun-seeking subscales (9).

Attention deficit and hyperactivity disorder (ADHD) is a chronic neurodevelopmental disorder with early onset, which may continue at a high rate in adulthood and is known for the continuity of attention deficit and/or hyperactivity-impulsivity patterns (5,10). The prevalence of ADHD in adults has been found to be 3.4-5% (11). The negative effects of ADHD symptoms that persist from childhood on quality of life, education, working life and social life continue similarly in adulthood (12). ADHD, which is associated with low socioeconomic status and low functionality, is also a serious risk factor for many psychiatric disorders such as personality disorders, MDD and mood disorders (13).

Individuals diagnosed with ADHD are at high risk for MDD in adolescence and adulthood. It is known that ADHD coexistence is high in patients with MDD. In a study, ADHD association was found to be 61-64% in 4936 adolescents with MDD (14). In a study in which people with and without ADHD were compared, it was found that adolescents with ADHD started smoking, alcohol and substance use at an earlier age. In the results of the same study, it was found that the period between the time of starting substance use and the time of substance addiction was shorter and dysfunction was more frequent in these individuals (15).

The aim of this study was to determine the presence and severity of ADHD in individuals with a diagnosis of MDD and to investigate its relationship with the BIS/BAS system and to compare it with individuals without a diagnosis of MDD. We hypothesised that the presence of ADHD may be more frequent and severe in individuals with MDD and that there may be a relationship in BIS/BAS sub-dimensions, especially in individuals with the coexistence of MDD and ADHD.

METHOD

This study was carried out with 99 male patients who were diagnosed with MDD according to DSM-5, who were over 18 years of age and who could read and write to fill in the self-report scales, and 91 male healthy controls with similar sociodemographic characteristics, who were admitted to a Mental Health and Diseases Hospital AMATEM outpatient clinic for outpatient treatment. The diagnosis of substance use disorder was made by a psychiatrist through a clinical interview in accordance with DSM-5. Being younger than 18 years of age, having mental retardation or cognitive deficit, not having sufficient intellectual ability to read and understand the consent form and scales, having a severe general medical condition, having active psychotic symptoms were determined as exclusion criteria. All participants were informed in detail about the study protocol and their written informed consent was obtained. Participants were given a sociodemographic data form including some questions about substance use characteristics, Adult ADHD Self-Report Scale (ASRS), Wender Utah Rating Scale (WURS), and BIS/BAS Scale

prepared by the researchers for this study. The study was conducted in accordance with the Declaration of Helsinki and approved by the local ethics committee of a university hospital (2021/1879).

Sociodemographic data form: The form given to the individuals who participated in the study included questions assessing age, gender, education, grade repetition, occupation, employment status, frequency of job change, total monthly income, presence of disciplinary punishment at school, whether they had problems with the police, whether they had received a traffic ticket, whether they had an accident, whether they smoked and drank alcohol, the type and duration of substance use, and the reason for use. It was prepared by the researchers.

WURS: It was developed to question ADHD symptoms retrospectively and to facilitate the diagnosis of ADHD in adulthood. This scale, which consists of twenty-five items, is a self-report scale with five-point Likert-type scoring. This scale can be scored between 0-100 (16). In the Turkish validity and reliability study, Cronbach's alpha coefficient was determined as 0.93 (17). The cut-off value is taken as 36.

ASRS: It is a scale developed by WHO (18). The questioned symptoms cover the last six-month period. The validity and reliability study was conducted by Doğan et al. (19). In the analysis, Cronbach alpha value of the scale was found to be 0.88. Cronbach's alpha value was 0.82 for attention deficit subscale and 0.78 for hyperactivity/impulsivity.

BIS/BAS Scale: Developed in 1994 by Carver and White, the BIS/BAS scale is a 4-point Likert-type scale.

"1=Fully agree, 2=Somewhat agree, 3=Somewhat disagree, 4=Never agree" and consists of 24 items in total. It was revised to a 5-factor structure model by Yusuf Bilge. Cronbach's alpha coefficients of the scale were reported as "0.74 for BIS-anxiety; 0.55 for BIS-fear; 0.63 for BAS-reward sensitivity; 0.65 for BAS-fun seeking; and 0.73 for BAS-impulse" (20).

Statistical Analysis

The analyses of the data in this study were performed with SPSS (Statistical Program in Social Sciences) 25 programme. The conformity of the data to normal distribution was checked by Kolmogorov Smirnow Test. The significance level (p) was taken as 0.05 for comparison tests. Variables that did not show normal distribution were subjected to nonparametric tests. Comparisons in independent paired groups were analysed by Mann Whitney U test since they did not show normal distribution. Categorical data were analysed with chi-square (x^2) test. Spearman rank correlation coefficient analysis was applied to check the relationships between the scales.

RESULTS

A total of 190 people, 99 patients and 91 healthy people, were included in the study. All of the patient and control groups consisted of male participants. The mean age of the patient group was 23.23 ± 5.66 years and the mean age of the control group was 23.8 ± 1.1 years. There is a statistically significant difference between the patient and control group according to marital status, education level, grade repetition, occupation, employment status, job change, total monthly income, disciplinary penalty, having problems with the police, receiving traffic penalty, whether they had an accident or not and age ($p<0.05$). It was examined whether there was a difference between the groups according to the demographic variables of the participants included in the study and the results are given in Table 1.

The addiction variables of the patients participating in the study are given in Table 2. While smoking and alcohol use were questioned in the patient and control groups, drug use and if any, what it was were questioned only in the patient group. There was a statistically significant difference between the patient and control groups in terms of smoking and alcohol use ($p=0.001$, $p=0.001$).

When the scores were evaluated according to the cut-off value of the Wender Utah scale, a statistically significant difference was found between the

Table 1. Comparison of sociodemographic variables of substance abusers and healthy control group

			Control	Patient	Total	p[a] value
Marital status	Single	n	85	79	164	*0.001**
		%	93.4	79.8	86.3	
	Married	n	6	18	24	
		%	6.6	18.2	12.6	
	Divorced	n	0	2	2	
		%	0	2	1.1	
Education level	Primary School	n	1	14	15	*0.001**
		%	1.1	14.1	7.9	
	Middle School	n	3	43	46	
		%	3.3	43.4	24.2	
	High School	n	3	34	37	
		%	3.3%	34.3%	19.5%	
	University	n	84	8	92	
		%	92.3	8.1	48.4	
Class repetition	Yes	n	12	51	63	*0.001**
		%	13.2	51.5	33.2	
	No	n	79	48	127	
		%	86.8	48.5	66.8	
Monthly income level	No income	n	22	39	61	*0.001**
		%	24.2	39.4	32.1	
	Low income	n	32	13	45	
		%	35.2	13.1	23.7	
	Middle income	n	28	16	44	
		%	30.8	16.2	23.2	
	High income	n	9	31	40	
		%	9.9	31.3	21.1	
Disciplinary action at school	Yes	n	7	51	58	*0.001**
		%	7.7	51.5	30.5	
	No	n	84	48	132	
		%	92.3	48.5	69.5	
Trouble with the police	Yes	n	13	68	81	*0.001**
		%	14.3	68.7	42.6	
	No	n	78	31	109	
		%	85.7	31.3	57.4	
			Control (n_1=91)	Patient (n_2=99)	p[b] Value	
Age	Mean – sd		23,58 – 1,1	23,23 – 5,66	*0.001**	
	M (Min - Max)		24(20-27)	22(18-57)		

n; sample size, %; Percentage, ss; standard deviation, M; Medyan, p[b]; Mann Whitney U test, p value, *p<0,05; there is a statistically significant difference between the groups.

patient and control groups (p=0.001). When the probability of ADHD was evaluated by taking the ASRS cut-off score into consideration, no high ADHD-related scale score was found in the healthy control group, whereas 10 cases (10.1%) in the substance abuse group were found to have high ADHD symptom severity. When classified as probable, highly probable and definite ADHD, ADHD symptom severity distributions in both groups are given in Table.3.

Table 2. Dependency variables

Variable	Group		Group		Total	p value
			Control	Patient		
Smoking	Yes	n	53	84	137	***0.001****
		%	58.2	84,8	72.1	
	No	n	38	15	53	
		%	41.8	15.2	27.9	
Alcohol use	Never	n	62	24	86	***0.001****
		%	68.1	24.2	45.3	
	Rarely	n	20	45	65	
		%	22	45.5	34.2	
	Once or twice a week	n	7	12	19	
		%	7.7	12.1	10	
	Every night	n	2	18	20	
		%	2.2	18.2	10.5	
Substance use	Yes	n	-	96	98	
		%	-	97	85.2	
	No	n	-	3	17	
		%	-	3	14.8	
If yes, what is it?	Cannabis	n	-	52	52	
		%	-	52.5	52	
	Opiate	n	-	31	32	
		%	-	31.3	32	
	Other	n	-	16	16	
		%	-	16.2	16	

n; sample size, %; percentage, p; Chi-square test value ($?^2$), *p<0,05; there is a statistically significant difference between the groups.

When the groups were compared according to BIS-BAS scale and ADHD scale scores, a statistically significant difference was found between the MB and control groups according to BIS-anxiety, BIS-BAS-fear, BAS-impulse, Wender Utah total scores and total ASRS scores (p=0.004, p=0.044, p=0.001, p=0.001, p=0.001 p=0.001 respectively) (Table.4). The substance addicted group accounted for the difference.

Table 3. ASRS and WURS values between groups comparisons

	ADHD	n / %	Control	Patient	p value
ASRS	None	n	44	18	**<0,001***
		%	51.8%	18.2%	
	Possible	n	18	16	
		%	21.2%	16.2%	
	High probability	n	23	55	
		%	27.1%	55.6%	
	Precise	n	0	10	
		%	0.0%	10.1%	
WURS	None	n	59	24	**<0,001***
		%	64.8	24.2	
	Yes	n	32	75	
		%	35.2	75.8	

n; number, %; percentage, *p<0.05; there is a statistically significant difference between the groups.

Table 4. Comparison of groups according to BIS-BAS and ADHD scale scores

	Groups	Mean – sd	M (Min - Max)	p value
BIS-ANXIETY	control	13.69 – 3.33	14(6-19)	0.004*
	patient	15.18 – 3.7	15(5-21)	
FFFS-FEAR	control	4.71 – 1.54	5(2-8)	0.044*
	patient	4.26 – 1.9	4(1-11)	
BAS- AWARD SENSITIVITY	control	16.22 – 3.17	16(1-26)	0.466
	patient	16.29 – 3.21	17(7-20)	
BAS-THE **PURSUIT OF FUN**	control	11.88 – 2.03	12(7-17)	0.068
	patient	12.37 – 2.35	12(5-16)	
BAS- IMPULSE	control	11.44 – 2.35	11(6-16)	0.001*
	patient	12.81 – 2.54	13(5-21)	
Wender Utah	control	30.49 – 17.88	26(0-83)	0.001*
	patient	54.47 – 22.06	54(11-94)	
Total ASRS	control	17.07 – 9.98	16(0-39)	0.001*
	patient	29.02 – 12.79	29(1-54)	

sd; standart deviation, M; medyan, p value; Mann Whitney U test, *p<0,05; there is a statistically significant difference between the groups.

In the correlation analysis, a statistically significant correlation was found between BAS Impulse and total ASRS scores in the substance addicted group (p=0.001) (Table.5).

When the substance addiction group was divided into two groups as ADHD (related symptom severity) + and ADHD (related symptom severity) - and BIS-BAS values were compared by Mann-Whitney U test, a statistically significant difference was found between the two groups only in BAS-impulse values (Table.6).

The correlations between BIS-BAS and ADHD scale values of the healthy control group and ADHD (related symptom severity)+ and ADHD (related symptom severity)- MB groups are shown in Tables 7, 8 and 9.

DISCUSSION

In this study, it was aimed to try to provide an explanation for the mechanism of motivational processes in substance addiction in terms of RST by comparing the presence of ADHD symptoms in childhood and adulthood and BIS/BAS characteristics in people with and without polysubstance abuse.

All of the participants in our study were male patients and the control group was also composed of male participants. When the studies on addiction in the literature were analysed, it was observed that the majority of the participants in the studies were male patients (21,22). The mean age of the patients participating in the study was 23.23 ± 5.66 and this result is one of the important findings of our study. In previous studies, it was reported that 9 out of 10 people with substance abuse or disorder started to use substances before the age of 18. Studies have shown that the risk of becoming addicted individuals until the age of 21 increases approximately 7-fold in people who start using addictive substances before the age of 15 (23). In our study, 43.4% (n=43) of the patient group had secondary school education, whereas 92.3% (n=84) of the control group were university graduates. In another similar study, it was determined that low educational level may be related with substance use (24).

In our study, 39.4% (n=39) of the group with substance use disorder had no regular income. The control group was found to have low and middle income group. In a study conducted by Güneltay (2017) on alcohol and substance addiction, it was found that the income level of the healthy control group was higher than that of people with addiction (25). In another study, low education level, low income status and unemployment of individuals are more common among alcohol and substance addicted individuals (26).

In many studies, it has been proved that there is a link between substance abuse and offending. In a similar study, it was found that the likelihood of committing a crime was 3-4 times higher in drug users than non-users (27). In our study, it was found that 68.7% (n=68) of the patients had problems with the police and 51.5% (n=51) had received disciplinary penalties during their education. Similarly, there are studies reporting a rela-

Table.5 Comparison of BIS-BAS subscale scores according to the presence of ADHD in substance dependence group with Mann Whitney U

	Grup	n	Mean – sd	M (Min-Max)	Test	p
BIS-ANXIETY	ADHD +	11	15.45 – 4.18	17(7-20)	444.500	0.659
	ADHD -	88	15.15 – 3.66	15(5-21)		
FFFS-FEAR	ADHD +	11	4.18 – 1.78	4(2-8)	470.500	0.878
	ADHD -	88	4.27 – 1.93	4(1-11)		
BAS- REWARD SENSITIVITY	ADHD +	11	17.45 – 2.7	19(13-20)	364.000	0.178
	ADHD -	88	16.15 – 3.26	17(7-20)		
BAS- FUN SEEKING	ADHD +	11	13.36 – 2.38	13(10-16)	362.500	0.172
	ADHD -	88	12.25 – 2.34	12(5-16)		
BAS- IMPULS**E**	ADHD +	11	14.18 – 3.82	14(5-21)	*304.500*	***0.044****
	ADHD -	88	12.64 – 2.31	13(7-16)		

Table 6. Distribution of correlations between BIS-BAS scale scores and ADHD scale scores in substance abuse group

		FFFS-FEAR	BAS-REWARD SENSITIVITY	BAS-FUN SEEKING	BAS-IMPULSE	WURS Total Score	Total ASRS
BIS-ANXIETY	r	-0.264**	0.624**	0.264**	0.093	-0.050	-0.074
	p	0.008	0.001*	0.008	0.360	0.626	0.467
FFFS-FEAR	r		-0.224*	-0.190	-0.192	-0.040	-0.100
	p		0.026	0.060	0.057	0.693	0.322
BAS-REWARD SENSITIVITY	r			0.424**	0.275**	-0.094	-0.003
	p			0.001*	0.006	0.352	0.976
BAS-FUN SEEKING	r				0.506**	0.173	0.265**
	p				0.001*	0.087	0.008
BAS- IMPULSE	r					0.193	0.376**
	p					0.056	0.001*
WURS	r						0.703**
	p						0.001*

tionship between substance addiction and having legal problems (28).

In our sample group, the rate of ADHD-related symptoms was found to be 11.1% in the substance abuse group. In the meta-analysis conducted by Rohrer et al (2023), the incidence of ADHD-related symptoms in substance addicts was reported to be 21%. The lower rate in our study may be due to the fact that ADHD was screened with a self-report scale and the cut-off point was kept high. When we include the high probability group, the rate increases to 65.7%.

In our study, personality characteristics of patients with and without a history of substance abuse were analysed in terms of BIS/BAS characteristics and compared with each other. According to the findings of our study, there was a statistically significant difference between the patient and control groups in BIS-anxiety, BIS-fear and BIS-impulse subscales of the BIS/BAS scale, whereas there was no statistically significant difference in BIS-sensitivity to reward and BIS-fun seeking subscales. When we compared the BAS reward sensitivity, fun seeking and impulse subscales scores independently of each other, it was found that the significant difference between the groups was only between the impulse subscales. As a result of this comparison, our prediction was that the group with substance use would score higher in all of the BAS subscales. In accordance with our expectation, although the BAS reward sensitivity and fun seeking scores were higher in the patient group, we attribute the lack of a statistically significant difference to the small size of our sample group and the individual differences of the participants in the patient group. In a study conducted by Mahmoud Aliloo and ParastooAmiri (2014), a significant difference was found between BAS scores in individuals using stimulants (cocaine) and drugs (heroin) (29). In our patient group, the "main substance" used by 52.5% (n=52) of the participants was cannabis. The difference in the substances used by the participants in the patient group may have had an effect on the BAS reward sensitivity subscale.

In our study, statistically significant differences between the patient and control groups in the BIS-anxiety, BIS-anxiety, BIS-anxiety-fear subscales of the BIS/BAS scale were among the findings we expected. As a result of studies conducted on substance addicts in our country, it has been shown that psychiatric disorders are high in this patient group (30,31). Ludman et al. found depression in 79% and anxiety disorder in 76% of alcohol and substance abusers (32). In studies, positive correlations were found between FFS and social anxiety (33), depression (34), and anxiety disorders (35).

Table 7. Correlations between ADHD and BIS-BAS scale scores in healthy control group

		FFFS-FEAR	BAS-REWARD SENSITIVITY	BAS-FUN SEEKING	BAS-IMPULSE	WURS Total Score	ASRS Attention Deficit	ASRS Hyperactivity	Total ASRS
BIS-ANXIETY	r	0.026	**0.415****	**0.214***	**0.362****	0.100	0.108	0.000	0.028
	p	0.814	0.000	0.049	0.001	0.362	0.326	0.997	0.799
FFFS-FEAR	r	1.000	-0.082	-0.102	**-0.327****	0.129	0.086	0.063	0.126
	p	0.000	0.456	0.352	0.002	0.239	0.434	0.566	0.250
BAS-REWARD SENSITIVITY	r	-0.082	1.000	**0.273***	**0.364****	0.029	-0.103	-0.018	-0.096
	p	0.456	0.000	0.011	0.001	0.794	0.350	0.869	0.382
BAS-FUN SEEKING	r	-0.102	**0.273***	1.000	**0.370****	**0.305****	**0.268***	**0.350****	**0.325****
	P	0.352	0.011	0.000	0.000	0.005	0.013	0.001	0.002
BAS- IMPULSE	r	**-0.327****	**0.364****	**0.370****	1.000	0.122	-0.054	0.192	0.056
	p	0.002	0.001	0.000	0.000	0.266	0.625	0.079	0.612

Table 8. Correlations between BIS-BAS scale scores in patients diagnosed with substance dependence without ADHD (score below 45 points)

		FFFS-FEAR	**BAS-REWARD** SENSITIVITY	**BAS-FUN SEEKING**	**BAS-**IMPULS**E**	WURS Total Score	ASRS Attention Deficit	ASRS Hyperactivity	Total ASRS
BIS-ANXIETY	r	**-0.253***	**0.621****	0.179	0.097	-0.058	-0.005	**-0.212***	-0.105
	p	0.018	0.000	0.096	0.370	0.591	0.965	0.047	0.328
FFFS-FEAR	r	1.000	-0.181	-0.153	**-0.265***	-0.017	-0.166	-0.113	-0.134
	p	0.000	0.091	0.155	0.013	0.873	0.123	0.293	0.213
BAS-REWARD SENSITIVITY	r	-0.181	1,000	0.364**	**0.288****	-0.111	-0.075	-0.076	-0.067
	p	0.091	0.000	0.000	0.006	0.305	0.488	0.482	0.535
BAS- FUN SEEKING	r	-0.153	**0.364****	1.000	**0.573****	0.166	0.185	**0.310****	**0.277****
	p	0.155	0.000	0.000	0.000	0.122	0.085	0.003	0.009
BAS- IMPULS**E**	r	**-0.265***	**0.288****	**0.573****	1.000	0.180	**0.214***	**0.371****	**0.337****
	p	0.013	0.006	0.000	0.000	0.094	0.045	0.000	0.001

*p<0,05 there is a relationship between scores.

It was found that ADHD comorbidity was approximately 25% in substance use disorders and the group with comorbidity had more severe psychopathology and severe addiction (36). In our study, ASRS and WURS were given to the patient group to evaluate ADHD in patients diagnosed with substance use disorder. However, it was not aimed to diagnose ADHD with these scales and the severity of symptoms related with ADHD was evaluated. A developmental disorder such as ADHD can be diagnosed by history and semi-structured clinical interview. When the patient and control groups were diagnosed according to the cut-off values of the scales, a statistically significant difference was found between the patient and control groups with the WURS (p=.0.001), while no statistically significant difference was found with the ASRS (p=0.148). However, when WURS and ASRS total scores were evaluated, mean WURS and ASRS scores were statistically higher in the patient group (p=0.001, p=0.001, respectively).

In substance use disorders, it can be predicted that there will be an imbalance in the form of an increase in motivation to use substances and a decrease in behavioural inhibition. In our study, there was no significant difference between the BAS-reward sensitivity and BAS-fun seeking scores in the healthy control group and the substance abuse group, whereas BIS-anxiety and BAS-impulse were higher in the patient group, and BIS-fear was higher in the healthy control group. In the healthy control group and in the substance dependent group without ADHD symptom severity, the positive correlation between BIS-fun seeking, BIS-reward sensitivity, BIS-impulsion, attention deficit, hyperactivity and ASRS scores was similar. These findings suggest that while there was no difference between healthy controls and substance abusers in terms of sensitivity to reward and pleasure seeking, the high BIS-anxiety and BAS-impulse scores suggest that the situation leading to substance use is more related to high anxiety and impulse. In the substance abuse group with low ADHD scores, BIS-anxiety was found to be negatively correlated with BAS-fear and BAS-impulse values were positively correlated with attention deficit, hyperactivity and ASRS scores, suggesting that an inhibitory system such as BAS-fear may not be activated as a negative feedback, and impulsive substance use

Table 9. Correlations between BIS-BAS scale scores in substance abuse patients with ADHD (score 45 points and above)

		FFFS-FEAR	**BAS-REWARD** SENSITIVITY	**BAS-FUN SEEKING**	**BAS-**IMPULS**E**	WURS Total Score	ASRS Attention Deficit	ASRS Hyperactivity	Total ASRS
BIS-ANXIETY	r	-0.314	**0.638***	**0.849****	0.000	-0.172	-0.56	0.245	-0.420
	p	0.347	0.035	0.001	1.000	0.613	0.075	0.468	0.199
FFFS-FEAR	r	1.000	-0.427	-0.457	0.523	-0.284	0.061	-0.128	-0.112
	p	0.000	0.190	0.158	0.099	0.398	0.858	0.708	0.742
BAS-REWARD SENSITIVITY	r	-0.427	1.000	**0.741****	0.150	-0.413	-0.281	0.247	-0.198
	p	0.190	0.000	0.009	0.659	0.206	0.403	0.464	0.560
BAS- FUN SEEKING	r	-0.457	**0.741****	1.000	-0.173	-0.213	**-0.649***	0.259	-0.469
	p	0.158	0.009	0.000	0.611	0.530	0.031	0.443	0.145
BAS- IMPULS**E**	r	0.523	0.150	-0.173	1.000	-0.047	0.346	-0.036	0.133
	p	0.099	0.659	0.611	0.000	0.892	0.297	0.916	0.696

*p<0,05 there is a relationship between scores.

may occur to cope with increased anxiety. The fact that only BAS-impulse scores were significantly higher in the MB group with ADHD (symptom severity) + compared to the ADHD (symptom severity) - group supports this view. The finding of positive correlations between BIS-anxiety and BAS-reward sensitivity, BAS-fun seeking and negative correlations between BAS-fun seeking and attention deficit in the ADHD (symptom severity) + group suggests that fun seeking may be the component of ADHD that reduces attention deficit in substance abusers. The fact that positive correlations related to impulsivity were not observed in this group suggests that substance use in individuals with ADHD may have an effect on attention by increasing the sense of pleasure rather than hyperactivity caused by impulsivity.

Our study has some limitations. The most important of these is that the effect of gender could not be evaluated in the study because female patients were not included in the study. The fact that the substance used by the patients in our substance addiction group was predominantly cannabis also limits the interpretation of the results. Situations in which stimulant substances such as methamphetamine are predominantly used may differ. In addition, the relatively limited sample size is another limitation. Another limitation is the demographic differences between the patient and control groups. The control group had a higher education level than the patient group. In addition, we think that the information about their substance use history was obtained verbally and the evaluation scales used were based on self-report.

Despite these limitations, we think that our study will contribute to the literature by showing the prevalence of ADHD in adult patients with a diagnosis of substance abuse and examining the relationship between this condition and behavioural activation and inhibition system.

As a result, it can be considered that the treatment approach should be different when individuals with substance addiction have ADHD comorbidity. Evaluation of individuals with substance use disorder in terms of ADHD will contribute positively to the treatment process. Longitudinal studies with more participants including both genders in adults with ADHD comorbidity will contribute more to the clarification of this issue.

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Clinical, genetic, and epigenetic markers associated with lithium response in bipolar disorder

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SUMMARY

Bipolar disorder is a chronic and common psychiatric disease that causes poor quality of life and loss of functionality. Although lithium remains in the first place in the acute mania and maintenance treatment of bipolar disorder, its mechanism of action is still unclear. In addition, the response to lithium varies widely among patients. Up to 30-55% of patients with bipolar disorder do not benefit from lithium treatment or experience side effects that cause them to discontinue the treatment. As a result of the studies carried out to date, some clinical variables that predict the difference in lithium response among individuals have been identified, but consistent results have not been obtained. Difficulties in detecting lithium response over clinical variables, lack of consistent peripheral and neuroimaging markers, and familial clustering of the disease and treatment response led researchers to conduct genetic studies. Researchers have primarily focused on candidate gene studies. However, whole genome association studies have begun to be performed due to the inadequacy of candidate gene studies in detecting the lithium response, which is estimated to be polygenic. Data on lithium response and some single nucleotide polymorphisms, noncoding RNAs, and polygenic risk score associations were acquired from these studies. Recently, researchers have been working to elucidate the epigenetic mechanisms involved in gene-environment interaction. In this article, both clinical features and both prominent genetic and epigenetic markers associated with lithium response are reviewed and critical points that should be considered in future research are emphasized.

Key Words: Lithium, bipolar disorder, genetic, epigenetic, biomarker

INTRODUCTION

Bipolar disorder is a chronic disorder characterized by recurrences of depression and mania/hypomania, with patients being almost completely functional between episodes. Although the lifetime prevalence is approximately 1%, this rate has been found to be between 5-7%, especially after the disease was considered as a spectrum in studies conducted since the 2000s. Bipolar disorder has a recurrence rate of up to 90%, more than half of the patients experience a new episode of illness within the first 2 years and the disease has a high heritability rate of around 70% (1).

Following the discovery of the effects of lithium on psychiatric disorders by psychiatrist John Cade in 1949, lithium was approved in the USA for use in manic episodes in 1970 and for maintenance treatment four years later. Today, although the mechanisms of action are not clearly known, glycogen synthase kinase 3, inositol monophosphatase, adenylyl cyclase and G proteins have been identified as the 4 main targets of lithium. In addition, lithium shows indirect effects through many pathways such as antioxidant pathways, DNA methylation processes, production of stress proteins, inhibition of proinflammatory cytokines, lipid peroxidation, mitochondrial functions, remyelination, neuronal differentiation, apoptosis and circadian rhythm. An increasing number of publications have found that bipolar disorder is not only caused by alterations in neurotransmitter levels, but also by

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genetic disruptions affecting synapses and neuronal cycles. Therefore, lithium, which is thought to be effective on intracellular pathways that may control neuronal plasticity and the continuity of cellular life, still maintains its place as the gold standard treatment (2). However, lithium response in bipolar disorder shows significant differences and familial clustering. In this review, it was aimed to review the clinical features related with lithium response and current results related with genetic and epigenetic markers.

Clinical evaluation of lithium response

In lithium treatment, patients are divided into 3 groups: those who have no mood episodes during treatment with lithium (excellent responders), those who have a 50% or more decrease in the number of mood episodes compared to the period before lithium use (partial responders) and those who have less than 50% decrease in the number of mood episodes compared to the period before lithium use, those who have no change in the disease course or those who worsen (non-responders/poor responders) (3). Although lithium is among the first-line drug therapies in the treatment of bipolar disorder, only 30% of patients respond well to lithium and 40% of patients are nonresponsive to treatment and discontinuation of the drug due to side effects. These well-responsive patients are generally patients with a classic pattern of manic-depressive disorder in whom periods of complete remission are observed between periods of illness, who do not have a history of psychiatric comorbidity, who have a family history of frequent bipolar disorder and good response to lithium (2). In addition, in studies conducted to determine the clinical factors that may predict lithium response, predominance of manic episodes, late age of onset, hyperthymic personality characteristics were found to be associated with good response to lithium, whereas predominance of depressive episodes, rapid cyclicity, diagnosis of additional psychiatric illness, history of multiple hospitalizations, cyclothymia, depressive and anxious personality characteristics, cognitive impairment, severity of psychotic symptoms and family history of schizophrenia were found to be associated with poor response to lithium (3).

To date, the ALDA Scale has been used in the majority of studies conducted to evaluate lithium treatment response. This scale includes criterion A, in which the relationship between clinical improvement and treatment is scored between 0-10, and criterion B, in which the number and frequency of disease episodes in the treatment-free period, duration of treatment, compliance and additional treatments are evaluated. The total score is obtained by subtracting the score of criterion B from the score of criterion A. Scores of 7 and above are considered as lithium responders and scores below 7 are considered as lithium non-responders. However, recent studies have yielded results suggesting that the evaluation made especially with criterion B is prone to error (4). It should be kept in mind that possible errors in phenotypic classification may affect the reliability and validity of the findings obtained in genetic studies.

To date, different results have been obtained in studies in terms of clinical characteristics used in the evaluation of response to lithium. The difficulties in determining lithium response based on clinical variables, the lack of consistent peripheral and neuroimaging markers, and the familial clustering of the disease itself and the response to lithium treatment have pushed researchers to conduct genetic studies to evaluate lithium response.

Genetic and epigenetic markers of lithium response

1. Candidate Gene Studies

The first genetic studies for the evaluation of lithium response were conducted on candidate genes affecting neuronal transmission, intracellular signaling, neuroprotection and circadian rhythm, which are thought to be involved in the neurobiology of bipolar disorder and lithium mechanisms of action. There are many candidate genes that have been examined to date for this purpose and the most frequently emphasized genes are presented in Table 1.

The serotonin transporter is a key determinant involved in serotonin inactivation after release at synapses and is involved in the mechanism of action

of many antidepressants. Polymorphisms in the serotonin transporter-linked promoter region (*5-HTTLPR*) activity regulator gene have been associated with both bipolar disorder and major depression. Therefore, evaluations in terms of polymorphisms of this gene were thought to be important in predicting lithium response in bipolar disorder. *5-HTTLPR* contains a deletion/insertion variant leading to a 'short (s)' or 'long (l)' allele. In a clinical study, it was observed that in bipolar patients with prophylactic lithium use for more than 3 years, patients with the l/l variant tended to develop more mood episodes. In the study, it was found that the group with the l/l genotype had an earlier age of onset of disease and higher doses of lithium use in this group, but no statistically significant relationship was found between the difference in genotypes and lithium response (5). In another study, it was found that bipolar patients with s/s genotype showed worse lithium response (6).

In bipolar disorder, dopamine hypoactivity during periods of depression and dopamine hyperactivity during periods of mania are known. The dopaminergic system consists of dopamine receptors, dopamine transporter and destructive enzymes. Within this system, dopamine receptor 1 (*DRD1*) has an important role in prefrontal cortex activity. In a study in which lithium response and *DRD1* gene -48A/G polymorphism were evaluated in

Table 1. Candidate genes frequently studied in lithium treatment response, pathways and findings

Candidate Gen	Effective Pathway	Findings
5HTTLPR	Serotonin transport	Having the L/L genotype is associated with worse response (5), Having S/S genotype was found to be associated with worse response (6).
DRD1	The most common dopamine receptor in the central nervous system, neuronal development and emotional-behavioral processes	In genotyping for -48A/G polymorphism, G/G genotype was observed more frequently in partial and poor responders (7).
DRD2, DRD3, DRD4	Inhibitory-acting dopamine receptors	No relation was found with lithium response (8,9).
COMT	Catecholamine metabolism	Carrying the Val allele instead of the Met allele is associated with better lithium response (10). No association with lithium response (11).
GSK3	Energy metabolism, neuronal development, oxidative stress	Having the T allele was associated with poor response (12,13).
TPH1	Serotonin synthesis	Gene variants are weakly associated with lithium response (5).
INPP1	Phosphoinositol signaling pathway	C973A polymorphism is associated with better response to lithium (15).
BDNF	Neuronal proliferation, synaptic plasticity	Presence of Met allele in Val66Met polymorphism is associated with better response (16). However, there are studies that found no association (17).
XBP1	Regulation of MHC genes and endoplasmic reticulum stress response	Being a carrier of the C allele (-116C/G) is associated with a better response to lithium (49).
CREB1	cAMP pathway	CREB1-1H and CREB1-7H polymorphisms are associated with lithium response (12).
FYN	Cell growth control, ion transport	rs3730353 polymorphism is associated with lithium protective response (49).
TIM CLOCK PER3 ARNTL	Regulating circadian rhythm, cell survival, metabolism and behavior	6 single nucleotide polymorphisms in ARNTL and 3 haplotypes in TIM were associated with better lithium response (19).
MMP9	Endopeptidase acting outside the cell	No association with lithium response (16).
CACNG2	Calcium transport, synaptic response, neuroplasticity	rs22884017, rs2284018, rs5750285 polymorphisms are associated with lithium response (22).
COMT	Catecholamine metabolism	Carrying the Val allele rather than the Met allele is associated with better lithium response (10). No association with lithium response (11).
BCR	Neuronal development	Ser976 allele frequency is higher in lithium non-responders than in responders (50).
REV-ERB-Alfa	Circadian rhythm	Having an allele T for rs2314339 is associated with poor response to lithium (20). Rs2071427 and rs8192440 are associated with better response to lithium treatment (21).
GADL1	Coding of proteins involved in decarboxylation	rs17026688 and rs17026651 polymorphisms are associated with good response to lithium (23).
PDLIM5	Protein kinase C-related neurosignaling	No association was found between PDLIM5 polymorphisms and lithium response (51).

Abbreviations: 5HTTLPR: serotonin transporter-associated promoter region, DRD: dopamine receptor, GSK: glycogen synthase kinase, TPH: tryptophan hydroxylase, INPP: inositol polyphosphate 1 phosphatase, BDNF: Brain-derived neurotrophic factor, XBP: X-Box binding protein, CREB: cAMP-responsive element-binding protein, ARNTL: aryl-hydrocarbon receptor core tranclocator-like protein, MMP: matrix metalloproteinaze, CACNG: calcium channel voltage-dependent gamma subunit, COMT: catechol-o-methyltransferase, BCR: breakpoint cluster protein, GADL: glutamate decarboxylase-like.

bipolar disorder, G/G genotype was found at a lower rate in excellent responders compared to partial responders and non-responders (7). Dopamine receptor 2 (*DRD2*) agonists show antidepressant and antagonists show antimanic effects. Dopamine receptor 4 (*DRD4*) also has similar activities. Therefore, *DRD2* and *DRD4* gene variants were also examined to evaluate lithium response in bipolar disorder, but no significant relationship was found between them and lithium response (8). Dopamine receptor 3 (*DRD3*) acts as both an autoreceptor and a postsynaptic receptor. This receptor is frequently located in the mesolimbic area, shows high affinity for dopamine and regulates the monoamine cycle. Therefore, *DRD3* polymorphisms thought to be related with lithium response were examined, but no relation was found with lithium response (9). Catechol-o-methyltransferase (COMT) enzyme is an enzyme that plays a role in the metabolism of catecholamines. Although there are studies in which no relation was found between COMT polymorphisms and the development of bipolar disorder, the presence of met allele was associated with susceptibility to the disease and rapid cyclicity in some studies. COMT enzyme activity is affected by Val158Met polymorphism. Val/Val genotype is associated with high, Val/Met genotype with moderate and Met/Met genotype with low enzyme activity. In bipolar disorder, Met/Met genotype resulting in low enzyme activity was found more frequently in the lithium non-responsive group (10). However, unlike these data, there are also studies in which no significant relationship was found between lithium response and COMT genotype (11).

Glycogen synthase kinase 3β (GSK-3β) regulates many pathways such as energy metabolism, oxidative stress, neuroplasticity, protein synthesis etc. by inactivating glycogen synthase enzyme. GSK-3β inhibition is one of the main pathways in the mechanism of action of lithium. In studies, having TT genotype in rs334558 and rs6438552 polymorphisms associated with transcriptional power for GSK-3β was associated with worse lithium response than having CC genotype. After statistical adjustments, it was found that this effect persisted only for the rs334558 polymorphism. Having the C allele was found to be associated with lower enzyme activity and having the T allele was found to be associated with stronger transcription of GSK-3β, stronger enzyme activity as a result of hyperphosphorylation and neurodegeneration (12,13). In the first clinical study evaluating the relationship between lithium response and genetic markers in our country, the relationship between 5 different polymorphisms for GSK-3β and lithium response in patients with bipolar disorder was examined and it was observed that only patients with rs17183839 AG genotype had higher lithium response scores determined by ALDA Scale (14).

The other main pathway of action of lithium is the changes it induces through the second messenger system. The enzyme inositol-polyphosphate 1-phosphatase, which is part of the phospholipase C system and involved in dephosphorylation, is encoded by INPP-1. The frequency of having a C to A transversion in this gene region and having the 973A allele is higher in the lithium-responsive group in bipolar disorder compared to the lithium non-responsive group and healthy controls. However, similar results could not be obtained when this study conducted among 23 bipolar disorder patients and 20 healthy controls was repeated in a larger sample (15).

Brain-derived neurotrophic factor *(BDNF*) has important roles in neuronal proliferation and synaptic plasticity processes. It is known that BDNF levels decrease during manic or depressive episodes of bipolar disorder and are similar to healthy controls outside of the episode periods. Having the Val allele for *BDNF* has been associated with many outcomes such as development of bipolar disorder, rapid cycling and better cognitive functions. The presence of Met allele in Val66Met polymorphism in bipolar disorder was found to be associated with better lithium response (16), but there are also studies in which no association was found (17). One of the most striking results of these studies is that simultaneous presence of the s allele for the serotonin transporter *5HTTLPR* and the Val/Val genotype for BDNF was found to be associated with a 70% rate of lithium non-response (18). This seems to point to the geneXgen interaction and the importance of molecular level studies in revealing more mechanisms.

In bipolar disorder, there are irregularities in circadian rhythms, sleep/wake cycles and related hor-

monal systems. Biological rhythms are regulated by clock genes. Lithium is known to prolong the circadian period. Therefore, polymorphisms in circadian locomotor output cycle caput (*CLOCK*), aryl-hydrocarbon receptor core translocator-like (*ARNTL*), timeless circadian clock (*TIM*) and periodic circadian clock (*PER 3*) genes, which are among clock genes related with circadian rhythm, were examined and *ARNTL* and *TIM* polymorphisms were found to be related with lithium response (19).

In a study evaluating lithium response in bipolar disorder, carrying a homozygous C allele at rs 6438552 for GSK-3β and a homozygous A allele at rs2071427 for nuclear receptor subfamily 1 group D member 1 (*NR1D1*), which encodes Rev-Erbα involved in circadian rhythm regulation, was associated with being in the 75% lithium-responsive group. On the contrary, carrying homozygous T allele at rs6438552 and homozygous G allele at rs2071427 was associated with being in the 44% lithium-responsive group (20). Rev-Erbα, which is stable when phosphorylated under normal conditions, becomes dephosphorylated and disintegrates as a result of lithium inhibition of GSK-3β, which phosphorylates it. Having the rs2071427 variant in *NR1D1* results in structurally different Rev-Erbα production. This variant form lacks amino acids, proteins and additional sequences targeted for phosphorylation by GSK-3β. This makes variant Rev-Erbα a poor substrate for GSK-3β and the protein becomes more stable than the full-length form. Thus, this new configuration, which seems to be against the effects of lithium, provides regulatory results for circadian rhythm (21). However, the number of studies examining the relationship between lithium response and circadian rhythm genes in bipolar disorder is very limited.

Recently, the calcium channel γ2 subunit (*CACNG2*) gene has been associated with the development of both schizophrenia and bipolar disorder. The fact that this gene is involved not only in disease development but also in processes such as synaptic response and neuroplasticity has made this gene a candidate gene to be used in the evaluation of lithium response. In a study combining two cohort samples in which post-mortem prefrontal cortex samples of schizophrenia and bipolar disorder patients and control group were examined, it was reported that having C allele and CC genotype for rs2284017 for *CACNG2* in both cohorts, and for rs2284018 and rs5750285 polymorphisms in different cohort groups may be associated with better lithium response (22).

In addition to the candidate genes shown in Table 1, clinical studies have been conducted on many other genes and related polymorphisms. Candidate gene studies have revealed a number of associations between the polymorphism of a particular gene and lithium response. However, the number of candidate genes that have shown significance in more than two studies and whose results can be replicated is very low. With regard to lithium, single nucleotide polymorphisms of a particular gene can each explain a small proportion of the total variance in lithium response, at best around 1%.

2. Genome-Wide Association Studies (GWAS)

Researchers who think that simultaneous evaluation of multiple genes and multiple variants within these genes would be more effective in the examination of lithium response, which is thought to be polygenic, have turned to genome-wide association studies that allow whole genome examination (16). Polygenic analyses are computational methods that help quantify the effects of multiple independent genetic variants across the entire genome on a clinical outcome, especially in diseases with complex genetic features. A successful polygenic model can help detect disease risk at an early stage, confirm the diagnosis, and determine treatment response and disease course.

To date, there are a total of 5 genome-wide association studies on lithium response (23-27). These studies are summarized in Table 2. In GWASs, which were initially conducted in small samples, no single nucleotide polymorphism was able to pass the genome-wide association threshold ($P<5x10^{-8}$). To address this sampling problem, in 2008 a group at the US National Institute of Mental Health (NIMH) interested in the genetics of mood disorders established the International Consortium for Lithium Genetics (ConLiGen). The first results of ConLiGen were published in 2012 and in a sample of more than 1200 patients, the *SLC4A10*

Table 2. Results of genome-wide association studies of lithium response

Study	Sample	Findings	Recommendations
Perlis et al. (2009) (23)	N=458 patients with bipolar disorder type I and type II were included.	No polymorphism crossed the genome-wide association threshold.	Polymorphisms in the GRIA2 gene encoding the glutamate AMPA receptor on chromosome 4q32 have been thought to be associated with lithium response.
Squassina et al. (2011) (24)	N=52 patients with bipolar disorder were included.	No polymorphism crossed the genome-wide association threshold.	Polymorphisms in the ACCN1 gene on chromosome 17q12 have been thought to be associated with lithium response.
Chen et al. (2014) (25)	N=294 bipolar type I patients were included.	The rs17026688 and rs17026651 polymorphisms on the GADL1 gene on chromosome 3p24.1 were associated with good response to lithium.	
Song et al. (2016) (26)	N=3874 patients with bipolar disorder were included. Lithium response was assessed by self-report in 2698 patients and clinically documented in 1176 patients.	No polymorphism crossed the genome-wide association threshold.	The rs116323614 polymorphism in the SESTD1 gene on chromosome 2q31.2 is thought to be associated with lithium response.
Hou et al. (ConLiGen) (2016) (27)	N=2563 patients with bipolar disorder were included.	Four polymorphisms (rs74795342, rs75222709, rs79663003, rs78015114) in 2 lncRNA-encoding regions (AL157359.3 and AL157359.4) on chromosome 21q21.1 were associated with lithium response..	

Abbreviations: AMPA: Alfa amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, GRIA: glutamate ionotropic receptor AMPA type subunit, ACCN: amiloride-sensitive cation neuronal channel, GADL: glutamate decarboxylase-like, SESTD: containing SEC14 and spectrin field, SLC: solute carrier gene.

gene, which encodes solute carrier family 4 of the sodium bicarbonate transporter family, was found to be associated with lithium response. This gene is located on chromosome 2q24 and is highly expressed in the cortex and hippocampus. This bicarbonate-related pathway plays an active role in the intracellular uptake of lithium (28).

In GWASs, the results obtained in only two studies were able to pass the genome-wide association threshold. The first of these studies was conducted by Chen et al. in 2014. In the study, only rs1702688 ($p=5.50 \times 10^{-37}$) and rs17026651 ($p=2.52 \times 10^{-37}$) polymorphisms in glutamate decarboxylase-like protein 1 (*GADL1*) introns on chromosome 3p24.1 were found to be associated with better lithium response. These polymorphisms were found to predict lithium response with a sensitivity of 93% and 86%, respectively, and similar results were obtained in the replicates performed for control. Among these polymorphisms, carrying the T allele for rs1702688 was associated with better lithium response than a different allele. Since the polymorphisms were concentrated on *GADL1*, local variants that may affect *GADL1* gene expression were evaluated in the study and 1 base deletion in *GADL1* intron 8 (IVS8+48delG) was found to be nonrandomly associated with rs17026688 polymorphism. Although the physiological effects of *GADL1* protein are not clearly known, it is thought to have similar effects to glutamate decarboxylase, which plays a key role in the glutamate cycle and γ-aminobutyric acid (GABA) biosynthesis. It has been suggested that these genetic alterations found for *GADL1* associated with lithium response may have effects on both structural and functional changes in excitatory/inhibitory neurotransmitter balance (23). In the GWAS with the largest number of participants conducted by ConLiGen (n=2563), rs79663003 ($p=1.3 \times 10^{-8}$), rs78015114 ($p=1.31 \times 10^{-8}$), rs74795342 ($p=3.31 \times 10^{-9}$) and rs75222709 ($p=3.50 \times 10^{-9}$) polymorphisms were found to be associated with lithium response. These polymorphisms are located in two long non-coding RNA (lncRNA) regions (AL157359.3 and AL157359.4) on chromosome 21 and their effects are not yet known. In the continuation of the study, 73 bipolar disorder patients receiving lithium monotherapy were followed up for 2 years. Lower recurrence

rates were found in patients carrying the polymorphisms and alleles associated with lithium response (27).

Despite all these attempts, in order to detect the effects of genetic variants with small effects in genome-wide association studies, samples ranging from hundreds of thousands to millions of participants are needed. As observed in the study conducted by Chen et al. when the current population was grouped according to ethnicity, the effects of some polymorphisms could be sustained only in certain groups (25).

The largest genomic dataset evaluating lithium response in bipolar disorder, including 47.465 single nucleotide polymorphisms, was analyzed using machine learning methods. In this analysis, which included participants from different regions, overlapping genetic variants associated with lithium response were found in two regions. These variants were most frequently associated with increased expression of postsynaptic membrane genes ankyrin (*ANK3*), *DISC1*, Homer scaffold protein (*HOMER1*), various glutamate and adhesion molecule-related genes, etc.). These genes have important roles in cellular excitation and plasticity. However, lithium response in bipolar disorder could not be predicted as a result of the whole data set analysis (29).

In a recent study, it was found that the schizophrenia polygenic risk score was associated with poor response to lithium in bipolar disorder, as approximately 68% similar genetic variation was found between schizophrenia and bipolar disorder. After the polygenic risk score was calculated, a meta-analysis based on single nucleotide polymorphism was performed within the same study. In this meta-analysis, genome-wide differences exceeding the association threshold were identified in 15 genetic regions. The genetic regions with the highest association were clustered in various human leukocyte antigen (HLA) genes. Two related functional networks were also identified. In these networks, tumor necrosis factor-α (TNF-α), interleukin-4 (IL-4) and interferon-γ (IFN-γ) play an important role in the association with schizophrenia risk and lithium response. This result is thought to explain the findings observed clinically in the past such as i) severity of psychotic symptoms in bipolar disorder being inversely proportional to lithium response, ii) delayed resolution of psychotic symptoms in acute mania being associated with poor lithium response and iii) poorer response to lithium in patients with a family history of schizophrenia rather than bipolar disorder (30).

Since tissue compatibility antigens and inflammatory markers are prominent in lithium response in bipolar disorder, two genome-wide association studies conducted by ConLiGen were reanalyzed in terms of HLA regions. As a result of this study, no HLA variant exceeded the association threshold as a result of Bonferroni corrections. However, in the first study, for *HLA-DRB1*, tyrosine or leucine at position 37, arginine at position 71 and phenylalanine at position 67 were associated with better lithium response. For *HLA-DQB1*, leucine at position 26 was associated with poor lithium response. However, none of these results were replicated in the second study group. Analyzing both studies together identified two signals that almost reached the threshold. *HLA-DQB1*02* heavy chain was associated with lithium unresponsiveness. For *HLA-DRB1*, carrying alanine or leucine at position 74 is associated with better lithium response, while carrying arginine or glutamic acid is associated with poorer lithium response. In the past period, in diseases such as inflammatory polyarthritis, multiple sclerosis, Graves' disease, hepatitis C with different complex genetic mechanisms, associations of changes in similar HLA regions with disease risk, disease course and treatment response have been shown (31).

As with schizophrenia, bipolar disorder is genetically correlated with major depression at a rate of approximately 47%. In a study examining the effect of major depression polygenic risk score on lithium response in bipolar disorder, increased polygenic loading for major depression was associated with poor treatment response in bipolar disorder. In this study, more significant results were obtained in a multi-ethnic and European population. In the Asian group, the association between polygenic risk score for depression and lithium response was closer to borderline significance. This difference is mainly due to the fact that the Asian group had almost 10 times fewer participants in the sample than the European group. However, the polygenic

risk score was previously determined by alleles from the ConLiGen cohort. However, in the present study, the genetic correlation for depression between the East Asian and European groups ranged between 0.33-0.41. Therefore, it has been suggested that the risk score may have underestimated the effect in the Asian group. This study supports the findings that i) patients with good lithium response show a manic episode-dominant disease course, ii) lithium is more successful in preventing manic episodes than depression, and iii) accompanying features of different genetic psychiatric diseases are associated with worse lithium response (32).

A combined polygenic risk score for major depressive disorder and schizophrenia was calculated to assess lithium response in bipolar disorder. The 10% group with the lowest combined score had approximately 2.5 times better lithium response than the 10% group with the highest combined score. In these combined risk score variants, genes associated with metabolic diseases such as histone biology and diabetes were found to be the most common. In addition, no association was found between bipolar disorder polygenic risk score and lithium response. The reason for this has been suggested that polygenic risk scores in schizophrenia and depression are calculated in larger samples (33). Although research on polygenic risk calculation is promising, the success of the polygenic score is related to the strength of initial genome-wide association studies, homogeneity of the population and sample size. The scarcity of previous genome-wide association studies in bipolar disorder, the heterogeneous nature of the disease and the small sample size make it difficult to conduct polygenic research and obtain new data.

3.Epigenetic Markers

Epigenetic alterations are heritable changes in gene expression or cellular phenotype caused by mechanisms independent of DNA nucleotide sequence. Histone modification, DNA methylation, genomic imprinting and regulation mediated by non-coding RNAs are the most important epigenetic mechanisms that cause changes in gene expression due to environmental effects during development. For this reason, studies related to lithium and epigenetic changes in bipolar disorder, which is thought to have polygenic multifactorial inheritance, have started to be conducted in the last 5 years.

Studies examining methylation changes in bipolar disorder patients using lithium have mostly focused on global DNA methylation changes. In a study evaluating global methylation changes, lower global methylation rates were found in bipolar disorder patients using antipsychotic drugs compared to patients treated with mood stabilizers. In another study evaluating global methylation, decreased methylation was found in patients using lithium monotherapy compared to patients using lithium-valproic acid combination and healthy controls. However, no relationship was found between lithium response and global methylation levels. Consistent and reproducible definitive results could not be obtained in studies conducted in small samples. There are single gene studies reporting methylation changes in BDNF promoter region, prodynorphin (*PDYN*) promoter region and two *ARNTL* CpG islands in bipolar disorder patients with lithium use. Generally, lower methylation rates were observed in BDNF and *PDYN* promoter regions in patients using lithium (34).

There are two genome-wide studies analyzing the relationship between lithium and methylation changes in bipolar disorder. In the first one, patients with bipolar disorder exposed to different psychotropic drugs were analyzed in terms of methylation changes. At the end of the study, it was found that valproic acid and quetiapine caused methylation changes, but no such effect was observed in lithium (35). The second study was the first genome-wide analysis of the relationship between lithium response and methylation changes in patients with bipolar disorder. In this study, 15 patients diagnosed with bipolar disorder type 1 with good lithium response and 11 patients diagnosed with bipolar disorder type 1 without lithium response were included. At the end of the study, 111 different methylation sites were found between the two groups, only 7 of which were statistically significant. 17% of these changes distributed on 14 different chromosomes were in the promoter region, 39% in the intergenic region, 11% in the exonic region, 27% in the intronic region and 6% in

the non-coding region. Three of these 7 regions with different methylation changes were found to be associated with defined genes such as eukaryotic translation initiation factor 2B epsilon subunit (*EIF2B5*) and Ral GTPase activating protein catalytic alpha 1 subunit (*RALGAPA1*) (36).

Micro RNAs (miRNAs) constitute a subclass of non-coding RNAs. These short RNA molecules function specifically as post-transcriptional regulators. Previous studies have found that miRNAs are associated with complex diseases such as cancer, psoriasis and treatment response. In addition, miRNAs are also involved in synaptic plasticity and brain development. In a genome-wide association study for bipolar disorder, 9 miRNAs were associated with the development of bipolar disorder. These 9 candidate miRNAs were also analyzed for their association with lithium response in bipolar disorder and only miR-499a was found to be associated with lithium response. In the same study, other genome-wide miRNAs were analyzed and 15 miRNAs were found to be associated with different phenotypes in terms of lithium response, but after multiple testing corrections, no significant association was observed in any of them, including miR-499a. Although not statistically significant, the strongest associations with lithium response were found between miR-633 and miR-607 (37). Recent studies have shown that miR-499 targets the voltage-dependent L-type calcium channel subunit beta-2 (*CACNB2*), which is thought to play an important role in the development of bipolar disorder. *CACNB2* is the regulatory subunit of these calcium channels and is involved in depolarization-related calcium entry into neurons. miR-499a deficiency was thought to be associated with increased *CACNB2* and increased intracellular calcium levels. In another study in which postmortem examinations were performed, expression changes were found for miR-499a in patients with bipolar disorder (38). miR-633 and miR-607 have more limited information in the literature. miR-633 deletion has been shown to play a role in the development of lupus by activating the AKT/mTOR pathway in lupus. The AKT family ranks high in candidate gene research for the development of bipolar disorder and schizophrenia. One of the proteins with a key role in this pathway is phosphotidylinositol-3-kinase (PI3K), which is involved in cell survival, proliferation, protein synthesis and vesicle transport. PI3K activates AKT, and activation of the pathway signals the release or inhibition of many molecules such as insulin, glucose, cytokines and growth factors. The AKT/mTOR-related risk locus has shown stronger overlaps in schizophrenia and bipolar disorder with psychosis (39). In chronic lymphocytic leukemia, if miR-607 accessibility is blocked, activation of the WNT/β-Catenin pathway was found and miR-607 was thought to suppress the progression of this cancer type. In the inactive WNT/β-Catenin pathway, β-Catenin is bound to a complex including GSK-3β, which has an important role in the mechanisms of action of lithium, and the intracellular stabilization of β-Catenin is regulated by this complex (40). Therefore, miR-607, which is thought to have an effect on this basic mechanism mediated by GSK-3β, may play an important role in predicting lithium response in bipolar disorder. In a recent study conducted in our country, the relationship of 13 miRNAs including miR-499, miR-607 and miR-633 with lithium response was examined in 66 euthymic bipolar disorder patients with lithium use and 66 healthy controls, but no statistically significant results were obtained. In the same study, a decrease in miR-155-5p levels was found in bipolar disorder patients compared to healthy controls (41).

In the first genome-wide association study using next-generation sequencing in lymphoblastoid cell lines, 12 lithium-responsive and 12 lithium non-responsive patient samples were analyzed. As a result of the examinations, changes in miR-320a and miR-155-3p expression were detected. A decrease in miR-320a expression, which is involved in neuronal differentiation, apoptosis and synaptic plasticity processes, and an increase in the expression of calpain small subunit 1 (CAPNS1) and ribosomal protein S16 (RSG16) genes involved in circadian rhythm were observed. CAPNS1 has regulatory functions for neuroprotective calpain-1 and neurodegenerative calpain-2. There is no research on CAPNS1 in bipolar disorder yet. RSG16 is involved in the circadian regulation of cyclic AMP (cAMP) in the suprachiasmatic nucleus (42). Circadian rhythm irregularities are known to predict relapses in bipolar disorder. There are different results regarding the role of miR-155 in the inflammatory response. Some studies suggest that miR-155 suppresses the inflammatory response through negative feedback (43), while others suggest that it has

a proinflammatory role through activation of the interleukin-1 pathway (44). SP4 is a transcription factor and is involved in many complex neuronal processes such as dendritic development, hippocampal long-term potentiation, memory, etc. There are studies suggesting that SP4 gene has a role in both bipolar disorder and schizophrenia predisposition (45). SP4 degradation in neurons by calcium-activating proteases in response to glutamate-induced cytotoxicity has been demonstrated. Calcium-dependent regulation and recent post-translational modifications leading to ubiquitin-dependent degradation are key pathways for SP4 stabilization in neurons. Non-depolarization of the membrane and inhibition of N-methyl-D-aspartate receptor (NMDA)-related signaling increase SP4 phosphorylation and accelerate SP4 degradation. In a postmortem study of bipolar disorder patients and controls, most (80%) of whom died by suicide, decreased SP4 levels were found in the cerebellum and prefrontal cortex of bipolar disorder patients. In addition, a decrease in SP4 mRNA levels was observed in the prefrontal cortex, but not in the cerebellum. Therefore, when all results were analyzed, it was thought that decreased SP4 levels in the cerebellum may be related to posttranscriptional reasons. In the later part of the study, neurons were treated with lithium under non-depolarized conditions and it was shown that lithium prolonged SP4 half-life and partially stabilized SP4 which would be rapidly degraded by ubiquitin proteasome complex. No similar effect was observed when neurons were treated with 3 specific GSK-3 inhibitors other than lithium. This effect observed under in vitro conditions and at doses higher than therapeutic doses limits the generalizability of the results (46). Postmortem examinations showed that SP4 S770 phosphorylation increased in the cerebellum of patients with bipolar disorder and severe schizophrenia who died with suicide attempt. In addition, in this study, a decrease in SP4 levels and an increase in SP4 phosphorylation in the prefrontal cortex and cerebellum were found independent of the disease course. Increased phosphorylated SP4/SP4 ratio in the cerebellum was correlated with more severe negative symptoms in schizophrenia patients (47).

The results of the first study in which transcriptomic data sets obtained from lymphoblastoid cell lines were used to evaluate lithium response in bipolar disorder were published in 2023. This study included 9 lithium-responsive and 10 lithium non-responsive bipolar disorder patients and 10 healthy controls. The study was strengthened by adding the results of 12 lithium-responsive and 12 lithium non-responsive bipolar disorder patients from another cohort study. RNA sequencing and machine learning methods were used to identify differentially expressed genes. Increased expression of genes related to immunoglobulin light and heavy chain regions was observed in the lithium non-responsive group compared to the lithium-responsive group. Unlike immunoglobulin genes, the expression of HLA-U, zinc finger protein 300 (*ZNF300*) and T cell receptor-associated transmembrane adaptor 1 (*TRAT1*) genes decreased in the lithium-responsive group. These genes are associated with major histocompatibility complex (MHC) and neurodevelopment. In addition, interleukin-18 (IL-18) was suppressed in the lithium non-responsive group. Proinflammatory IL-18 is known to be involved in neuroinflammation processes. When the results obtained from this study were compared with the results of previous GWAS, it was seen that there were commonalities with a total of 5 studies in terms of one or two differently expressed gene regions. Regulator of synaptic membrane exocytosis 1 (*RIMS1*) and *BCL11B* were reported as the most common genes. Previous studies have shown changes in *RIMS1* expression in schizophrenia and autism. *BCL11B* is known to be involved in neuronal cycles and to have immunologic functions (48).

Working on lymphoblastoid cell lines is more economical than working with induced pluripotent stem cells and provides convenience in terms of standardization and sampling. However, the possibility that these changes detected in the periphery may not reflect the effects in the brain and the small sample size are the most important limitations of the studies (37). The miRNA analyses are still in their infancy because there is no miRNA database for all normal tissues, tissue-specific miRNAs cannot be studied, and perhaps miRNAs that are expressed at the onset of the disease but whose effect on drug response is still ongoing may be ignored. However, the results obtained so far suggest that miRNAs may have effects on the

development of bipolar disorder, the course of the disease and lithium treatment response.

The results of studies conducted to predict response to lithium, the gold standard treatment for bipolar disorder, are currently not very reproducible and generalizable. Differences in the methods used in the evaluation of clinical response to lithium in the studies, the absence of evaluations for subthreshold symptoms, whether the patients were under monotherapy for lithium, the relationship between lifetime lithium levels and lithium response, which mood episodes lithium inhibits more, ignoring the effect of life events on the process, not including patients whose lithium treatment was terminated in the past due to side effects but who had good lithium response, etc. It was thought that factors may be the reason for the inconsistencies in the results. However, the results obtained from the studies conducted to date make some pathways candidates for detailed investigations. Recently, multiomics approaches have been tried in pluripotent stem cell lines to evaluate lithium response in bipolar disorder. In order to better predict lithium response in the future and to create personalized treatment methods, genetic and epigenetic studies to be conducted in large samples, in well-defined bipolar disorder groups and with advanced techniques are needed. It is thought that the data to be obtained from such studies may help to better understand the etiology of bipolar disorder, which is a chronic disease, and to predict the treatment responses of patients more easily. Personalized treatments may increase the likelihood of patients recovering in a shorter period of time by experiencing fewer side effects with less amount and appropriate medication. Thus, patients' medication adherence may increase, and the ability to identify the drug that may be more effective in preventive treatment may reduce the frequency of attacks. It is thought that all these gains may contribute to alleviating the disease burden of bipolar disorder, which can lead to serious functional losses and death.

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