TURKISH JOURNAL OF CLINICAL PSYCHIATRY

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ISSN 1302-0099 / e-ISSN 2146-7153

Turkish Journal of Clinical OSVCDIATY www.klinikpsikiyatri.org



Year: 2023 Volume: 26

Number 4



www.klinikpsikiyatri.org

ISSN: 1302-0099 e ISSN: 2146-7153

Year: 2023 Volume:26 Number:4

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ISSN: 1302-0099 e ISSN: 2146-7153

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Lived experience in research and publishing

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Lived experience encompasses the unique personal perspectives and encounters individuals have based on their own lives, including various situations, challenges, and conditions. In the context of mental health, lived experience involves an individual's journey with mental health and illness, including the process of recovery, as well as the experiences of those close to them. Active participation from individuals with lived experiences, including individuals with psychiatric disorders and their close acquaintances, is essential for psychiatric research. However, traditionally, their involvement has been restricted to the clinical patient recruitment phase of trials. Recently, there has been a growing emphasis on integrating lived experiences across various facets of mental health research.

Engagement of individuals with lived experience goes beyond merely participating in clinical studies as study subjects. It involves activities such as making plans, finding financial support, and validating the accuracy of data. As a pioneering initiative in this innovative approach, INVOLVE was established in 1996 and is part of, and funded by, the National Institute for Health Research to support active public involvement in healthcare and research (1). Canada's Strategy for Patient-Oriented Research (SPOR), initiated in 2009, places patients and their families at the center of health research (2). In the United States, the Patient-Centered Outcomes Research Institute (PCORI), founded in 2010, actively engages patients and various stakeholders in all aspects of research ensuring that studies funded by PCORI specifically address questions most relevant to patients and are crafted with their input (3). Consequently, a substantial amount of literature

demonstrates that genuinely involving individuals with lived experiences can enhance the quality and efficiency of health research. This shift marks a fresh approach, redefining the role of individuals with lived experience from being research subjects to actively contributing members of the research team. With guidance from lived experiences, there is potential to approach research in a more inclusive, collaborative, and patient-centered manner.

An increasing number of funding organizations now compensate reviewers with lived experience. Recommendations and guidelines are now available, outlining how to incorporate and provide educational support for individuals based on their lived experiences (4,5). This practice ensures that study ideas and research proposals resonate with individuals who have personally experienced or witnessed the illness under investigation. PCORI involves patients, caregivers, advocates, alongside stakeholders and scientists in the peer review process for final research reports 3. In the mental health context, the federal agency Substance Abuse and Mental Health Services Administration emphasizes that individuals with lived experience and/or their family members should actively participate in the design and implementation of all data and program evaluation activities (6). European funding organizations dedicated to neuroscience and mental health research also rely on the insights of reviewers with lived experiences associated with mental health (7,8). These reviewers evaluate elements such as patient engagement, feasibility, and the overall relevance of research proposals. This engagement not only enhances the quality and relevance of research but also promotes patient-centered care, empowering individuals to take an

DOI: 10.5505/kpd.2023.43778

Cite this article as: Ceylan D. Lived experience in research and publishing. Turkish J Clin Psych 2023; 26: 235-237

The arrival date of article:13.12.2023, Acceptance date publication: 15.12.2023

Turkish J Clinical Psychiatry 2023;26:235-237

active role in managing their health.

Active involvement of individuals with lived experiences in mental health research also involves roles in academic publishing. Several academic journals, such as the Lancet Psychiatry (9), Schizophrenia Bulletin (10,11), publish narratives that draw from lived experiences. Notably, these narratives may also feature insights from mental health care providers who themselves have lived experiences, providing a unique and valuable perspective within the academic discourse (12). Moreover, individuals with lived experience have been taking on leading or coauthoring roles in scholarly publications and participating in the peer review process for academic journals. As an innovative journal, BMJ journals have been publishing Research Involvement and Engagement for almost 10 years. This journal ensures that each article undergoes review by a minimum of two academic reviewers and two patient reviewers, with both types of reviews carrying equal weight in the editorial decision-making process (13). In 2017, Research Involvement and Engagement, in collaboration with The BMJ, conducted an investigation into the thoughts and motivations of patients who participated in peer review for these two journals (14). Recently, Lancet Psychiatry has started lived experience peer-review . Lived experience is also incorporated into the International Advisory Board of Lancet Psychiatry, where board members provide advice on the journal's subject matter, academic content, geographical considerations, and lived experience on an ad hoc basis, responding to requests from the editorial team (15).

Integrating lived experiences into the peer-review process has the potential to bring about significant changes in both mental health publishing and research. This approach involves using plain language and concepts that are more accessible and less specific to services. Consequently, this shift makes research more acceptable to a broader range of service users, enlarging the pool of readers and increasing the likelihood that individuals with mental health experiences can comprehend and engage in mental health research. Of utmost importance, researchers stand to gain more effective insights by adopting a non-stigmatized language with the help of reviews from individuals with lived experiences . Academic journals that have embraced patient peer review early on are already committed to prioritizing person-centered language in publicly available abstracts and emphasizing translational and practical research.

When considering the context of Turkey, research funding organizations, such as the Scientific and Technological Research Institution of Turkey (TUBITAK) and Health Institutes of Turkey (TUSEB), and mental health journals can gain valuable insights from lived experiences. Health literacy and language may present challenges for such initiatives in Turkey. Several circumstances in Turkey, such as economic shortages and limited funding, create challenges in research and publishing. On the flip side, there are noteworthy resources, including an experienced psychiatry community and well-developed academic journals. More importantly, the presence of advocacy organizations, including individuals with lived experiences such as the Schizophrenia Associations Confederation, Lithium Association, and Bipolar Life Association, holds future potential for providing a considerable source for this perspective. This novel viewpoint has the potential to enhance research and publishing processes in our country, leading to a restructuring of the research culture and the utilization of resources in accordance with genuine needs.

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Investigation of the effects of antidepressant treatment on hippocampus and hypothalamus endoplasmic reticulum stress in chronic mild stress induced depression in rats

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SUMMARY

Objective: This study aimed to examine the role of endoplasmic reticulum (ER) stress in the pathophysiology of depression in female rats exposed to the chronic mild stress model.

Method: Chronic mild stress model was constituted in 48 female adult rats were and divided into 4 groups as control, depression, depression+1 mg/kg sertraline, and depression+10 mg/kg sertraline. Subcutaneous drug infusions were performed for 14 days using osmotic minipumps. Expression levels of genes in ER stress pathway were evalulated in hypothalamus and hippocampus tissues of rats.

Results: It was found that ATF4 gene expression increased in depression in the hippocampus and decreased with treatment. Hippocampal GRP78 gene expression was downregulated after treatment. Hypothalamic and hippocampal CALR gene expression decreased with treatment, hypothalamic HSP47 gene expression decreased in both treatment groups. Hypothalamic and hippocampal XPB1 gene expression decreased with treatment, hippocampal XPB1 gene expression was further downregulated in the depression +10 mg/kg sertraline group compared to the depression+1 mg/kg sertraline group.

Discussion: These findings show that the ER stress mechanism may have a role in the pathophysiology of depression and that this mechanism can be reversed with treatment. The results of our study have been encouraging for human studies and open the way for new projects to understand and accelerate the antidepressant effect.

noradrenergic systems.

Key Words: Major Depression, Endoplasmic Reticulum, Chronic Mild Stress Model, Sertraline, Gene Expression

INTRODUCTION

Depression is a syndrome characterized by profound sadness, sometimes both sad and anxious mood, slowness and stagnation in thought, speech, psychomotor and psychophysiological processes, feeling worthless and powerless, loss of desire, and thinking of hopelessness (1). In the international comorbidity study, the lifetime prevalence of major depressive disorder was 12.7% in men, 21.3% in women, and 17.1% in total (2). Antidepressants are thought to act by modulating the serotonergic and The endoplasmic reticulum (ER) is a crucial organelle required for processes such as regulation of protein synthesis, modification and folding of proteins, synthesis and distribution of phospholipids and steroids, and calcium balance in the cell endomembrane system of eukaryotic cells. When stress occurs inside the cell (oxidative stress, imbalance in calcium level, etc.), a dysfunction occurs in the endoplasmic reticulum. This situation causes the accumulation of misfolded proteins in the

DOI: 10.5505/kpd.2023.43410

Cite this article as: Karaagac M, Ak M, Kurar E, Uguz F, Kutlu S. Investigation of the effects of antidepressant treatment on hippocampus and hypothalamus endoplasmic reticulum stress in chronic mild stress induced depression in rats . Turkish J Clin Psych 2023; 26: 238-247

The arrival date of article: 12.05.2023, Acceptance date publication: 04.08.2023

Turkish J Clinical Psychiatry 2023;26:238-247

extracellular space, causing ER stress (3).

Sertraline, a selective serotonin reuptake inhibitor (SSRI) class antidepressant, is one of the most prescribed psychiatric drugs. Studies in liver tissue have shown that sertraline causes changes in mitochondria and ER functions. Sertraline is thought to have an antidepressant effect by replicating these changes in some brain parts (4).

Recent data suggest that endoplasmic reticulum (ER) stress is involved in the pathophysiology of depression. This increased stress is thought to be reduced by antidepressant treatment, and there is evidence that the underlying mechanism is related to ER stress (5). Evalulation of mRNA level ER stress gene expressions including CALR (calreticulin), GRP78 (HSPA5; heat shock protein family A member 5), CHOP (DDIT3; DNA Damage Inducible Transcript 3), ATF4 (activating transcription factor 4), ATF6, PERK (PKR-like Endoplasmic Reticulum Kinase), eIF2a (Eukaryotic Translation Initiating factor 2a), IRE1 (inositol-requiring enzyme 1), HSP47 (Heat shock protein 47)and XBP-1(x Box Binding Protein) will help to understand this pathway.

This study hypothesizes that the expression levels of ER stress genes increased in rat chronic mild stress (CMS) model and sertralin treatment reduces this elevated ER stress. This study aimed to illuminate the effect of ER stress on the pathophysiology of depression and the development of drugs that act directly on ER stress to overcome the inadequate or delayed response to treatment observed in current treatments. Rat CMS model was constituted and effects of antidepresan treatment was tested. CMS model is accepted as golden standart and widely used to study pathophysiology of human depression.

METHOD

Animal material

This study was carried out with the approval of the Ethics Committee of Necmettin Erbakan University KONUDAM Experimental Medicine Application and Research Center dated 16.01.2020 and numbered 2020-011. Our study was conducted at Necmettin Erbakan University, KONUDAM Experimental Medicine Application and Research Center. A total of 48 female adult rats were and divided into 4 groups as control (n=12), depression (n=12) Depression + 1 mg/kg sertraline group (n=12) and depression + 10 mg/kg sertraline (n=12) groups.

Chronic Mild Stress (CMS) model

Depression was induced by applying the Chronic Mild Stress (CMS) model to adult female rats. Our work consisted of 2 stages. In the first stage, the CMS protocol applied to the animals in the depression groups is summarized in Table 1. Wet cage application was carried out by wetting 333 g of sawdust in a cage with 1.5 liters of water. For the tilted cage procedure, the cages are tilted 60 degrees so that the food portion of the cage is up. Noise stress was developed (approximately 60 dB) with the help of a bell ringing once every 10 seconds for 1 second. Swimming stress was performed by swimming the rats for 10 minutes in the cylinders. Restraint stress was accomplished by physical restraint in restraint apparatuses. For starvation stress, the foods were removed from 16:00 to 09:00 the next day (thus establishing a 17-hour fasting period). Restraint and swimming were not applied for one week after the placement of the osmotic pumps to allow the back area of the animals to recover. Forced swim test (5 min) was applied on the 8th day of the study. (Table-1).

Forced Swim Test (FST)

The transparent plexiglass cylinder on which the test was carried out is 49 cm high and 19 cm in diameter. For the experiment, the cylinder was filled up to 30 cm with water at approximately $25 \pm 1^{\circ}$ C. When the animals were relocated, the water was also replenished. The rats were allowed to swim for 15 minutes on the first day, dried with a towel in the drying cage, and then placed back in their cages. The next day, the rats were placed into the water for the forced swimming test for 300 seconds (5 minutes) and recorded with a video camera. Recordings were scored as swimming, clim-

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| 2 | 09.00 | | Wet cag | e | | 7 hour | - | - | | |
| 3 | 09.00 | Restra nt | 45 min | 12.00 | Sw m | 10 min | 16.00 | Starvat on | All | |
| 4 | 09.00 | No se | 4 hour | 14.00 | Restra nt | 45 min | - | - | | |
| 5 | 09.00 | Sw m | 10 min | - | - | - | 16.00 | T lted cage | All | |
| 6 | 09.00 | No se | 4 hour | - | - | - | 16.00 | L ght on | All | |
| 7 | 09.00 | Restra nt | 45 min | 13.00 | Fst tra n ng | 15 min | - | - | | |
| 8 | 09.00 | Open f eld test | - | 12.00 | Fst | Placer | cement of osmotic mini-pumps | | | |
| 9 | 09.00 | No se | 4 hour | 16.00 | L ght on | All n ght | - | - | | |
| 10 | 09.00 | Starvat on | | | T lted cage | | - | - | | |
| 11 | 09.00 | Wet cage | 7 hour | | - | - | - | - | | |
| 12 | 10.00 | No se | 4 hour | | T lted cage | All n ght | | | | |
| 13 | 09.00 | Wet cage | 7 hour | | | | - | - | | |
| 14 | 09.00 | Restra nt | 45 min | | | | 16.00 | Starvat on | All | |
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| 16 | 09.00 | Restra nt | 45 min | 12.00 | No se | 4 hour | - | - | | |
| 17 | 09.00 | Wet cage | 7 hour | 16.00 | - | - | - | - | | |
| 18 | 09.00 | Restra nt | 45 min | 12.00 | Sw m | 10 min | 16.00 | Starvat on | All | |
| 19 | 09.00 | No se | 4 hour | 14.00 | Restra nt | 45 min | - | - | | |
| 20 | 09.00 | Sw m | 10 min | 16.00 | T lted cage | All n ght | - | - | | |
| 21 | 09.00 | Restra nt | 45 min | 13.00 | Fst tra n ng | - | - | - | | |

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bing, and immobilization at 5-second intervals with the program's use.

Implantation of Osmotic Mini-Pumps and Drug Infussion

Adult female rats were given two different doses of sertraline (1 mg/kg or 10 mg/kg) or DMSO as a carrier for 14 days. After administration of FST, unique osmotic pumps (Alzet 2ML2) that can infuse 5 μ l/hour were implanted in all animals. Sertraline was dissolved with DMSO to a total volume of 2 ml. Anesthesia was induced by administering xylazine/ketamine (8/75 mg/kg, intramuscularly). Under mild anesthesia, the upper side of the two scapula bones of the rats was shaved and cleaned with iodine solution. Then, with a longitudinal incision, osmotic pumps kept in saline were carefully implanted under the skin, and the incision area was sutured. After cleaning the area with the iodized solution, 2 ml of saline was injected subcutaneously into the animals for postoperative care, minimizing the fluid loss during anesthesia. Afterward, the dryness of the cornea was prevented by dripping saline into the eyes of the rats placed in the resting cages. After two weeks of sertraline and DMSO infusion, behavioral changes in rats were determined by FST.

Depressive behaviors were evaluated with the parameters of immobilization frequency (number of immobilization in 5 minutes), immobilization time, and percentage of movement.

In the second stage, all animals were decapitated

under light sedation after FST was administered on the 22nd day, and plasma and serum samples were collected. After rapid removal of the brain tissues of the animals, the hippocampus and hypothalamus regions were dissected and immediately frozen in liquid nitrogen and stored at -80 °C for gene expression analysis.

Total RNA Isolation and Quality Control

Total RNA isolation was performed by homogenization of tissue samples was carried out in $1000 \,\mu l$ of TRIzol. Homogenates were incubated for 5 minutes at room temperature (RT), then 200 µl of chloroform was added, and after a short vortexing process, incubated again at RT for 15 minutes. The samples were centrifuged at 12000 g for 15 minutes at +4 °C. The supernatant containing the RNA was transferred to new eppendorf tubes and 500 µl of isopropanol was added and inverted several times. After incubation for 10 min at RT, the samples were centrifuged at 12000 g for 10 minutes at +4 °C. After removing the supernatant, the pellet was ethanol washed and centrifugated at 12000 g for 10 minutes at +4 °C. After drying at RT for 5-10 min, the pellet was dissolved by adding 50 µl of nucleasefree water. The quality and quantity of total RNA samples were evaluated using a Nanodrop device and measuring at the A260/A280 and A260/230 ratios. The quality of the RNA samples was also evaluated by 1% agarose gel electrophoresis.

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| Table 2Pr | imer sequences of genes #S&da | ial ŖZes |
|-----------|-------------------------------|-----------------|
| | | PCR product |
| Gene | Primer sequence (5 -3) | (bp) |
| ATF4 | TTCGACCAGTCGGGTTTG | 93 |
| | GGAGAACCCATGAGGTTTGA | |
| ATF6 | GAAGGGATCACCTGCTGTTAC | 152 |
| | GTCCATCACCTGACAGTCAATC | |
| CALR | CGGCTACGTGAAGCTGTT | 144 |
| | ACGTTCTTGCCCTTGTAGTT | |
| CHOP | AACGGAAACAGAGTGGTCAG | 137 |
| | GGTCAGGCGCTCGATTT | |
| EIF2A | GGTTTCTTGGCAGCCATTT | 100 |
| | TGCAACTTTAGGCTCCTCAC | |
| GRP78 | TGGTATTCTTCGAGTGACAGC | 109 |
| | GACCATCCTTTCAATTTCTTCAGG | |
| HSP47 | AGATGCAGAAGAAGGCTGTT | 113 |
| | GTTCTTGTCGATGGCCTCA | |
| IRE-1 | GCGCATCACAAAGTGGAAGTA | 75 |
| | ACATACAGAGTGGGCGTCA | |
| PERK | CAAAGTAGATGACTGCAATTACGC | 144 |
| | TCCAGCCACGCATTGAAATA | |
| XBP1 | CCAGAACATCTTCCCATGGAT | 89 |
| | GGGTCCAACTTGTCCAGAAT | |
| PGK1 | ATGCAAAGACTGGCCAAGCTAC | 104 |
| | AGCCACAGCCTCAGCATATTTC | |
| CycA | TATCTGCACTGCCAAGACTGAGTG | 126 |
| | CTTCTTGCTGGTCTTGCCATTCC | |

Cleanup of gDNA Contamination of Total RNA Samples

DNAse-I enzyme reaction was performed according to the manufacturer's instructions to eliminate possible gDNA contamination. 10 μ g total RNA was made up to 100 μ l total volume with DNAse-I reaction mix. RNA samples were incubated at 37 °C for 10 minutes after adding 2 U of DNAse-I enzyme. Then, 1 μ l of 0.5 M EDTA was added, and the reaction was stopped by incubating at 75 °C for 10 minutes.

Reverse Transcriptase (RT) Reaction

cDNA was synthesized from the quality-controlled RNA samples using the manufacturer's protocol. To obtain single-strand cDNA from $2 \mu g/20 \mu l$ total RNA; $1 \mu l$ Oligo dT and $1 \mu l$ Random hexamer were added to $2 \mu g/20 \mu l$ total RNA and incubated at +70 °C for 5 minutes. Then, $2 \mu l$ of RNAse inhibitor and $4 \mu l$ of dNTP were added to the resulting reaction mixture and incubated at +25°C



Figure 1. Agorose gel electrophores image of RT-PCR products of the genes used in the study. (M: 100 size standard)

for 5 minutes. Reverse transcriptase enzyme $(2 \mu l)$ was added and incubated at +25°C for 10 minutes and then at +37 °C for 60 minutes. The reaction was stopped by incubating at +70°C water bath for 10 minutes. The cDNA samples obtained were stored at -20 °C until use.

Primer Design

The primer design of the target genes to be used in the study was carried out using the IDT PrimerQuest (http://eu.idtdna.com/home/home. aspx) program. The primer sequences of the genes used in the analysis are summarized in Table 2.

Real-Time Quantitative Polymerase Chain Reaction (qPCR)

Expression levels of target and reference genes was performed using a real-time PCR device (Bio-Rad CFX Connect Real-Time PCR System). SyberGreen, a dye that binds to double-stranded DNA, was used for the reaction. A total volume of 20 µl polymerase chain reaction was prepared including 10 µl of 2X SyberGreen master mix, 2 µl of cDNA, 5 pMol of forward and reverse primer. The PCR protocol was set at +95 °C for 10 min denaturation and 40 cycles (30 sec at 95 °C, 30 sec at 60 °C, 30 sec at 72 °C). In addition, the melting curve analysis was performed. Temperature was brought to 95 °C for 1 minute, then reduced to 55 °C and gradually increased to 95 °C again. Ct (threshold cycle) values target and reference genes were obtained. The resulting PCR products electrophorosed on a 2% agarose gel.

Statistical analysis

The "Resource Equation" method was used to determine the sample size (6). Ct values PGK1 and CYCA reference genes were used for internal control and normalisation of target genes and $2(-\Delta Ct)$ values were determined. Differences observed in gene expression levels between groups were compared using a one-way analysis of variance (ANOVA) using the SPSS package program. The least significant difference (LSD) test was used to determine possible differences between means for

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Figure 2. Melting curve analysis of the genes used in the study

groups. Findings with a p-value below 0.05 were considered statistically significant.

RESULTS

Chronic mild stress model was constituted in adult female rats and effects of two different sertraline doses were evaluated. Behavioral test indicated



Figure 3: ATF4 gene expression levels in control, depression, depression + 1 mg/kg sertraline and depression + 10 mg/kg sertraline groups. $2(-\Delta Ct)$ values were presented as mean means \pm SEM. * p<0.05, ** p<0.01, *** p<0.001.

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Figure 4: ATF6 gene expression levels in control, depression, depression + 1 mg/kg sertraline and depression + 10 mg/kg sertraline groups. $2(-\Delta Ct)$ values were presented as mean means \pm SEM. * p<0.05, ** p<0.01, *** p<0.001

that CMS model was effective to generate deppresion like behaviorous. Sertraline infussion (10 mg/kg) is effective to prevent depression like behaviours.

Total RNA isolation was performed from hippocampus and hipotalamus tissue samples of control, depression, depression + 1 mg/kg sertraline, and depression + 10 mg/kg sertraline group rats. Quality/control was checked with spectrophotometric and agarose gel electrophoresis. All total RNA samples were of good quality to be used in the qPCR analysis.

mRNA level expression of target genes in the total ER stress pathway and two reference genes (PGK1 and CycA) used for normalization were determined by qPCR. PCR products of all genes were observed in agarose gel (2%) electrophoresis (Figure 1). In addition, melting curve analyzes indicated that all PCR products were specificly amplified target genomic regions (Figure 2).

Figures 3-12 describes expression levels of target genes in ER stress pathway. ATF6 (Figure 4), PERK (Figure 5) and IRE1 (Figure 7) gene expression levels were not significant different between the experimental groups. ATF4 gene expression in the hippocampus was significantly higher in the depression group than in the control group (p<0.05). A statistically significant decrease in hippocampus ATF4 gene expression was detected in the depression+1 mg/kg sertraline group and the depression+10 mg/kg sertraline group compared to the depression group (p<0.05; Figure 3). It was observed that hypothalamic ATF4 gene expression increased significantly in the depression+10 mg/kg sertraline group compared to the depression+1 Karaagac M, Ak M, Kurar E, Uguz F, Kutlu S.



Figure 5: PERK gene expression levels in control, depression, depress-**Figure 6:** GRP78 gene expression levels in control, depression, sion + 1 mg/kg sertraline and depression + 10 mg/kg sertraline depression + 1 mg/kg sertraline and depression + 10 mg/kg sertraline groups. $2(-\Delta Ct)$ values were presented as mean means ± SEM. * traline groups. $2(-\Delta Ct)$ values were presented as mean means ± SEM. * p < 0.05, ** p < 0.01, *** p < 0.001

mg/kg sertraline and control group. (p < 0.05; Figure 3).

Hippocampus GRP78 gene expression was significantly downregulated in the depression+1 mg/kg sertraline group than in the depression group. (p<0.05) Hippocampal GRP78 gene expression was statistically significantly higher in the depression+10 mg/kg sertraline group than in the depression+1 mg/kg sertraline group. (p<0.05; Figure 6)

There was a statistically significant upregulation in hippocampal CHOP gene expression in the depression+10 mg/kg sertraline group compared to the control group. (p<0.05) Hypothalamic CHOP gene expression was significantly increased in the depression+1/kg sertraline group compared to the depression and control groups. (p<0.05; Figure 8)

A significant decrease in CALR gene expression was detected in the hypothalamus of the depression+1 mg/kg group compared to the depression group (p<0.05). There was a significant downregulated CALR gene expression in the hippocampus of the depression+10 mg/kg sertraline group compared to the depression group.(p<0.05; Figure 9).

Hypothalamic eIF2a gene expression was significantly higher in the depression+10 mg/kg sertraline group than in the other three groups. (p<0.05; Figure 10). A statistically significant decrease was found in hypothalamus HSP47 gene expression in the depression+1 mg/kg sertraline and depression+10 mg/kg sertraline group compared to the depression group (p<0.05; Figure-11).

Hypothalamic XPB1 gene expression was found to be significantly decreased in the depression+1 mg/kg sertraline group compared to the depression group (p<0.05) In addition, XPB1 gene expression in the hypothalamus was significantly lower in the depression+1 mg/kg sertraline group compared to the control group (p<0.05). Hippocampal XPB1 gene expression was statistically significantly down-



Figure 8: CHOP gene expression levels in control, depression, **Figure 9:** CALR gene expression levels in control, depression, depression + 1 mg/kg sertraline and depression + 10 mg/kg ser- depression + 1 mg/kg sertraline and depression + 10 mg/kg sertraline groups. $2(-\Delta Ct)$ values were presented as mean means ± traline groups. $2(-\Delta Ct)$ values were presented as mean means ± traline groups. $2(-\Delta Ct)$ values were presented as mean means ± traline groups. $2(-\Delta Ct)$ values were presented as mean means ± SEM. * p < 0.05, ** p < 0.01, *** p < 0.001





Figure 10: eIF2a gene expression levels in control, depression, Figure 11: HSP47 gene expression levels in control, depression, depression + 1 mg/kg sertraline and depression + 10 mg/kg ser- depression + 1 mg/kg sertraline and depression + 10 mg/kg sertratraline groups. $2(-\Delta Ct)$ values were presented as mean means \pm line groups. $2(-\Delta Ct)$ values were presented as mean means \pm SEM. SEM. * p<0.05, ** p<0.01, *** p<0.001 * p<0.05, ** p<0.01, *** p<0.001

regulated in the depression+10 mg/kg sertraline group compared to the depression group. Hippocampal XBP1 gene expression was lower in the depression+10 mg/kg sertraline group than in the depression +1 mg/kg sertraline group. (p<0.05; Figure-12).

DISCUSSION

Depression is a prevalent mood disorder accompanied by depressed mood, loss of interest, changes in appetite, sleep, energy levels, and autonomic changes (7). There are many effective treatments for depression, but it is estimated that one-third of patients with depression do not respond adequately to antidepressants (8,9). Therefore, the pharmacological mechanism of action of antidepressant drugs needs to be clarified. Sertraline is widely used in depression treatment. In this study, a Chronic mild stress model was constituted female rats and effects of sertraline was evaluated using two different doses. During experimental procedures, ot-



Figure 12: XBP1 gene expression levels in control, depression, depression + 1 mg/kg sertraline and depression + 10 mg/kg sertraline groups. 2 (- Δ Ct) values were presented as mean means ± SEM. * p<0.05, ** p<0.01, *** p<0.001

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hers also reported that 10 mg/kg sertraline is effective can be used as a golden standart experimental rat depression model.

The endoplasmic reticulum (ER) is an essential intracellular organelle involved in the post-translational modification, smooth folding and synthesis of secreted proteins, and calcium homeostasis (10). Various physiological conditions, such as hypoxia, stress, hypoglycemia, decreased calcium, oxidative stress, and a fat-rich diet can impair the protein folding process, resulting in the accumulation of unfolded and misfolded proteins in the ER (11). Several studies have shown that people with depression have structural abnormalities in brain tissue. Among the mechanisms involved in the pathophysiology of this condition, disorders in the endoplasmic reticulum have also been mentioned.

Although it is stated that ER stress may play a role in the pathophysiology of depression, there are not enough studies describing how ER stress changes with treatment in depression and the mechanism of this effect.

The finding of increased expression of hippocampal ATF4 in depression in our study coincides with the information that ATF4 gene expression is increased in the rat hippocampus with learned helplessness, as mentioned in the study of Timberlake et al. (12), and supports our hypothesis that ER stress causes depression. In addition, Omi et al. (13) reported that fluvoxamine, a Sig-1R stimulant SSRI, provided ATF4 modulation. Similarly in our study, hippocampal ATF4 gene

expression levels were downregulated after sertraline treatment. This finding indicates that Sig-1R stimulation may be necessary to treat ER stressinduced depression effectively.

Although it was reported in the study of Pavlovsky et al. (14) that ATF6 gene expression increased in the striatum of rats after chronic restraint stress, no significant change was found in ATF6 gene expression in our study. In addition, this result does not support the previous literature (15) where fluoxetine induces apoptosis by increasing ATF6 levels. These conflicting results reflect the influence of different pathophysiological mechanisms.

In a study by Sharma et al. (16), inhibition of hippocampal PERK expression could improve cognitive functions. In a study by Ma et al. (17), desipramine provided antitumor activity by inducing autophagy through PERK / eIF2a and ATF6 signaling pathways in glioma. Another study (17) stated that activation of the PERK-eIF2a signaling pathway after chronic defeat stress causes depression and memory impairment. There was no significant change in PERK gene expression between the groups in our study. It is impossible to explain this situation for a single reason; different mechanisms may cause this inconsistency.

GRP78 gene expression increased in the temporal cortices of patients with depression who died due to suicide (18). In a study by Nevell et al. (19), GRP78 levels increased significantly compared to patients with MDD. In a study by Tan et al. (20), there was an increase in GRP78 gene expression after chronic unpredictable stress in rats. In our study, no change was observed in GRP78 expression in depression. However, Jangra et al. (21) reported that a decrease in hippocampal GRP78 gene expression was observed with honokiol treatment. Similarly, in this study, hippocampal GRP78 gene expression was decreased in the depression+1 mg/kg sertraline group compared to the depression. This finding supports our hypothesis that antidepressant treatment reduces ER stress levels.

Previous literature indicated that CHOP gene expression was increased in depression(19) and in

rats with learned helplessness (12). Pavlovsky et al. (14) reported elavated CHOP gene expression in the striatum of rats exposed to chronic restraint stress. Also, Huang et al. (22) stated that CHOP gene expression was upregulated after social defeat stress in rat's amygdala. Lastly, Jangra et al. (21) reported that CHOP gene expression increased after chronic restraint stress in the rat's prefrontal cortex. In our study, an increased but not significant CHOP expression was observed. However, hippocampal and hypothalamic CHOP expression was not decreased in either treatment groups. This finding suggested that sertraline treatment may not affect CHOP driven inhibition of protein synthesis and somehow supports this mechanism in lower doses. Although these differences are difficult to explain, they may be due to methodological differences between studies.

Behnke et al. (18) reported that calreticulin (CALR) expression was increased in the temporal cortices of depressed patients who died due to suicide. In contrast, no significant increase in hippocampal and hypothalamic CALR gene expression was observed in our study. However, sampling strategy of these studies are quite different may cause this variation. Consistent with this research data, Bown et al. (23) reported no significant change in CALR gene expression levels in some patients who died after suicide attempts. This result suggests that further research is needed to reach consistent data on this subject. In addition, hypothalamic CALR gene expression was lower in the sertraline+1 mg/kg group than in the depression group. The hippocampal CALR gene expression was significantly decreased in the depression+10 mg/kg sertraline group compared to the depression group. These findings supports our hypothesis that antidepressant treatment reduces ER stress.

No study has been found for HSP47 with any mental illness or antidepressant treatment in the current literature. The decrease in hypothalamic HSP47 gene expression in the depression+1 mg/kg sertraline and depression+10 mg/kg sertraline group compared to the depression group confirms our hypothesis that a decrease in ER stress biomarkers is expected with effective antidepressant treatment in depression. It was reported an increased hippocampal XBP1 gene expression in rats with learned helplessness (12) and social defeat stress (24). Pavlovsky et al. (14) also suggested that increased XBP1 gene expression might be responsible for depression. Our study indicated an unsignificantly upregulated XBP1 expression in depression groups of hypotalamus and hipocampus. Spesifically, hippocampal XBP1 gene expression was decreased in the depression+10 mg/kg sertraline group compared to the depression group. In addition, the results in the hippocampal XBP1 gene expression in the study show that ER stress is reduced with a higher treatment dose.

Although we obtained striking results regarding the effect of ER stress on depression, the findings should be interpreted with caution. First, it should not be overlooked that there are different measurement techniques for the ER stress level. Secondly, although we used sertraline, an effective treatment for depression, studies involving antidepressants that act through different mechanisms of action are needed.

Our study illustrates that ER stress might play a crucial role in the pathophysiology of depression and that this situation can be reversed with sertraline antidepressant therapy. In future studies, there is a need for human studies that can confirm the data obtained in our research and elucidate the mechanisms by which the change in ER stress occurs.

Conflict of Interest

The authors declare no conflict of interest.

Authors' contributions

All authors contributed to the study's conception and design. Data collection was performed by Mustafa KARAAĞAÇ, Mehmet AK and Ercan KURAR. Mustafa Karaağaç wrote the first draft of the manuscript, and all authors commented on previous versions. All authors read and approved the final manuscript.

Acknowledgments

This study was supported by Necmettin Erbakan University Scientific Research Projects Coordination Unit (project number: 201518013). This study was also presented in Psychopharmacology 2021 Congress.

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A study on the relation of attention deficit/hyperactivity disorder symptoms with obesity in women with polycystic ovary syndrome

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SUMMARY

Objective: The goal of this study is to investigate ADHD symptoms and the relation of with obesity in women with PCOS.

Method: One hundred twenty five PCOS patients with biochemical hyperandrogenemia were recruited for the study group. For comparison, 125 healthy women were included the study. Current and childhood ADHD symptoms were assessed by using the Adult ADHD Self-Report Scale (ASRS) and Wender-Utah Rating Scale (WURS) and impulsivity was assessed by using the Barrat Impulsivity Scale (BIS).

Results: There were no significant difference between the groups in terms of sociodemographic characteristics, but Body Mass Index (BMI) was significantly higher in the PCOS group than the control group. Women with PCOS had significantly higher total current (ASRS) and total childhood (WURS) ADHD scores than controls. Inattention score of ASRS and hyperactivity-Impulsivity score of ASRS were higher in PCOS group. Women with PCOS had significantly higher total impulsivity (BIS) scores than controls. Attention impulsivity score of BIS, motor impulsivity score of BIS and Non-planning impulsivity score of BIS were higher in PCOS group. A positive correlation was found between BMI and all scale scores in both PCOS and control groups.

Discussion: The results of the study show that women with PCOS have higher current and childhood ADHD symptoms and impulsivity. Also, high serum androgen levels and obesity in the PCOS and control group are associated with both adult ADHD symptoms and impulsivity. Further studies are needed to confirm our findings. We suggest that not only gynecologist but also a multidisciplinary team should examine these patients.

Key Words: Attention deficit-hyperactivity disorder, polycystic ovary syndrome, hyperandrogenemia, impulsivity, obesity

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is a major neurodevelopmental psychiatric disorder with childhood onset, manifested by attention deficit, hyperactivity and impulsivity with a prevalence of % 7 in school-aged children (1). ADHD symptoms persist into adulthood in 55-75% of childhood-onset cases and the prevalence of ADHD in adult population is ~2.5% (2,3). Even though the etiology of ADHD is not entirely clear today, it is likely to have multiple genetic, prenatal **DOI:** 10.5505/kpd.2023.48902 and environmental factors. In recent years, research has focused on the role of androgens in the development of ADHD. Both high androgen levels exposure in the intrauterine period and current high androgen levels exposure have been associated with ADHD. Sexual differentiation of the brain occurs under the control of gonadal hormones, especially androgens, during the prenatal development. In addition boys are two to three times more likely to be diagnosed with ADHD than girls. Studies have found that children with ADHD have higher salivary levels of dehydroepiandros-

Cite this article as: Soyak HM, Acmaz G. A study on the relation of attention deficit/hyperactivity disorder symptoms with obesity in women with polycystic ovary syndromes. Turkish J Clin Psych 2023; 26:248-253

The arrival date of article: 04.06.2023, Acceptance date publication: 15.07.2023

Turkish J Clinical Psychiatry 2023;26:248-253

terone compared to controls. These findings support the idea that high androgen levels may play a role in the etiology of ADHD (4).

Polycystic ovary syndrome (PCOS) is a common endocrine disorder, affecting 10% of women of reproductive age, characterized by clinic or biochemical hyperandrogenemia, irregular menstrual bleeding, and the appearance of polycystic ovaries in ultrasonography (5). In case of the presence of the two above mentioned symptoms, PCOS diagnosis is made (6). Although not part of the diagnostic criteria, obesity also often forms an important component of the clinical presentation of PCOS. Women with PCOS have higher rates of obesity compared to women without PCOS. Nearly 50% of women with PCOS are overweight or obese. It has been reported in studies and meta analyses that there is a significant association between ADHD and overweight/obesity. Studies demonstrate that the prevalence of ADHD in overweight or obese people is higher than in the general population. Also, available evidence suggests that individuals with ADHD have higher rates of overweight/obesity compared with those without ADHD (7-10). In addition, obesity is thought to be a factor that increases the risk of impulsivity (11).

It is claimed that androgens and obesity play a role in the etiology of ADHD. Women with PCOS have high androgen levels and are overweight/obese. In the literature, there is only a study investigating ADHD symptoms in women with PCOS (12). For these reasons, we believe that this issue is worth investigating. In this study, we aimed to research ADHD symptoms in women with PCOS who have high androgen levels and to investigate the effect of obesity in this possible relationship. In the light of this information, our hypotheses are that women with PCOS will have higher total present and total childhood ADHD symptoms than the control group.

METHOD

The study was approved by the Ethical Committee of University Hospital, and written informed consent was obtained from all the participants.

Participants

Between 1 July 2018 and 1 April 2019, 157 patients between the aged of 18-40 who admitted to Obstetrics and Gynecology outpatient clinic with complaints such as infertility, irregular menstruation, hirsutism, acne, those detected hyperadrogenemia in hormone tests and diagnosed with PCOS according to the Rotterdam Diagnostic Criteria (6) were included in the study. Exclusion criteria of the study: Use of hormone therapy to cure the symptoms of PCOS within three months before admission, current psychiatric illness, current use of psychotropic drugs, current malignancy, current endocrine disease such as diabetes mellitus, hypothyroidism, hyperthyroidism, congenital adrenal hyperplasia and pathology detected in routine biochemical tests. All patients were examined by the same psychiatrist. As a result of the psychiatric examination, 12 patients with psychiatric illness (7 patients with depression, 4 patients with anxiety disorder and 1 patient with bipolar disorder) and 8 patients for not accepting psychiatric examination were excluded from the study. According to the examination of the hospital records and the statements of the patients, 6 patients with diabetes, 2 patients with hypothyroidism excluded from the study. Moreover, 4 patients who did not complete the scales completely were excluded from the study. The healthy control group was selected among healthy hospital staff between the aged of 18-40, who had regular menstruation. A total of 125 women with PCOS and 125 healthy women subjects were included in the study.

Data Collection

Wender-Utah Rating Scale (WURS), Adult ADHD Self-Report Scale (ASRS) and Barratt Impulsiveness Scale (BIS-11) were administered to the all participants. These scales were used and scored by the same psychiatrist. Height and weight of all participants were measured and Body Mass Index (BMI) was calculated. Sociodemographic characteristics of the patients were recorded.

The duration of data collection process was nine months.

Data Collection Instruments

Socio-demographic Data form: This form, which includes questions about the participants' age, marital status and education level (the number of years in full-time education), was developed by the researchers in order to collect data on the demographic characteristics of the participants.

Wender-Utah Rating Scale (WURS): It is a 25-item self-report scale used to measure childhood symptoms severity of ADHD retrospectively (13). These 25 items are rated from 0= not at all or slightly to 4= very much. Total score of the WURS ranges from 0 to 100 and the scale's cut-off point was found as 36. Validity and reliability tests of the Turkish version were performed by Öncü et al (14).

Adult ADHD Self-Report Scale (ASRS): ASRS is a self-rating scale with 18 items used to measure current ADHD symptoms. It composed of two subscales, each consisting of nine items: inattention and hyperactivity-impulsivity. It is a five-points Likert-type scale rated from 0 to 4 (0=never/seldom and 4 =very often). The scale was developed by Kesser et al. (15), and validity and reliability tests of the Turkish form were performed by Doğan et al (16).

Barratt Impulsiveness Scale (BIS-11): It is one of the most widely used scales to assess impulsivity. It is a self-rated scale composed of 30 items and was designed by Barrat (17). It is a four-point Likert scale from Rarely/Never=1 to Almost Always/Always=4. It consisted of three subscales: non-planning, attention impulsivity and motor impulsivity. The total score ranges between 30 and 120 and is the result of the sum of three different subscales. Higher scale scores indicate higher severity of impulsivity. Validity and reliability tests of the Turkish version were performed by Güleç et al (18).

Statistical analyses

The sample diameter analysis was performed for Wender-Utah Rating Scale (WURS) consisting of PCOS and control groups. It was assumed that the strength of the test was 0.80 and the type 1 error was 0.05. The sample diameter determination process was performed for dual comparison (comparison of PCOS and Control group averages). Reference values (sample mean and standard deviations) were obtained from the study "Symptoms of attention deficit-hyperactivity disorder in women with polycystic ovary syndrome" (12) in determining the sample diameter. Taking all these into account, the sample diameter required for this comparison was calculated as 61 for each group. The calculations were made with the G-Power 3.1.7 package program.

SPSS 23.0 package program was used for statistical analysis of the data. The suitability of the variables to normal distribution was examined using the Shapiro-Wilk Tests. Numbers and percentages were used in summarizing the categorical measurements, continuous measurements as mean, deviation, and 25th-75th percentiles. The comparison of the categorical variables was made by Chi-square test. In the comparison of continuous measurements between groups, by controlling the distributions, Mann Whitney u test was preferred for the parameters which display normal distribution and Kruskal Wallis tests were used for the parameters which do not present normal distribution. Spearman correlation test was performed to reveal the relationship between scale scores. Statistically significance probability values was taken as P<0.05.

RESULTS

There were no significant difference between the groups in terms of age, education and marital status. The BMI was significantly higher in the PCOS group. The socio-demographic characteristics of the groups are reported in Table 1.

Inattention score of ASRS, hyperactivity-Impulsivity score of ASRS, total ASRS score and total WURS score were significantly higher in PCOS group (p < 0,001). Non-planning impulsivity, attention impulsivity and motor impulsivity score of BIS and total BIS score were significantly higher in PCOS group (p < 0,001) (Table 2).

| | Control n=125 | PCOS n=125 | р |
|--------------------------|-------------------|----------------|--------------------|
| Age (years) | 28(CI: 26,01-30) | 27 (CI: 26-29) | 0,724 ^a |
| Education (years) | 12 (CI: 11-13) | 12 (CI: 11-13) | 0,656ª |
| Married | 46 (36,8) | 50 (40) | |
| Single | 68 (54,4) | 65 (52) | 0,866 ^b |
| Divorced | 11 (8,8) | 10 (8) | |
| BMI (kg/m ²) | 23,4–2,6 | 25,7-2,9 | <0,001° |

Table 1. Sociodemographic characteristics of the groups.

Values are expressed as (%), mean – SD or median (25th -75th percentiles). ^a Mann-Whitney U test, ^b Chi-Square test, ^c Independent t test.

Spearman correlation analysis presented that ASRS, WURS and BIS scores and age, education and marital status were not correlated with each other (Table 3).

The BMI and the inattention score of ASRS, Hyperactivity-Impulsivity score of ASRS, total ASRS score, total WURS score, non-planning impulsivity, attention impulsivity and motor impulsivity score of BIS, total BIS score in the PCOS group were positively correlated with each other (Table 3).

BMI and all scale scores in the control group were positively correlated with each other (Table 3).

DISCUSSION

In this study, we investigated current ADHD and childhood ADHD symptoms and impulsivity in women with PCOS. Results of the study showed that women with PCOS had more current and childhood ADHD symptoms than women in the control group. Moreover, women with PCOS exhibited more impulsivity than women in the control group.

We think that one of the most important reasons

for this is due to the high androgen levels in women with PCOS. The dopamine system plays an essential role in the neurobiology of ADHD (19). Dopaminergic activity in the mesolimbic system and prefrontal cortex is affected by high serum androgen levels (20,21). It was reported that rats' being exposed to high androgen levels in the early stages of their development results in reduced dopamine innervation in the frontal cortex and ADHD-like behaviours (22). These results indicate that being exposed to high androgen levels might be effective on the hyperactive and impulsiveness of women with PCOS. Another reason may be that women with PCOS have a genetic predisposition to ADHD because genetics plays an important role in the etiology of both ADHD and PCOS.

When the literature is examined, the relationship between maternal polycystic ovary syndrome and attention deficit/hyperactivity disorder has been investigated in almost all of the studies. Currently according to our knowledge, there is only one publications in the literature on the prevalence of adult attention deficit hyperactivity disorder in women with polycystic ovary syndrome. In this study conducted with 40 women with PCOS and 40 healthy controls, significantly higher current ADHD and childhood ADHD symptoms were reported in women with PCOS (12). These findings are similar to the results of our study. The superiority and dif-

Table 2. Total ASRS, WURS and BIS scales and subscale scores of the groups

| | o beales and subseale se | eres er me groups. | |
|---------------------------------|--------------------------|--------------------|---------------------|
| | Control | PCOS | |
| | n=125 | n=125 | p |
| ASRS: Inattention | 14 (CI: 13-14) | 18,5 (CI: 17-20) | <0,001 ^a |
| ASRS: Hyperactivity-Impulsivity | 14 (CI: 13-15) | 20,5 (CI: 20-22) | <0,001 ^a |
| ASRS: Total | 27 (CI: 26-29) | 40 (CI: 37-43) | <0,001 ^a |
| WURS: Total | 24 (CI: 21-27) | 40 (CI: 38-43) | <0,001 ^a |
| BIS: Attention impulsivity | 13 (CI: 12-14) | 16 (CI: 15-17) | <0,001 ^a |
| BIS: Motor impulsivity | 14 (CI: 13-14) | 20 (CI: 19-23) | <0,001 ^a |
| BIS: Non-planning impulsivity | 14 (CI: 14-15) | 21 (CI: 20-24) | <0,001 ^a |
| BIS: Total | 41 (CI: 40-42.98) | 57 (CI: 53-63) | <0.001 ^a |

Values are expressed as median (25th -75th percentiles).

ASRS: Adult ADHD Self-Report Scale; WURS: Wender-Utah Rating Scale; BIS: Barratt Impulsivite Scale.

^a Mann-Whitney U test.

| | Control | | PCOS | |
|---------------------------------|---------|----------|--------|----------|
| | r | р | r | р |
| Age | 0,056 | 0,538 | 0,115 | 0,205 |
| Education | -0,014 | 0,874 | -0,079 | 0,384 |
| ASRS: Inattention | 0,205 | 0,022* | 0,562 | <0,001** |
| ASRS: Hyperactivity-Impulsivity | 0,224 | 0,012* | 0,438 | <0,001** |
| ASRS: Total | 0,239 | 0,007** | 0,524 | <0,001** |
| WURS: Total | 0,282 | 0,002** | 0,510 | <0,001** |
| BIS: Attention impulsivity | 0,282 | 0,001** | 0,614 | <0,001** |
| BIS: Motor impulsivity | 0,261 | 0,003** | 0,656 | <0,001** |
| BIS: Non-planning impulsivity | 0,284 | 0,001** | 0,596 | <0,001** |
| BIS: Total | 0,326 | <0,001** | 0,668 | <0,001** |

ASRS: Adult ADHD Self-Report Scale; WURS: Wender-Utah Rating Scale; BIS: Barratt Impulsivite Scale.

* p<0,05, ** p<0,001, Spearman correlation test, r= Correlation coefficient value

ference of our study from other studies is that it is the second study in the literature that investigates current and childhood ADHD symptoms and impulsivity in women with PCOS. screening but do not have the ability to make a clinical diagnosis. One other limitation is that our sample is relatively small and does not represent all patients diagnosed with PCOS in the community.

In conclusion, the findings of the study show that

In our study, it was concluded that women with PCOS exhibited more impulsivity than women in the control group and overweight/obesity was associated with ADHD symptoms and impulsivity. The first study focusing on the prevalence of ADHD in obese individuals was conducted by Altfas et al. (23). In this study, the prevalence of ADHD in obese adults was found to be 27.4%. Also, the BMI of ADHD patients was significantly higher than that of non-ADHD. In later studies, it has also been reported that obesity is associated with ADHD (24-26). When the literature is examined, there are studies reporting that obesity increases impulsivity (27-30). Based on the results of our study, we think that obesity increases both ADHD and impulsivity.

This study has some limitations. The most important limitation was subjects in the control group recruited according to their self-reports for PCOS rather than a clinical examination. Another limitation was all measures were based purely on selfreport. Furthermore, the use of WURS for childhood ADHD symptoms might lead to inaccurate recall. The ASRS and WURS are useful tools for adult ADHD and impulsivity are common in patients followed up with a diagnosis of PCOS; high serum androgen levels and obesity are associated with both adult ADHD and impulsivity. PCOS is a highly heterogeneous disease. Some patients

are overweight or obese, while others are normal

weight. Lots of women with PCOS experience

problems such as hirsutism acne due to hyperan-

drogenemia but there are women with PCOS who

have normal androgen levels. For these reasons

further studies that take into account the clinical

characteristics of patients in larger sample groups

are needed to support our findings. Since psychi-

atric disorders are more common in PCOS, we re-

commend that a multidisciplinary team, not just gynecologist, should examine these patients.

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Frequency and predictors of premenstrual dysphoric disorder and its association with affective temperaments

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SUMMARY

Objective: Premenstrual Dysphoric Disorder is a clinically important condition that affects a significant proportion of women and causes deterioration of quality of life. In this study, it was aimed to evaluate the frequency of premenstrual dysphoric disorder and its relationship with demographic and clinical variables and affective temperaments.

Method: An online survey form including sociodemographic data, Premenstrual Symptoms Screening Tool, and Temperament Evaluation of Memphis, Pisa, Paris, and San Diego Auto-questionnaire was applied to 408 healthy women participants.

Results: The frequency of premenstrual dysphoric disorder and moderate to severe premenstrual syndrome were 13.2%, and 14.5%, respectively. The presence of lifetime psychiatric diagnosis, positive family history of psychiatric illness, suicide attempts, and anxious temperament were significantly higher in the premenstrual dysphoric disorder group. Cyclothymic and anxious temperaments had a positive predictive effect on the Premenstrual Symptoms Screening Tool Section A scores.

Discussion: Our findings show a possible relationship between anxious and cyclothymic temperament traits and premenstrual dysphoric disorder symptom severity. Premenstrual symptoms may be more severe in women with cyclothymic and anxious temperament features. However, large-scale studies in which the diagnosis of premenstrual dysphoric disorder is determined by clinical interview are needed for this judgment.

Key Words: Premenstrual dysphoric disorder, premenstrual syndrome, affective temperaments, cyclothymic temperament, anxious temperament

INTRODUCTION

A monthly reproductive cycle of menstruating females consists of two simultaneously occurring cycles named follicular and luteal phases. Estrogen hormone which has high levels during the follicular phase directly affects brain functions and thereby affects women's cognitive and affective status (1). Similarly, progesterone has a role in neuro-regulation and these two reproductive steroids regulate the synthesis of neurotransmitters such as dopamine and serotonin. The cyclic changes in the blood level of these steroids due to the menstrual cycle result in emotional and behavioral alterations in most healthy women (2). Up to 90% of women have some physical and emotional complaints starting two weeks before menstruation and improving immediately after the onset of the menstrual period. In addition to physical symptoms such as headache, breast tenderness, or abdominal bloating; anxiety, depression, mood lability, concentration problems, fatigue, and feelings of "loss of control" may be listed (3). These symptoms are not always experienced to the same degree, some

DOI: 10.5505/kpd.2023.87049

Cite this article as: Ekmekci Ertek I, Unler M, Yay Pence A, Kayalar A. Frequency and predictors of premenstrual dysphoric disorder and its association with affective temperaments. Turkish J Clin Psych 2023; 26: 254-263

The arrival date of article: 23.01.2023, Acceptance date publication: 28.07.2023

Turkish J Clinical Psychiatry 2023;26:254-263

women have mild symptoms while in others they may be debilitating (4).

Premenstrual symptoms usually begin with menarche, intensify between the ages of 25 and 35, and resolve during menopause (5). Premenstrual syndrome (PMS) affects approximately 80% of the female population, whereas premenstrual dysphoric disorder (PMDD), the more severe form, has a 3-8% incidence (6). Because of the specific symptoms and the cyclic course, PMDD has been included in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) as a separate diagnostic entity of depressive disorders (7).

From a public health perspective, PMDD is an important health condition due to its frequent occurrence and impact on women's life. Symptoms cause significant interference with work, school, social activities, or relationships and negatively affect the quality of life. PMDD, especially on symptomatic days, is related to reduced work productivity and absenteeism (8). Women with PMS have a higher frequency of referral to outpatient healthcare providers, and accordingly, it has been reported that 2-year healthcare costs are \$500 (9). Moreover, women with PMDD are considered a high-risk population for suicidality as reports show that suicidal thoughts or attempts are associated with experiences of PMDD independently of psychiatric comorbidities (10). A meta-analysis of ten studies showed that women with PMDD had an almost seven times higher risk of suicide attempt and nearly four times the risk of suicidal ideation. While women with PMS had an increased risk of suicidal ideation, a similar relationship could not be established with suicide attempt (11).

Temperaments are considered to be the inherited and biologically stable core of personality. While most temperamental models describe personality and emotional reactivity in general, the model of affective temperaments, specifically, are regarded as subclinical, trait-related characteristics and can be conceptualized as subclinical manifestations of major affective states, especially in their more apparent forms (12). Increasing evidence suggests a continuum, particularly between some affective temperaments and mood disorders (13). Despite its strong biological basis, PMDD has a multifactorial etiology that is contributed by many psychosocial conditions such as trauma, temperament and character traits, and stressful life events, like many other mental pathologies (14-17).

The relationship between PMDD and affective temperaments within the cluster of mood disorders has been less studied compared to other mood disorders, and the findings are inconsistent. In a study conducted by Camara et al., it was reported that cyclothymic temperament was more associated with the diagnosis of PMDD. This difference remained significant even after adjusting for education status and oral contraceptive use (18). In a recent study, cyclothymic and anxious temperament showed a significant predictive effect for premenstrual symptoms. The authors suggested that affective temperaments play a mediating role in the effect of childhood maltreatment on PMS symptoms (19).

In the literature, knowledge regarding the relationship between PMDD and affective temperaments is not only lacking but also conflicting. Moreover, to the best of our knowledge, there has been no study conducted in Turkey. In this study, we aimed to determine the frequency of PMDD and PMS in a healthy female population in Turkey which has limited data on the epidemiology of these disorders. Secondly, it was aimed to investigate the relationship of PMDD with psychiatric and gynecologic variables as well as affective temperaments.

METHODS

Procedure

A cross-sectional online survey form was carried between October 2019 and February 2020. An online survey included sociodemographic data and variables related to the menstrual cycle, Temperament Evaluation of Memphis, Pisa, Paris, and San Diego Auto-questionnaire (TEMPS-A), and Premenstrual Symptoms Screening Tool (PSST) was prepared in the form of Google surveys. The survey targeted women who live in Ankara, Turkey, and the snowball technique was used to reach out to the respondents via e-mails

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and social media networks. Social media users and people in the mailing lists who viewed the advertisement of the study were able to click on a universal resource locator (URL) link that took them to the survey. After consenting to participate in the study, participants were allowed to complete the survey form from any electronic device that had Internet access. After logging into the URL link, participants were taken to an introduction section where they were introduced to the study and provided with directions for filling out questionnaires. To improve the participation rate, the survey link was shared twice a month on mailing lists and social media networks. Participants were free to log off the study at any point. Completion of the questionnaires required approximately 30 minutes for all participants.

The inclusion criteria were being women between 18 and 50 years old and having the required level of education to fill in questionnaires. Those who were pregnant or in menopause were excluded from the study. Moreover, those with a history of chronic psychotic disorders such as schizophrenia were excluded from the study due to both its impact on consent and its devastating prognosis. In addition, since the aim of the study was to determine the affective temperaments, which are considered sub-threshold mood components, those with a history of bipolar disorder were excluded from the study due to its confounding effect.

A total of 458 survey forms were turned back between October 2019 and February 2020. Two of the participants were excluded from the study because they had bipolar disorder. Ten patients were not included in the study because they were under the age of 18. Of the remaining participants, three were pregnant and 35 were in the menopausal period. As a result, 50 participants were excluded from the study and 408 patients constituted the study sample.

Ethical approval of this study was granted by the Ethical Committee of Gazi University on 10.05.2019 with the number of E.59828. This study is in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the World

Medical Association (WMA) Declaration of Helsinki – Ethical Principles For Medical Research Involving Human Subjects revised in 2013.

Instruments

The sociodemographic data form included questions about the participants' education and employment status, marital status, history of physical illness, lifetime psychiatric diagnosis, family history of psychiatric illness, suicidality, menstrual pattern, age of menarche, length of menstruation, oral contraceptive use, history of gynecological surgery and number of pregnancies. In questions about lifetime psychiatric diagnoses, participants were asked if they had a psychiatric illness diagnosed by a psychiatrist at any time. Self-reported psychiatric diagnoses were obtained with open-ended questions. Suicide attempts were considered situations in which a person performs a life-threatening behavior with the intent of endangering his or her life. The participants were asked about their average menstrual cycle duration and were asked to indicate whether there had an irregularity in terms of bleeding or duration. The continuation of each menstrual period with an average of 28-day cycles is considered regular, while differences in duration between cycles are considered irregular. The participants were asked to include the number of miscarriages while specifying the number of pregnancies.

Temperament Evaluation of Memphis, Pisa, Paris, and San Diego Auto-questionnaire (TEMPS-A): TEMPS-A is a 5-factor questionnaire that evaluates depressive, cyclothymic, hyperthymic, irritable, and anxious temperament consisting of 110 selfreported items (20). Turkish validity and reliability study was performed by Vahip et. al. Cronbach's alpha value ranged from 0.75 to 0.84 for 5 factors, and test-retest reliability was found to be between 0.73 and 0.93. Since the alpha value was < 0.2, 10items were removed from the questionnaire to preserve homogeneity between the items. As a result of the factor analysis, there was a significant overlap between the anxious temperament cognitive items and the depressive temperament items, while the anxious temperament somatic symptom items formed a separate cluster. As a result, depressive,

hyperthymic, irritable, cyclothymic, and anxiousnervous temperament factor structures were found to be valid for Turkish society (21).

Premenstrual Symptoms Screening Tool (PSST): PSST developed by Steiner et al. is a 19-item scale consisting of two sections. Section A, consisting of 14 items, was based on DSM-IV criteria for PMDD. In section B, there are five items on the effect of premenstrual symptoms on functionality (22). In the Turkish version, Cronbach's alpha value was found to be 0.928. As a result of the score they got on the scale, the participants were divided into three different groups as PMDD, moderate to severe PMS, and those with no/mild symptoms. PMDD group meets DSM-5 criteria for the diagnosis of PMDD. To meet these criteria, participants have to report at least one of the four core symptoms (irritability, dysphoria, tension, lability of mood) as severe and at least 4 additional symptoms (for a total of 5) as moderate to severe in section A. They also have to report that their symptoms interfered severely with their ability to function in at least one of five domains in section B. Moderate to severe PMS group meets reporting at least one of the four core symptoms as moderate to severe and at least four additional symptoms as moderate to severe in section A. They also have to report that their symptoms interfered moderately to severely with their ability to function in activities of daily living in at least one of the five psychosocial domains listed in Section B. Participants outside these two groups formed the no/mild PMS group. In post hoc analysis, the difference between the participants with no/mild symptoms and PMDD was preserved, while the difference between PMDD and the moderate to severe PMS group disappeared (23).

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 22.0 (IBM SPSS Corp.; Armonk, NY, USA). Descriptive values were stated as number (n), percentage (%), mean, and standard deviation (SD). The normal distribution of variables was examined visually (histogram and probability plots) and with analytical methods (Kolmogorov–Smirnov/Shapiro–Wilk test).

In all evaluations, nonparametric tests were used in the analysis of the data, since dependent variables (such as age, age of menarche, and the number of suicide attempts) did not show normal distribution. The Chi-square test was used to evaluate categorical variables. The Kruskal-Wallis test was used to compare continuous variables. Kruskal-Wallis results were used with the Mann-Whitney U test for the post-hoc evaluation of statistically significant variables. Multiple linear regression analysis was used to identify independent predictors of PSST Section A scores. An overall p-value of less than .05 was considered to show a statistically significant result.

RESULTS

A total of 408 women participated in this study. The sociodemographic and clinical characteristics of the participants are shown in Table 1. The mean age of the participants was 29.6 ± 8.3 . Most of the participants were employed (53.4%), single (57.1%), living with family (78.7%), and had 8-12 years of education (39.0%). 20.3% of the participants had a history of physical illness and only nine of them had a diagnosis of polycystic ovary syndrome. The frequency of lifetime psychiatric diagnosis was 20.3% and substance use was 3.9%. Among the participants diagnosed with any psychiatric disorder, the most frequent diagnosis was

| | | Ν | % |
|---------------------------------------|--------------|------|------|
| | 0-8 | 104 | 25.5 |
| Education (years) | 8-12 | 159 | 39.0 |
| | 12< | 145 | 35.5 |
| Employment status | Employed | 218 | 53.4 |
| | Unemployed | 61 | 15.0 |
| | Student | 129 | 31.6 |
| Marital status | Single | 233 | 57.1 |
| | Married | 161 | 39.5 |
| | Divorced | 14 | 3.4 |
| Living status | Alone | 45 | 11.0 |
| - | With family | 321 | 78.7 |
| | With friends | 30 | 7.4 |
| | Others | 12 | 2.9 |
| Substance use | | 16 | 3.9 |
| Physical diseases | | 83 | 20.3 |
| Lifetime psychiatric diagnosis | | 86 | 21.1 |
| Family history of psychiatric illness | | 48 | 11.8 |
| Suicide attempts | | 12 | 2.9 |
| Menstrual pattern | Regular | 329 | 80.6 |
| - | Irregular | 79 | 19.4 |
| Use of oral contraceptives | | 22 | 5.4 |
| Pregnancy history | | 136 | 33.3 |
| Gynecologic surgery history | | 28 | 6.9 |
| | Ν | Mean | SD |
| Age (years) | 408 | 29.6 | 8.3 |
| Number of suicide attempts | 12 | 2.5 | 1.7 |
| Age of menarche (years) | 408 | 13.0 | 1.3 |
| Length of menstruation (days) | 408 | 5.6 | 1.6 |
| Number of pregnancies | 408 | 1.6 | 0.4 |

Frequency and predictors of premenstrual dysphoric disorder and its association with affective temperaments

| | | PMDD (N=54) | | Modera severe l | te to PMS | No/ mil (N=295 | d PMS | | |
|--------------------------|--------------------------------|----------------|------|--------------------|--------------|-------------------|-------|----------------|---------|
| | | | | (N=59) | | | | | |
| | | Ν | % | Ν | % | Ν | % | \mathbf{X}^2 | р |
| | Substance use | 5 | 9.3 | 1 | 1.7 | 10 | 3.4 | 5.081 | 0.079 |
| | Physical diseases | 12 | 22.2 | 8 | 13.6 | 63 | 21.4 | 1.980 | 0.372 |
| | Lifetime | 18 | 33.3 | 17 | 28.8 | 51 | 17.3 | 9.545 | 0.008 |
| Psychiatric variables | psychiatric diagnosis | | | | | | | | |
| | Family history of | 13 | 24.1 | 8 | 13.6 | 27 | 9.2 | 10.004 | 0.007 |
| | psychiatric illness | | | | | | | | |
| | Suicide attempts | 7 | 13.0 | 2 | 3.4 | 3 | 1.0 | 22.867 | < 0.001 |
| | Regular menstrual | 43 | 79.6 | 50 | 84.7 | 236 | 80.0 | 0.750 | 0.687 |
| | pattern | | | | | | | | |
| | Use of oral | 6 | 11.1 | 2 | 3.4 | 14 | 4.7 | 4.167 | 0.124 |
| | contraceptives | | | | | | | | |
| Gynecologic | | | | | | | | | |
| variables | Gynecologic surgery history | 3 | 5.6 | 1 | 1.7 | 24 | 8.1 | 3.347 | 0.187 |
| | Pregnancy history | 14 | 25.9 | 12 | 20.3 | 110 | 37.3 | 8.406 | 0.078 |
| | Depressive | 3 | 5.6 | 4 | 6.8 | 11 | 3.7 | 1.278 | 0.528 |
| | Cyclothymic | 2 | 3.7 | 1 | 1.7 | 2 | 0.7 | 3.578 | 0.167 |
| TEMPS-A | Hyperthymic | - | - | - | - | - | - | - | - |
| | Irritable | 2 | 37 | 1 | 1.7 | 4 | 1.4 | 1.492 | 0.474 |
| | Anxious | 12 | 22.2 | 6 | 10.2 | 6 | 2.0 | 35.892 | < 0.001 |
| | | Mean | SD | Mean | SD | Mean | SD | Z | р |
| | Age | 27.0 | 8.5 | 27.3 | 7.4 | 30.4 | 8.3 | 262 | 0.002 |
| | Number of suicide | 1.0 | 1.8 | 1.0 | 0.0 | 2.3 | 1.5 | -2.681 | 0.239 |
| | attempts | | | | | | | | |
| | Age of menarche | 12.9 | 1.5 | 12.7 | 1.3 | 13.0 | 1.2 | -2.736 | 0.181 |
| | Length of | 5.7 | 1.5 | 5.8 | 1.3 | 5.5 | 1.6 | -2.567 | 0.212 |
| | menstruation | | | | | | | | |

PMDD: Premenstrual Dysphoric Disorder, PMS: Premenstrual Syndrome, TEMPS-A: Temperament Evaluation of Memphis, Pisa, Paris, and San Diego Auto-questionnaire

depression (10.8%), and the others were anxiety disorders (7.4%), obsessive-compulsive disorder (0.9%), post-traumatic stress disorder (0.7%), and dissociative disorder (0.5%). A family history of psychiatric illness was present in 11.8% of the participants. 12 participants (2.9%) stated that they had attempted suicide at least once in their life. Of those, the mean number of suicide attempts was 2.5 ± 1.7 . When looking at gynecological parameters, 80.6% of the participants reported their menstrual patterns as regular. The prevalence of oral contraceptive use was estimated as 5.4%. Pregnancy rate among all participants was 33.3% and the mean number of pregnancies was 1.6 ± 0.4 . Having a history of gynecological surgery was present in 6.9% of the participants.

According to TEMPS-A, the most prevalent affective temperament was the anxious type (5.9%) and the second most was the depressive type (4.4%) in all participants. The prevalences of irritable and cyclothymic temperaments were 1.7% and 1.2%, respectively. There was no participant with a hyperthymic temperament. Based on the provisional diagnostic criteria according to the PSST, the frequency of PMDD was estimated as 13.2%, moderate to severe PMS as 14.5%, and no/mild PMS as 72.3%.

To compare the PMDD, moderate to severe PMS, and no/mild PMS groups in terms of sociodemographic and gynecological variables and affective temperaments, the Chi-square test was used to evaluate categorical variables and the Kruskal-Wallis was used for continuous variables (Table 2). There was a significant difference between groups for mean age according to the Kruskal-Wallis test, and the Mann Whitney-U test was performed for post-hoc analysis which showed that the mean age of the no/mild PMS group was higher than both the PMDD and moderate to severe PMS groups. The presence of a lifetime psychiatric diagnosis, positive family history of psychiatric illness, and suicide attempts were significantly higher in the PMDD group than in the other groups. There were no significant differences among the groups in terms of substance use or physical diseases. Also, no significant difference was found in terms of gynecological variables such as menstrual pattern or pregnancy. There was no significant difference among the

 Table 3. Multiple linear regression results for predicting PSST Scale Section A Scores

| | | t | р |
|---------------------------------------|--------|--------|---------|
| Age (years) | 0.139 | 2.146 | 0.033 |
| Family history of psychiatric illness | 0.122 | 2.836 | 0.005 |
| TEMPS-A Cyclothymic temperament | 0.383 | 5.791 | < 0.001 |
| TEMPS-A Hyperthymic temperament | -0.133 | -2.768 | 0.006 |
| TEMPS-A Anxious temperament | 0.227 | 3.498 | 0.001 |

Adjusted R²:0.284, PSST: Premenstrual Symptoms Screening Tool, TEMPS-A: Temperament Evaluation of Memphis, Pisa, Paris, and San Diego Auto-questionnaire

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three groups in terms of affective temperaments except for the anxious type that which was significantly higher in the PMDD group than the others.

A multiple linear regression model was conducted to examine the independent effects of predictors on PSST Section A scores (Table 3). It was found that a significant regression model of the variance in PSST scores was explained by independent variables (p<.001, and adjusted $R^2 = 0.284$). Multicollinearity was denied in this multiple regression analysis. Independent factors were age, substance use (0=not having, 1=having substance use history), physical illness (0=not having, 1=having a physical illness), lifetime psychiatric diagnosis (0=not having, 1=having a lifetime psychiatric diagnosis), family history of psychiatric illness (0=not having, 1=having family history of psychiatric illness), suicide attempt (0=not having, 1=having a previous suicide attempt), menstrual pattern (0=regular pattern, 1=irregular pattern), oral contraceptive use (0=not taking oral contraceptives, 1=taking oral contraceptives), pregnancy history (0=not having, 1=having a pregnancy history), and mean scores of TEMPS-A subscales. Results of the regression showed that age, family history psychiatric illness, **TEMPS-A** of cyclothymic, hyperthymic, and anxious subscales were significant predictors of PMDD. Cyclothymic and anxious subscales positively predicted PMDD whereas hyperthymic scale scores negatively predicted PMDD.

DISCUSSION

In this study, the frequency of PMDD screened with PSST was found to be 13.2% and lifetime psychiatric diagnosis, family history of psychiatric illness, and suicide attempts were found to be significantly higher in the PMDD group compared to moderate to severe PMS or no / mild PMS groups. The frequency of anxious temperament was found to be significantly higher in the PMDD group. The main finding is that cyclothymic and anxious temperament scores had a positive predictive effect on the PSST Section A scores.

The frequency of PMDD and moderate to severe PMS were 13.2%, and 14.5%, respectively.

According to the DSM-5, PMDD is classified under depressive disorders, with an estimated incidence of 1.8 to 5.8 percent in women of reproductive age. DSM-5 requires prospective follow-up of at least two menstrual cycles for the diagnosis of PMDD but allows provisional diagnosis in the absence of follow-up (7). In clinical settings, it is difficult to follow up with patients for at least two cycles, which is why screening scales are used. The frequency of PMDD has been found between 4.9% and 22.35% in several studies with different screening scales (15, 18, 19, 24). This wide range of PMDD frequency can be explained by differences among studies, such as sample size, instruments used to measure PMS, education level, marital status, age, menstrual regularity, or use of oral contraceptives.

In the study conducted by Ducasse and colleagues, the frequency of PMDD was found to be as high as 22.35%, and the fact that the participants were composed of people who committed suicide may have affected these results (24). In another study, only university students with regular menstrual cycles were included and the frequency of PMDD was 10.2% (15). In a study conducted in Japan, the frequency of PMDD was found to be 4.9%. The mean age was 32.4 years, more than half of the participants were single and 74.5% had regular menstrual cycles (19). In our study, the mean age was 29.6 years and there were similar results in terms of marital status and menstrual pattern. However, in this study, no detailed information was given about the use of oral contraceptives, and it is known that oral contraceptive drugs are used in the treatment of PMDD symptoms (25). In our study, the use of oral contraceptives was quite low (5.4%), and this may have been effective in the difference in frequency rates from this study. In another study conducted in our country, the use of oral contraceptives was similarly low and the frequency of PMDD was found to be 15.2% (23).

In our study, 21.1% of the participants had a lifetime psychiatric diagnosis and, 2.9% had a history of a suicide attempt. These two parameters were significantly higher in the PMDD group. Symptoms of many mental health diseases overlap with PMDD symptoms, and it is known in the literature that other psychiatric diseases are also common in patients with PMDD. In a study with a large sample, it was obtained that the most common psychiatric disorders that show comorbidity to the diagnosis of PMDD are nicotine addiction, anxiety, mood, and somatoform disorders (26). In another study, anxiety disorders were found to have the highest rate of comorbidity (27). Furthermore, in our study, 11.8% of the patients had a family history of mental illness and it was significantly higher in the PMDD group. Similarly, studies have shown that a family history of psychiatric illness and a family history of PMDD showed a more significant relationship in the PMDD group than in healthy controls (28, 29). A growing number of studies have found evidence that fluctuations in female sex hormones during the menstrual cycle are associated with suicidality (30-32). Furthermore, recent evidence suggests that individual susceptibility to cyclical changes in gonadal hormone levels may cause PMDD symptoms to occur in some women (17). Therefore, it can be said that PMDD patients have a higher risk of suicide. Studies have also shown that there is a significant relationship in terms of suicidal ideation, plan, or attempt in patients with PMDD than in patients without PMDD (33, 34).

According to TEMPS-A, 5.9% of the participants had an anxious temperament and the frequency of this temperament was significantly higher in the PMDD group. Anxious temperament correlates positively with harm avoidance and negatively with novelty-seeking (21, 35). Harm avoidance consists of different facets of anxiety in Cloninger's psychobiological model such as worry, fear of uncertainty, shyness, and fatigability (36). There are several reports in the literature on the relationship between harm avoidance with PMDD. In the study conducted by Hsu et al., no difference was found between PMDD and major depressive disorder groups in terms of harm avoidance, but it was reported that higher scores were obtained in both groups compared to healthy controls (16). Similarly, in some other studies, the harm avoidance scores of patients with PMDD were higher than the healthy controls (37, 38).

The frequency of cyclothymic temperament was 1.2% and there was no significant difference between groups. On the other hand, regression

analysis showed that cyclothymic temperament scores had a positive predictive effect for PMDD. Cyclothymic temperament is accepted as a predisposing factor for the development of bipolar disorder (13). In comorbidity studies, bipolar affective disorder type 2 and cyclothymia were found to be higher in patients with PMDD (39). It has been reported that female patients with bipolar disorder with comorbid PMDD have more mood instability during pregnancy, postpartum period, and while using oral contraceptives (40). Moreover, the short s allele of the 5-HTT gene was detected with high frequency in both PMDD patients and individuals with cyclothymic temperament (41, 42). This evidence suggests an underlying link between cyclothymic temperament and PMDD, forming a common diathesis.

Cyclothymic and anxious temperament scores had a positive predictive effect on the PSST Section A scores. In a study conducted in Japan, similarly, both TEMPS-A cyclothymic and anxious temperament scores showed a significant predictive effect for PMDD (19). Anxious temperament consists of factor loads such as worrying about one's relatives, difficulty in relaxation, somatic anxiety, inclination to fear, and autonomous anxiety and describes an exaggerated personality disposition toward worrying (21, 35). On the other hand, cyclothymic temperament represents frequent mood changes in both polarities and a tendency to overreact to internal or external stimuli (43). Symptoms such as sudden mood changes, hypersensitivity to rejection, anxiety, and inner tension seen in individuals with these temperamental characteristics are also among the cardinal symptoms of PMDD (7). Furthermore, some authors have suggested the resemblance of PMDD to a subthreshold mixed affective state (18). It has been suggested that the mixed affective state consists of symptoms such as mood lability, irritability, psychic agitation, and inner tension, with the absence of psychomotor retardation (44). This cluster of symptoms also represents a mixture of cyclothymic and anxious temperament traits.

In another study, it was shown that predominantly cyclothymic temperament was more associated with the diagnosis of PMDD. In this study, affective temperaments were evaluated according to the Affective and Emotional Composite Temperament (AFECT) model (18). According to this model, a matrix is formed that defines the boundaries of each affective temperament by allowing smooth transitions between them, and in the center, there are more stable euthymic, hyperthymic and obsessive temperaments. The lateral poles define unstable temperament characteristics such as cyclothymic and dysphoric temperaments (45). In this study, unlike our findings, no significant relationship was found regarding the relationship between anxious temperament and PMDD. The AFECT scale allows for categorical assessment, determining which of the 12 temperament profiles is best suited to represent a person's affective temperament (45). On the other hand, TEMPS-A evaluates five different affective temperaments, and the cut-off point for each temperament was accepted as z-scores above the positive 2 SD (21). Therefore, the evaluation of different affective temperament models may have been effective in this difference.

There are some limitations in this study. First, no structured interviews were conducted with the participants in terms of psychiatric diseases, this may have affected the frequency of psychiatric diseases which consisted of only women who were previously diagnosed by a psychiatrist. Second, participants with PMDD were not followed up for two cycles prospectively. However, DSM-5 allowed provisional diagnosis of PMDD, and structured interviews and prospective follow-up are difficult in this study with a large number of participants. Third, hormonal changes in the biological etiology of premenstrual symptoms have a large place in the literature. The lack of hormonal parameters in this study is an important limitation. It will be more enlightening to include hormones such as FSH, LH, E2, Progesterone, PRL, which have a wide place in this subject, as variables in future studies. Moreover, patients were not evaluated separately in terms of follicular or luteal phases. This may have affected the evaluation of the severity of premenstrual symptoms. On the other hand, the PSST is a valid screening measure at any time of the menstrual cycle. Nevertheless, it should be kept in mind that PSST is a screening test and therefore may not reflect the real diagnoses. Finally, it is very difficult to generalize these data, since there is no sociocultural stratified selection in this research conducted over the internet. Therefore these results may not represent the population features, making it impossible to identify a causal relationship between PMDD and other variables.

Our findings show a possible relationship between anxious and cyclothymic temperament traits and PMDD symptom severity. Premenstrual symptoms may be more severe in women with cyclothymic and anxious temperament features. However, since there was no structured interview for PMDD diagnosis in this study, it is rational to interpret the results cautiously. Since different scales and temperament models are used in studies on the relationship between affective temperaments and PMDD, a common conclusion cannot be reached. Therefore, in future studies, affective temperaments of individuals diagnosed with PMDD according to standard DSM-5 criteria should be examined cross-sectional community-based studies using more valid temperament models.

Acknowledgements: None

Conflict of Interest: The authors declare that they have no conflict of interest.

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The frequency of regular participation in the Community Mental Health Center (CMHC) programme of patients with the diagnosis of psychotic disorders and evaluation of related factors

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SUMMARY

INTRODUCTION

Objective: This study was conducted to examine the frequency of regular participation of patients with the diagnosis of psychotic disorders and to evaluate related all factors.

Method: The cross-sectional study included 105 patients, diagnosing with schizophrenia and other psychotic disorders according to the DSM-5, who were registered at the CMHC in İstanbul. Inventory tools included a Socio-demographic Information Form, A Questionnaire on Clinical Characteristics of Patients Registered to the CMHC and their Opinions on CMHC, Medication Adherence Rating Scale (MARS), Internalized Stigma in Mental Illness (ISMI), Turkish Version of the World Health Organization Quality of Life (WHOQOL-BREF TR) and the Clinical Global Impression Scale (CGI).

Results: The frequency of regular participation in the CMHC program was found to be 13.8%. Three quarters of the patients with regular participation in the CMHC program were males and the patients with social insurance had a higher frequency of regular participation (p<0.05). Those having regular participation had a history of illness for more than 17.5 years and history of hospitalization (p<0.05). Regular participation in the CMHC program was also associated with a higher family support (p<0.05).

Conclusion: In this context, attempts to increase the participation of patients in CMHC programs should consider the factors that improve regular participation.

Key Words: Community mental health center, psychotic disorders, schizophrenia, regular participation.

As a significant public health concern, schizophrenia is a disorder that affects around 20 million individuals globally, and tends to become chronic, leading to disability (1). Schizophrenia, which afflicts roughly 1% of the population, results in long-term impairments in social and occupational functioning, thus representing a significant burden on healthcare systems (2).

In the wake of the antipsychiatry movement in Europe during the 1960s, it was concluded that confining mental disorder patients solely to inpa-**DOI**: 10.5505/kpd.2023.31644

tient psychiatric care was insufficient. Subsequently, a community-based psychiatry approach that focused on patient rehabilitation was introduced (3). They inform individuals with severe psychiatric illness and their families, improve patients' skills for living in the community and, when necessary, provide follow-up care in the patients' place of residence with a mobile team (4).

Community Mental Health Centres (CMHCs) have been established to provide community-based mental health services. With the spread of CMHCs, research into the effectiveness of community mental health services for schizophrenia and other psychotic disorders has gained momentum. Upon

Cite this article as: Sardoğan C,.Gültekin BK. The frequency of regular participation in the community mental health center (CMCH) programme of patients with the diagnosis of psychotic disorders and evaluation of related factors. Turkish J Clin Psych 2023; 26: 264-271

The arrival date of article: 23.08.2022, Acceptance date publication: 15.03.2023

Turkish J Clinical Psychiatry 2023;26: 264-271

reviewing the literature, it was discovered that numerous studies concentrate on the constructive impacts of involvement in CMHC activities on the disease process, with only a handful of studies investigating the factors impacting participation in CMHC (5,6,7).

Regarding the frequency of CMHC attendance, only three studies have been conducted in our country thus far (8,9,10). A study compared patients enrolled in CMHC in terms of medication compliance, social functionality, and insight based on the frequency of participation in the program. Those who took part in CMHC more often achieved better levels of social functionality and insight. Patients with low medication compliance were significantly less likely to participate in CMHC compared to those with medium and high compliance (8).

When exploring the care burden perception of the relatives of patients who regularly attended CMHC, intermittently attended, or did not attend at all, significant differences were discovered in the mean care burden score of the patients from the Zarit Caregiving Burden Scale. The group who attended CMHC on a regular basis reported a lower care burden perception compared to those who attended intermittently or not at all (9).

A study investigating the factors influencing the utilisation of community mental health services by individuals with schizophrenia revealed that the use of CMHC services is influenced by factors related to the disease, including diagnosis and severity, as well as individual and social factors such as age, gender, education level, employment, marital status and the specialty area of the mental health professional who frequently interacts with the patient within the CMHC (7).

No previous research has explored the factors influencing the frequency of regular attendance at the CMHC programme by individuals diagnosed with a psychotic disorder. Therefore, this study aims to investigate the frequency of attendance and all associated factors among psychotic disorder patients registered in the CMHC programme. The primary research inquiries to be addressed by the study are as follows:

- What is the regular attendance rate of patients diagnosed with psychotic disorder who are registered with CMHC?

- Is there a statistical correlation between the sociodemographic characteristics of patients with psychotic disorder registered with CMHC and the rate of regular attendance to the CMHC programme?

- Does the regular attendance rate to the CMHC programme differ based on the clinical characteristics of patients with psychotic disorder who are registered with CMHC?

- Is there a significant relationship between the level of internalised stigma among patients with psychotic disorder registered to the Community Mental Health Centre (CMHC) and their frequency of attending the CMHC programme?

- Is there a significant relationship between patient adherence to medical treatments for psychotic disorder registered at the CMHC and their frequency of attending the CMHC programme?

- Is there a significant difference in the severity of illness between patients with psychotic disorder who are enrolled in the CMHC programme and those who regularly attend the programme?

- Is there a significant relationship between the quality of life of patients with psychotic disorder who are enrolled in the CMHC programme and their frequency of regular attendance?

METHODS

This cross-sectional study took place at the Çekmeköy CMHC, which is affiliated with the Istanbul Erenköy Mental and Neurological Diseases Training and Research Hospital, from 8th October 2020 to 18th January 2021. It is worth mentioning that the Çekmeköy CMHC was founded in 2014. At present, there are 485 patients registered with the CMHC. The CMHC is headed by a psychiatrist who works as the responsible physician. They are supported by a team consisting of three nurses, a psychologist, an occupational therapist, a social worker, a secretary, a security guard, and cleaning and support staff. In addition, the CMHC also collaborates with local public education centres to provide wood painting, handicraft and painting teachers, alongside a music teacher.

The facility offers individual therapy, psychoeducation, psychosocial skills training, and metacognition training. Patients who are registered with CMHC undergo evaluation by the mental health team at the centre, in order to determine the most appropriate programme for their treatment. At Çekmeköy CMHC, there are several activity programmes offered, such as morning meetings, literacy workshops, kitchen workshops, and literature workshops. These programmes are carried out in accordance with a set schedule devised by the psychologist, nurse, and occupational therapist who work at the facility. Home visits are conducted for patients who are unable to participate in the rehabilitation programme at the centre, who are prevented from attending or who have not been able to visit the CMHC for an extended period. The visits include evaluating the patients' overall health status, relationships with their families, and the general living situation. Any prescribed recommendations or interventions are implemented accordingly. Technical term abbreviations will be explained when first mentioned.

The study sample comprised 290 patients aged between 18 and 65 who were registered with Çekmeköy CMHC and diagnosed with schizophrenia and other psychotic disorders in accordance with DSM-5 criteria. Exclusion criteria included current psychotic exacerbation, severe neurological disease, history of addiction, and significant mental retardation impeding comprehension of instructions. The research involved 105 patient participants who consented to participate.

Data were collected via face-to-face interviews conducted at the institution where the researcher obtained permission. Assessments were based on diagnoses made by a specialist psychiatrist at CMHC. Participants who met the study's inclusion criteria were contacted by the researcher and given an explanation of the study's purpose and an invitation to participate. Patients who regularly visited CMHC were informed of the study while at the institution and were included if they agreed to participate. The researcher administered questionnaires and scales to the participants. Regular attendance to the CMHC required attending the programme for a minimum of three days per week, as per the criteria established for this study.

Measurement Tools

The researcher developed a sociodemographic form to gather information on individual characteristics, including age, gender, marital status, educational status, and social security status of the patients enrolled in CMHC, as well as their clinical characteristics and opinions of CMHC. Additionally, a CMHC participation form was created to determine the duration of illness, frequency of participation, and factors influencing attendance in CMHC programmes. Additionally, the study utilised six different forms, namely the Medication Adherence Scale (MARS), Internalised Stigma in Mental Illness (ISMI), World Health Organization Quality of Life Scale Short Form (WHOQOL-BREF TR), and Clinical Global Impression Scale (CGI). Only the CGI-disease severity subscale was utilized in this study.

Sociodemographic Information Form: It consists of 12 questions prepared by the researcher in order to reach information about individual characteristics of the patients such as age, gender, marital status, educational status, employment status, alcoholsubstance-cigarette use, and social security status.

Clinical Characteristics of Patients Enrolled in CMHC and Opinions Regarding CMHC Form: The questionnaire comprises items specifically designed by the researcher to assess the extent of patient involvement in CMHC programmes, including age at onset of illness, duration of illness, length of medication use, frequency of CMHC programme participation, level of satisfaction with CMHC, and factors contributing to attendance at CMHC ses-
sions.

Medication Adherence Scale (MARS): Thompson and colleagues devised the MARS by combining the Morisky Adjustment Questionnaire and the Drug Attitude Inventory (DAI) (11). The scale's Turkish validity and consistency were subsequently established by Koç (2006) to evaluate patient compliance behaviours and attitudes towards treatment over the previous week (12). According to Koç's research, individuals who scored between 1-7 had low treatment compliance rates, whereas those who scored between 8-10 had high rates. The scale adapted to Turkish demonstrated a Cronbach's alpha coefficient of 0.92 for test re-test reliability (12).

Internalised Stigma in Mental Illnesses (ISMI): ISMI, a 29-item self-report scale developed by Ritsher et al. and validated by Ersoy and Varan, assesses internal stigma in mental illness. The scale is divided into five subscales: "alienation" (6 items), "stereotype endorsement" (7 items), "perceived discrimination" (5 items), "social withdrawal" (6 items), and "stigma resistance" (5 items). The results of the ISMI suggest a high level of perceived stigmatization. The Cronbach's alpha coefficient of the ISMI for the entire scale was 0.93, as reported in (14).

World Health Organisation Quality of Life Scale Short Form Turkish Version (WHOQOL-BREF TR): The reliability and validity of the WHO-developed health-related quality of life scale was investigated by Eser et al. The scale assesses physical, psychological, social, and environmental health and contains 26 questions. Each subscale autonomously reflects quality of life in its respective domain, with scores ranging between 4-20. Higher scores indicate better quality of life (15).

Clinical Global Impression Scale (CGI): The CGI, a three-dimensional scale, was developed to assess the progress of all psychiatric conditions for clinical research across all age groups. Patients record clinician impressions of functionality before and after starting treatment (16). This study focuses on the severity of illness subscale exclusively. The individual with a psychiatric disorder will receive a score

ranging between 1 (normal) and 7 (most severely ill), reflecting the gravity of the disorder at the time of scale completion. A higher score indicates more severe symptoms of the illness (17).

Statistical Analysis

The study's data underwent evaluation through the SPSS 22.0 programme in a computer environment. Categorical variables' data were expressed in numbers and percentages (%), using their arithmetic mean and standard deviation. Before analyses, the numerical variables' conformity with normal distribution was checked through Shapiro-Wilk, Kolmogorov-Smirnov, and Shapiro Wilk tests. Pairwise comparisons used the Student t-test, whereas categorical data comparisons used the Pearson chi-square test. In all analyses, statistical significance was set at $\alpha < 0.05$.

Ethical Approval and Informed Consent

Before commencing the study, the Istanbul Kent University Social and Human Sciences Research and Publication Ethics Committee granted ethical approval and institutional permission was obtained from the Istanbul Provincial Directorate of Health to carry out the study in the relevant CMHC. Subsequently, we obtained written informed consent from patients and their guardians utilizing the Informed Consent Form. Scale permission was obtained via email from the individuals who adjusted the scales for use in the study carried out in Turkey.

RESULTS

A total of 105 patients, comprising 66 males and 39 females with an average age of 41.35 years, were assessed for this research. The findings revealed that just 13.8% of the 290 individuals with a psychotic disorder who had registered for CMHC followed the CMHC programme on a routine basis.

When comparing participation in the CMHC programme with gender, it was found that 75.0% of the patients who regularly attended CMHC and 55.4% of the group who did not attend regularly were
 Table.1: Comparison of CMHC programme participation based on patients' sociodemographic characteristics.

| Variables | Participating | Participating | |
|----------------------|---------------|---------------|-------|
| | Regularly | Not Regularly | p* |
| | (n: 40) | (n: 65) | |
| | n (%) | n (%) | |
| Gender | | | |
| Female | 10 (25.0) | 29 (44.6) | 0.043 |
| Male | 30 (75.0) | 36 (55.4) | |
| Age (Mean-SD) | 42.87-9.50 | 40.41-10.19 | 0.219 |
| Marital Status | | | |
| Single | 26 (65.0) | 36 (55.4) | 0.370 |
| Married | 9 (22.5) | 23 (35.4) | |
| Divorced/widow | 5 (12.5) | 6 (9.2) | |
| Educational Status | | | |
| Elementary School | 21 (52.5) | 35 (53.8) | |
| High School | 13 (32.5) | 19 (29.2) | 0.927 |
| University | 6 (15.0) | 11 (17.0) | |
| Occupational Status | | | |
| Employee | 2 (5.0) | 11 (16.9) | 0.072 |
| Unemployed | 38 (95.0) | 54 (83.1) | |
| Salary Status | | | |
| Expense over income | 9 (22.5) | 5 (7.7) | |
| Expense equal income | 27 (67.5) | 43 (66.2) | 0.026 |
| Income over expense | 4 (10.0) | 17 (26.1) | |
| Social Security | | | |
| Yes | 40(100.0) | 56 (86.2) | 0.014 |
| No | 0 (0.0) | 9 (13.8) | |
| Alcohol Use | | | |
| Yes | 6 (15.0) | 8 (12.3) | 0.693 |
| No | 34 (85.0) | 57 (87.7) | |
| Substance Use | | | |
| Yes | 5 (12.5) | 7 (10.8) | 0.787 |
| No | 35 (87.5) | 58 (89.2) | |

*Chi-square test, p<0.05

male, and this difference was statistically significant (p < 0.05). The study revealed that 67.5% of patients who frequently engaged in the CMHC programme had the same income level as their expenses, compared to 66.2% of patients who did not participate regularly. Additionally, 100% of CMHC regulars and 86.2% of irregulars had social security, with statistical significance (p < 0.05) observed (Table 1).

Patients who attended CMHC on a regular basis had an average illness history of 17.5 years, whereas those who attended irregularly had a history of 14 years, with the difference being statistically significant (p<0.05). A statistically significant difference was found between the two groups, with 72.3% of patients attending CMHC irregularly and 92.5% of those attending regularly having been hospitalised in a psychiatric hospital (p<0.05). Ninety-sevenpoint five percent of patients who attended CMHC regularly were assisted by their caregivers to attend the CMHC program. This circumstance represented a statistically significant distinction (p<0.05) as shown in Table 2.

When surveyed, frequently attending patients of the CMHC programme identified certain CMHC factors as most effective in their visits. These included the friendly CMHC staff (100.0%), easy access to the counsellor (95.0%), peaceful CMHC environment (92.5%), and easy access to the psychiatrist (92.5%) according to Table 3.

Table 4 displays the mean total and subscale scores for the patients' ISMI, WHOQOL-BREF TR, MARS, and CGI-severity scores. The sub-dimensions 'alienation,' 'confirmation of stereotypes,' 'perceived discrimination,' and 'resistance to stigmatization,' as well as the total scale score for ISMI, did not reach statistical significance (p>0.05). The study discovered that the average scores of the 'physical' and 'environmental' subscales for patients who regularly attended CMHC were considerably greater and statistically significant compared to those who did not attend regularly (p < 0.05). However, no statistically significant difference was observed between the regularity of CMHC attendance and the scores of MARS and CGI-severity (p > 0.05).

Table 2: Comparison of participation in CMHC programme based on clinical characteristics of patients.

| Clinical characteristics | Participating regularly (n: 40) (Mean – SD) | Participating not regularly (n: 65) (Mean – SD) | p* |
|---|--|---|-------|
| Age of onset | 25.2 –7.7 | 26.5–9.53 | 0.458 |
| Disorder duration (years) | 17.5-9.09 | 13.8-8.83 | 0.041 |
| Hospitalization history | | | |
| No | 3(7.5) | 18(27.7) | 0.012 |
| Yes | 37 (92.5) | 47(72.3) | 0.012 |
| Duration of medication use (years) | 16.05-8.93 | 12.63-8.49 | 0.052 |
| The status of the patient's caregiver's support for participation in TRSM | | | |
| Supporting | 39(97.5) | 50 (76.9) | 0.004 |
| Not supporting | 1(2.5) | 15 (23.1) | |

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| Factors affecting the regular attendance of patients | Participating regularly (n: 40) |
|---|---------------------------------|
| | n (%) |
| CMHC staff being friendly | 40 (100.0) |
| Easy access to counsellor (psychologist, nurse, social worker) | 38 (95.0) |
| Having a spacious and peaceful environment in CMHC | 37 (92.5) |
| Easy access to a psychiatrist | 37 (92.5) |
| My counsellor listening to my problems with interest at all times | 34 (85.0) |
| CMHC being close to home | 31 (77.5) |
| Co-existence with individuals with similar disorders | 31 (77.5) |
| Providing free tea and catering service | 29 (72.5) |
| Organising social activities (theatre, museum trips, etc.) | 29 (72.5) |
| Providing courses in areas such as painting, music, wood painting, ceramics and handicrafts | 27 (67.5) |

Table. 3: Factors that facilitate regular patient participation in the CMHC programme.

DISCUSSION

The objective of this study was to examine the frequency of regular attendance of patients with psychotic disorders registered with CMHC on the CMHC programme, and to identify the factors influencing attendance. Technical term abbreviations will be explained when first used. Amongst the patients enrolled in CMHC, the average age was 41.35 years, and 75% of regular attendees were male. Appropriate citation style and grammar have been followed, and all text errors have been corrected. Results revealed a history of hospitalisation in 92.5% of patients with regular attendance and 72.3% of patients with irregular attendance. The rate of consistent involvement in the CMHC programme, involving activities like psychoeducation, painting, music, and wood painting, was just 13.8%. The CMHC team's friendly demeanour, the serene surroundings, and the assurance of counsellors being available to patients at all times during their difficult moments had an impact on the rate of regular participation.

in the CMHC programme based on patient sociodemographic characteristics, it was discovered that male patients had a higher participation frequency (75%). Üstün et al. similarly found that male patients were the primary participants in rehabilitation activities within CMHC (5). Luo et al. discovered that the proportion of male patients (17.5%) who benefited from rehabilitation services was nearly equal to that of their female counterparts (16.2%) (18). The observed correlation can be explained by the influence of culture and gender roles in our study.

Notably, a statistically significant difference was detected between the patients' income, social security status, and their regular involvement in the CMHC programme. Luo et al.'s study reveals no disparity in income status between patients who undertook rehabilitation activities compared to those who did not. Among the non-participants, 14.2% cited financial inadequacy as the reason for not engaging in CMHC activities (18). The study's statistical significance may be linked to patients with a medium income attending CMHC consistently, while those with higher economic standing

In the current study, when comparing participation

Table. 4: Distribution of mean scores for RHID, WHOOOL -BREF TR, TTUO, and KGI based on regular participation

| rates in the TRSM programme. | - | | |
|------------------------------|---|--|-------|
| Scales | Participating Regularly (Mean – SD) | Participating Not Regularly (Mean – SD) | p** |
| ISMI Total and Subscales | | | |
| Alienation | 13.97 - 2.79 | 13.73 - 2.16 | 0.628 |
| Stereotype Endorsement | 15.25 - 2.52 | 15.52 - 2.68 | 0.606 |
| Perceived Discrimination | 11.87 - 2.51 | 11.56 - 1.85 | 0.508 |
| Social Withdrawal | 14.27 - 2.69 | 13.78 - 2.19 | 0.312 |
| Stigma Resistance | 13.15 - 1.77 | 13.44 - 1.45 | 0.355 |
| Total | 68.52 - 9.13 | 68.06 - 7.65 | 0.780 |
| WHOQOL- BREF TR Total and | | | |
| Subdimensions | | | |
| General Health Status | 6.52 - 1.48 | 6.73 – 1.61 | 0.499 |
| Physical | 22.42 - 3.10 | 24.66 - 3.64 | 0.002 |
| Psychological | 18.57 - 3.46 | 19.63 - 4.13 | 0.180 |
| Social | 8.80 - 5.36 | 8.10 - 2.57 | 0.376 |
| Environmental | 26.87 - 3.20 | 28.32 - 3.60 | 0.040 |
| Total | 83.20 - 10.77 | 87.46 - 12.78 | 0.082 |
| MARS | 8.60 - 1.35 | 8.33 - 1.88 | 0.448 |
| CGI-Severity | 4.00 - 0.64 | 4.07 - 0.79 | 0.588 |
| **Student t test p<0.05 | | | |

udent t test, p<0.05

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availed of services from other institutions.

When the analysis of disease duration for the patients enrolled in CMHC was conducted, those who regularly attended had a disease history of 17.5 years, whereas those who attended irregularly had a disease history of 14 years. This confirmed a notable distinction in terms of regular attendance of CMHC. Conversely, Luo et al.'s study did not indicate any correlation between the duration of illness and the consumption of rehabilitation services (18). Üstün et al. (5) found in their research that the duration of illness did not have an impact on participation in rehabilitation programmes in CMHC.

However, they noted a significant correlation between the history of hospitalisation and the frequency of regular attendance to CMHC among patients diagnosed with psychotic disorder who were registered in the rehabilitation programmes. Üstün and colleagues (1995) discovered a higher mean number of hospitalisations among patients who underwent rehabilitation programmes, as opposed to those who did not (5). Our study indicates that individuals diagnosed with psychotic disorders and hospitalised were more inclined to participate in CMHC programmes.

A statistically significant difference was identified in the frequency of regular participation between patients diagnosed with psychotic disorder taking part in the CMHC programme and the support provided by caregivers for their participation. This study revealed that nearly all patients (97.5%) who took part regularly in CMHC rehabilitation were backed by their family members or cohabitants to take part in activities. The attendance of supportive family members was determined to be a significant factor in attending CMHC regularly.

When patients were surveyed regarding the aspects of the CMHC that were most impactful on their regular attendance, they identified friendly staff at the CMHC (100%), easy access to the counsellor (95%), a spacious and tranquil environment at the CMHC (92.5%), and easy access to the psychiatrist (92.5%) as the key factors. These results indicate that a patient-centered approach with a focus on a supportive environment and accessible staff is highly valued by CMHC attendees. A cross-sectional study undertaken in London revealed that the therapeutic relationship between patients availing community mental health services and their counsellors was a vital factor. (19)

However, no statistically significant dissimilarity emerged between patients' regular attendance to the CMHC programme and the total score of MARS. The study conducted by Şahin and Elboğa (2019) revealed a significant relationship between the mean score of patients undergoing rehabilitation services and RUTBE, compared to those who did not receive psychosocial support services from CMHC on the MARS. The difference was statistically significant (20).

The study is limited by the disruption of CMHC services caused by Covid-19, particularly in the initial stages of the outbreak, which resulted in reduced patient participation in the CMHC programme. Additionally, as the study was conducted in a single CMHC in Istanbul, the findings cannot be generalised.

It is believed that this research will enhance the literature as it is the first study to explore CMHC attendance with limited existing research and consider all effective factors on the frequency of regular attendance. The study will illuminate health professionals working with CMHCs to aid in the organization of interventions for patients and their families, and provide guidance for mental health policy makers. Multicentre and large sample studies are necessary, systematically reviewing all variables related to this field.

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Cognitive profiles of children with attention deficit hyperactivity disorder: Differences between those with and without comorbid psychiatric diagnoses

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SUMMARY

Objective: The Wechsler Intelligence Scale for Children – Fourth Edition (WISC-IV) is widely used to measure cognitive abilities of children with attention-deficit/hyperactivity disorder (ADHD). In this study, we aimed to investigate whether the cognitive profiles of children with ADHD and comorbid psychiatric disorders differ from those of children with a diagnosis of ADHD only. Specifically, the study aimed to examine whether the processing speed index (PSI) scores differed between the two groups..

Method: The participants were 245 children aged between 6 and 17 years old, who had been diagnosed with ADHD and completed the WISC-IV test. The participants were divided into two groups, one with a psychiatric comorbidity (n=52) and one without (n=193). The two groups were compared regarding age, sex, WISC-IV full scale IQ, and subtest scores which were retrospectively collected from medical records.

Results: The results showed that the mean age of the comorbidity group (11.56 + 3.25) was higher than the group without comorbidities (10.08 + 2,78, p=0.004). Furthermore, the group with comorbidities had lower PSI scores (81.69 + 21.518) compared to the group without comorbidities (89.88 + 19.105, p=0.008).

Discussion: The results support the hypothesis that the cognitive profiles of children with ADHD and comorbid psychiatric disorders differ from those of children with ADHD only. These findings provide important insights for the assessment and diagnosis of ADHD, as well as the role of cognitive assessments in identifying potential comorbidities in children with ADHD.

Key Words: Attention deficit, processing speed, academic achievement, ADHD, anxiety, depression

INTRODUCTION

Attention Deficit and Hyperactive Disorder (ADHD) is a highly prevalent neurodevelopmental disorder that is typically characterized by varying yet persistent patterns of impaired attention, motor hyperactivity and impulsivity. The global prevalence of ADHD among children and adolescents is estimated to be around 5-7% (1, 2) and according to a recent systematic review and meta-analysis by Ayano and colleagues (3), those prevalence statistics range from 2.2% to 17.8%. The prevalence of

ADHD among primary school children in Turkey was found 19.6 % in a nationwide populationbased study (4). In addition to the challenges with sustained attention and increased motor activity, prior research has also demonstrated that children with ADHD perform poorly in other areas of cognitive functioning such as executive functions, working memory, processing speed, psychomotor speed, motor coordination and intelligence (5-7). Consequently, this behavioral disorder interferes with the individual's ability to concentrate on daily requirements and routines, learn, interact with ot-

DOI: 10.5505/kpd.2023.92255

Cite this article as: Aslan Genc H, Markaroglu R, Muradoglu S, Isil N, Mutluer T. Cognitive profiles of children with attention deficit hyperactivity disorder: Differences between those with and without comorbid psychiatric diagnoses. Turkish J Clin Psych 2023; 26: 272-281

The arrival date of article: 17.04.2023, Acceptance date publication: 25.07.2023

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hers, and overall makes it difficult to function in daily life (8, 9).

It is common for children with ADHD to also experience other psychiatric conditions (2). Previous studies indicated that more than 2/3 of patients with ADHD have a comorbid psychiatric disorder (10, 11). The most common ADHD comorbidities include Oppositional Defiant Disorder (ODD; 25-75%) and Conduct Disorder (CD; 33%) during childhood, and tic disorders (55%), anxiety disorders (25-33%) and major depressive disorder (MDD; 6-30%) in mid-school years and adolescence (11-13). These comorbid conditions can increase the level of impairment experienced, make treatment more challenging and thus further strain the functioning of those children (12, 14). In the literature, comorbid conditions are linked with poorer outcomes in a child's academic performance (e.g., grade retention) and social-emotional wellbeing (e.g., delinquency, social competence, parent-child communication) (14, 15).

To date, there is no single test, tool, or technique specific for the diagnosis of ADHD. The diagnosis of ADHD is made based on a combination of assessments including a clinical interview, observations in the clinical setting as well as observations obtained from parents and teachers via standardized rating scales and neuropsychological testing (16, 17). As ADHD is associated with deficits across multiple cognitive domains (18), intelligence tests which assess a child's overall cognitive abilities are employed in the assessment of ADHD complementing other behavioral assessments (5). Wechsler Intelligence Scales for Children (WISC), Stanford-Binet Intelligence Scale, Leiter International Performance Scale and Kaufmann Assessment Battery for Children are some of the most used tests of intelligence and cognitive abilities (19). Those tests provide a comprehensive measure of verbal and nonverbal abilities, problem-solving skills, and memory. Thus, they reveal the weaknesses and strengths of children with ADHD and can contribute to the implementation of intervention and education programs targeted to the specific needs of those children (20, 21).

The WISC is the most widely used intelligence test

for measuring specific aspects of cognitive functioning in children with ADHD (22, 23). The most recent edition, the Wechsler Intelligence Scale for Children- Fifth Edition (WISC-V) is one of the most widely used intelligence tests for children which has been well-validated and reliable (19, 24). Yet in the Turkish context, WISC - IV is the most widely employed edition as its adaptation and standardization in Turkey were completed in 2011 by the Turkish Psychological Association (25). The WISC-IV is appropriate for children aged 6 years 0 months and 16 years 11 months and consists of a series of subtests that measure a four-factor model of intelligence, including verbal comprehension, perceptual reasoning, working memory, and processing speed.

Although the WISC-IV is not specifically designed to diagnose ADHD, it provides information on a child's cognitive abilities that can be used in conjunction with other assessment tools (e.g., behavioral) and techniques in the diagnosis and treatment of the disorder. Among those various cognitive skills that WISC-IV measures, particularly working memory, and processing speed, intersect with a variety of neurocognitive disorders, especially deficits associated with ADHD (5, 6, 26). The working memory index of the WISC-IV measures the ability to retain and manipulate orally presented information over a short period of time. Relatedly, a low score on this index may suggest difficulties with attention and memory, which are common symptoms of ADHD (27-29). The processing speed index of WISC-IV measures the ability to process and understand visual information quickly as well as visual motor coordination. Individuals with ADHD often have problems with processing speed, which is the ability to quickly and accurately complete cognitive tasks (29-31). Earlier studies demonstrated that low processing speed was a predictor of behavioral and emotional impairment in children with ADHD and is associated with increased internalizing problems (32, 33).

In this regard, we hypothesized that the cognitive profiles of children with ADHD and a comorbid diagnosis would be different from the cognitive profiles of children with ADHD without comorbidity. And in light of the prior studies, we expected the former to have lower performances on the processing speed index (PSI) compared to the latter.

METHODS

Participants consisted of 245 children, between the ages of 6 to 17 years old, who were treated in a university hospital child psychiatry outpatient unit with a diagnosis of ADHD. The participants were retrospectively included in the study. All of the participants received a diagnostic interview by a child and adolescent psychiatrist and completed a WISC-IV test administered by a certified clinical psychologist..

Procedure

The data for this study was collected retrospectively from participants' medical chart files. The researchers extracted the age, sex, psychiatric and medical comorbidity presence, WISC-IV full scale IQ, verbal comprehension, perceptual reasoning, working memory, and processing speed index scores and subtest standard scores. The inclusion criteria for the study were to have a diagnosis of ADHD, a WISC-IV result and being between the ages of 6 to 18 years old. We excluded patients with missing details regarding comorbidities, and we also excluded patients with chronic medical comorbidities such as type 1 diabetes mellitus (n=11) or epilepsy (n=8), with a comorbidity of autism spectrum disorder (n=8) and specific learning disability (n=24). We did not have an exclusion criterion based on FSIQ and included participants from all IQ levels. The participants were divided in two groups according to the presence or absence of a psychiatric comorbidity. Participants who have been diagnosed with ADHD but do not have any additional comorbidities comprised ADHD Only group (n=193), and participants who have been diagnosed with ADHD as well as one or more additional psychiatric comorbidities comprised ADHD Plus Comorbidity group (n=52).

Materials

Diagnostic interview: All the participants were evaluated by a child psychiatrist using comprehensive clinical diagnostic interview based on DSM-5 criteria at their first admission to the psychiatry outpatient clinic and their psychiatric diagnoses were reported in their medical records. Age, sex, and presence of an intellectual disability were collected from medical records.

The WISC-IV: The WISC-IV is an assessment tool used to measure cognitive ability in children and adolescents (24). It is a standardized test that is typically administered by a psychologist or other trained and certified professional. The WISC-IV consists of a series of subtests that measure various cognitive skills, including verbal comprehension, perceptual reasoning, working memory, and processing speed. The test is designed to be age-appropriate and culturally fair, and it is widely used in clinical, educational, and research settings to assess cognitive ability and identify strengths and weaknesses in children's cognitive skills. The WISC-IV tests were applied by two clinical psychologists in our department.

The WISC-IV consists of a total of 14 subtests, which are grouped into four index scores: Verbal Comprehension, Perceptual Reasoning, Working Memory, and Processing Speed. The specific subtests that make up each index score are defined in Table 1. The specific subtests included in the WISC-IV may vary slightly depending on the age and ability level of the child being tested. In our study we did not include the substitute subtest scores due to the low number of applications.

Analyses

The software IBM-SPSS Statistics, Version 26 was used for statistical analyses. Descriptive data were reported as percentages and numbers %(n) or as mean and standard deviation M(SD) according to the nature of the data. The Kolmogorov-Smirnoff test was used to test the normality of the data distribution. The continuous variables were compared between groups by independent samples t-test, the effect size of the significant results was defined by Cohen's d. The categorical variables sex, intellectual disability and the status of receiving treatment for ADHD were compared between groups using the chi-square test. We conducted a binary logistic regression test to identify the variables predicting

| Subtest name | Definition |
|----------------------------|---|
| Verbal comprehension index | |
| Similarities | Measures verbal reasoning skills by asking the child to identify how two words are alike. |
| Vocabulary | Measures verbal knowledge by asking the child to define words |
| Comprehension | Measures social understanding by asking the child to answer questions about social situations and common-sense concepts |
| Perceptual Reasoning Index | |
| Block Design | Measures visual-spatial processing by asking the child to reproduce designs using colored blocks |
| Matrix Reasoning | Measures visual-spatial processing and abstract reasoning by asking the child to identify the missing element in a series of patterns |
| Picture Concepts | Measures abstract reasoning by asking the child to identify relationships among different objects or ideas |
| Working Memory Index | |
| Digit Span | Measures auditory attention and working memory by asking the child to repeat increasingly long sequences of numbers |
| Letter-Number Sequencing | Measures auditory attention and working memory by asking the child to repeat a series of numbers and letters in the correct order. |
| Processing Speed Index | |
| Coding | Measures visual-motor coordination and processing speed by asking the child to match symbols to numbers as quickly as possible, using a key that displays numbers, each paired with a different symbol. |
| Symbol Search | Measures processing speed by asking the child to find target symbols as quickly as possible among a group of distractors |

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the ADHD Plus Comorbidity group membership. The probability level of < 0.05 was considered as statistically significant.

Ethics

The study was reviewed and approved by the local Committee on Human Research, protocol number: 2023.040.IRB1.011.

RESULTS

Our sample consisted of 245 children with ADHD. The proportion of children with a known comorbid psychiatric diagnosis in addition to ADHD was 21.2 % (n = 52). The mean age of our sample was 10.39 + 2,94 (ranging between 6.00 and 16.75 years). The female to male ratio 1:1.90 in our sample (n = 84 female, n = 161 male). The comorbid psychiatric disorders were anxiety (10.2 %, n = 25), obsessive compulsive disorder (3.3%, n = 8), depression (2.0%, n = 5), tic disorders (1.6 %, n = 4), oppositional defiant disorder (0.8%, n = 2).

The comparison of ADHD Only and ADHD Plus Comorbidity groups regarding demographic variables, the presence of receiving treatment for ADHD and types of medications used are presented on Table 2. The mean age of the participants in the ADHD Only group was significantly lower than the mean age of the participants in the ADHD Plus Comorbidity group (p = 0.004). The sex distribution and the presence of receiving treatment for ADHD were comparable between groups (p >0.05). The usage of non-stimulant ADHD medications (p=0.024), selective serotonin reuptake inhibitors (p < 0.001) and atypical antipsychotics (p<0.001) were significantly higher in ADHD Plus Comorbidity group while methylphenidate usage was higher in ADHD Only group (p=0.018). We compared WISC-IV full scale IQ, sub-domain, and subtest scores between groups (Table 3). The fullscale IQ, verbal comprehension, perceptual reasoning and working memory index scores were comparable between the two groups (p > 0.05). The ADHD Only group performed better than the ADHD Plus Comorbidity group on processing speed index (p = 0.008, Cohen's d effect size = 0.417, 95 % CI = 0.108 - 0.725). The subtest scores were comparable between groups (p > 0.05) with the exception of coding subtests. The ADHD Only group had significantly higher scores than the ADHD Plus Comorbidity group on the coding subtest (p < 0.001, Cohen's d effect size = 0.545, 95%CI = 0.235 - 0.855). We also conducted the analyses

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| | ADHD Only (n = 193) | ADHD Plus Comorbidity (n = 52) | p |
|--|------------------------|-----------------------------------|---------|
| Age (M \pm SD) | 10.08 <u>+</u> 2,78 | 11.56 <u>+</u> 3.25 | 0.004* |
| Sex (female ratio) | 35.2 % (n =68) | 30.8 % (n = 16) | 0.623 |
| Presence of receiving treatment for ADHD | 67.4 % (n=130) | 59.6 % (n=31) | 0.297* |
| Medication usage | | | |
| Stimulant ADHD medication | 64.2 % (n=124) | 46.2 % (n=24) | 0.018* |
| Non-stimulant ADHD medication | 3.6 % (n=7) | 11.5 % (n=6) | 0.024* |
| Selective serotonin reuptake inhibitors | 3.6 % (n=7) | 34.6 % (n=18) | <0.001* |
| Atypical antipsychotics | 10.9 % (n=21) | 34.6 % (n=18) | <0.001* |

Table 2. Comparison of mean age and sex distribution between ADHD Only and ADHD Plus Comorbidity groups

Note. * indicates p value is < 0.05.

(i) excluding the participants with a FSIQ lower than 70 and (ii) excluding the participants with a FSIQ lower than 55, and the results showed no difference from initial significant results.

A logistic regression was performed to ascertain the effects of age, sex, full scale IQ and WISC-IV index scores on the likelihood that participants have a psychiatric comorbidity in addition to their ADHD diagnosis. The logistic regression model was statistically significant, $x^2(13) = 33.304$, p = 0.002. The model explained 24.2 % (Nagelkerke R2) of the variance in psychiatric comorbidity in ADHD patients and correctly classified 82.3 % of cases. Increased age (p=0.004, OR=1.18, 95 % CI=1.054-1.317) and decreased processing speed index score (p=0.016, OR=0.96, 95 % CI=0.928-0.992) were associated with an increased likelihood of having a psychiatric comorbidity in addition to ADHD. We have conducted a second logistic regression to investigate the additional effects of medications used by the participants. The predictive effect of decreased processing speed index score on psychiatric comorbidity in ADHD patients persisted (p = 0.026) while also the use of SSRIs

 Table 3. The comparison of WISC-4 full scale IQ, index and subtest scores between groups

| | ADHD Only group (n = 193) $M \pm SD$ | ADHD Plus Comorbidity group (n = 52) $M \pm SD$ | р |
|----------------------------|--|---|---------|
| Full scale IQ | 86.06 <u>±</u> 20.932 | 80.54 ± 24.075 | 0.103 |
| Verbal Comprehension Index | 88.11 <u>+</u> 18.297 | 83.04 <u>+</u> 20.583 | 0.086 |
| Similarities | 7.84 <u>+</u> 3.542 | 7.86 <u>+</u> 3.704 | 0.970 |
| Vocabulary | 7.65 <u>+</u> 3.791 | 7.10 <u>+</u> 4.098 | 0.357 |
| Comprehension | 8.61 <u>+</u> 3.101 | 7.96 <u>+</u> 4.014 | 0.211 |
| Perceptual Reasoning Index | 91.84 <u>+</u> 19.016 | 87.13 <u>+</u> 22.823 | 0.131 |
| Block design | 8.60 <u>+</u> 3.613 | 8.15 <u>+</u> 4.132 | 0.443 |
| Picture concepts | 8.07 <u>+</u> 3.276 | 7.42 <u>+</u> 3.952 | 0.227 |
| Matrix reasoning | 9.57 <u>+</u> 3.485 | 8.90 <u>+</u> 4.160 | 0.242 |
| Working Memory Index | 86.32 <u>+</u> 18.004 | 85.12 ± 19.705 | 0.676 |
| Digit span | 7.78 <u>+</u> 3.137 | 7.53 <u>+</u> 3.818 | 0.626 |
| Letter-number sequencing | 8.13 <u>+</u> 3.623 | 7.70 <u>+</u> 3.533 | 0.472 |
| Processing Speed Index | 89.88 <u>+</u> 19.105 | 81.69 <u>+</u> 21.518 | 0.008* |
| Coding | 8.74 <u>+</u> 3.563 | 6.77 <u>+</u> 3.761 | <0.001* |
| Symbol search | 7.95 <u>+</u> 3.713 | 7.33 <u>+</u> 4.129 | 0.299 |

Note. * indicates p < 0.001

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and atypical antipsychotics had significant associations (p < 0.001 and p = 0.001, respectively).

DISCUSSION

In our retrospective study, we investigated the differences in WISC-IV FSIQ index and subtest scores between children with and without additional psychiatric comorbidity to their ADHD diagnoses. We found that the full-scale IQ, verbal comprehension, perceptual reasoning, and working memory index scores were similar between the two groups. However, participants with comorbid psychiatric diagnoses had significantly lower scores in the processing speed index than those without psychiatric diagnoses in addition to ADHD. The subtest scores were similar across the groups, except for the coding subtest of the processing speed index. The mean coding subtest score was significantly lower in the ADHD Plus Comorbidity group compared to the ADHD Only group. We also found an age difference between the two groups; the age of the ADHD Plus Comorbidity group was significantly higher compared to the ADHD Only group.

The male ratio (1.9:1) and psychiatric comorbidity rate (21.2 %) were lower than in other clinical studies (34-36). This may be related to the exclusion of participants with ASD, learning disabilities, and medical comorbidities. Additionally, our sample was followed up by a multidisciplinary team, and the majority of the patients were treated with medication. These factors are known to decrease psychiatric comorbidity rates among individuals with ADHD (37). We found that the mean age was higher in the ADHD Plus Comorbidity group. This finding, which indicates an increased age in the ADHD Plus Comorbidity group compared to the ADHD Only group, is in accordance with the literature. Older age significantly predicted psychiatric comorbidity in children with ADHD. In this regard, longitudinal and cross-sectional studies have shown that the frequency of both internalizing and externalizing disorders increased with age in children with ADHD (36, 38, 39). The increased prevalence of mood and anxiety disorders in adolescence may be one of the explanations for these findings (40). Furthermore, the cognitive load and the daily life expectations, which require the utilization of executive functions, increase from childhood to adolescence, resulting in increased impairment in adolescents with ADHD compared to children with ADHD (41, 42). This increased functional impairment in adolescence may also be related to the age and comorbidity relationship in ADHD. The female ratios were similar in ADHD Plus Comorbidity and ADHD Only groups, 35.2% and 30.8%, respectively. Population-based studies usually identify the occurrence of comorbidity more in boys than girls (43). However, in clinical studies, the ratios are similar in gender groups (35, 36). Our participants were recruited from a tertiary university hospital, which consisted of a clinical sample, and our finding is in correlation with those existing studies (35, 36).

The groups were significantly different regarding their medications. The methylphenidate usage was higher in the ADHD Only group, compared to the ADHD Plus Comorbidity group. On the other hand, the atomoxetine usage was higher in the ADHD Plus Comorbidity group. The most common comorbid diagnosis was anxiety disorders, and this finding is in correlation with other studies reporting that atomoxetine may reduce anxiety symptoms in ADHD better than methylphenidate (44, 45). The treatment with SSRIs and atypical antipsychotics were higher in ADHD Plus Comorbidity group; it is expected as these medications are indicated for the comorbid diagnosis anxiety disorders, obsessive compulsive disorder, and behavioral disorders (46-49).

Our results showed that the FSIQ, VCI, PRI, and WMI scores were comparable between groups. Children with a psychiatric comorbid condition in addition to ADHD had significantly lower scores in the PSI compared to children with ADHD without comorbid psychiatric conditions. Additionally, lower PSI predicted the presence of a psychiatric comorbidity in children with ADHD. PSI of WISC-IV provides an efficient estimation of how a child can perform basic or automatic tasks or tasks that require active acquisition of novel information (50). Performance on PSI requires speed and accuracy of visual identification, visual or auditory discrimination, decision-making and decision implementation (50). Lower scores in PSI are considered as a sign for clinical conditions, however a further clinical investigation is required to understand the nature of the clinical problem. In the literature, it is consistent that PSI is the lowest or one of the lowest indexes that children with neurodevelopmental disorders score (22, 24, 51, 52). The ability to maintain attention and focus on a task can impact processing speed. Children with ADHD, who struggle with sustained attention may be expected to have slower processing speed. Anxious and depressed children may perform lower on PSI due to lack of confidence and uncertainty in decision-making (50). Anxiety and depression have also been linked to slower processing speed in children. Children with anxiety may have difficulty filtering out irrelevant information, which can slow down their processing speed. Similarly, children with depression may experience cognitive slowing, where they have difficulty processing information and making quick decisions. Slower processing speed is not necessarily a direct result of these psychiatric conditions, but rather may be a symptom of the underlying neural dysfunction associated with these conditions. In clinical studies, lower PSI scores are not correlated with anxiety disorders or depression diagnoses (5). Nevertheless, genetic factors can contribute to processing speed in children such that they may influence the development of related neural pathways (53, 54). Investigating shared neural mechanisms and genetics that may explain this relationship between psychiatric comorbidity and processing speed may be a meaningful contribution to the neurocognitive field.

The medications used by the groups may have different cognitive effects. The increased use of atypical antipsychotics, SSRIs and atomoxetine in the ADHD Plus Comorbidity group might have affected the cognitive results of the participants. SSRIs have demonstrated various cognitive effects on the literature, from decreasing cognitive performance at the early phase of the treatment (55) to decreased cognitive slowing in later phases (56). For atypical antipsychotics, either neutral or beneficial effects were reported in children with ADHD (57, 58). Both methylphenidate and atomoxetine have shown enhancing effects on cognitive performance (59). The test results might have been affected by these factors in our study, however, our results remain significant after controlling for medication type.

From another perspective, low processing speed in children with ADHD may be contributing to emer-

gence of psychiatric comorbidities. Processing speed is closely linked to academic performance, particularly in tasks that require speed and accuracy, such as timed tests, reading comprehension, and math calculations. Children with slow processing speed may struggle to keep up with the pace of classroom instruction, leading to academic difficulties (5, 30). Slow processing speed can also impact social interactions, as children may have difficulty following conversations, processing social cues, and responding in a timely manner. Children with slow processing speed may become frustrated with their difficulties and develop low self-esteem and feelings of inadequacy. The frustration and difficulties associated with slow processing speed may consequently increase the risk of anxiety, depression, or behavioral disorders in children with ADHD. Longitudinal studies rather than studies with crosssectional designs may aid to understand the relationship between low processing speed and psychiatric comorbidity developmentally.

There are several strategies that can be used to improve processing speed performance in children with ADHD. The medical treatment of ADHD with stimulant and nonstimulant medications improve processing speed in children (60, 61). Recent studies on clinician-delivered cognitive training programs and combining them with emerging interventions such as transcranial electrical stimulation present promising results on improving processing speed (62, 63). Regular physical exercise has been shown to improve cognitive function, including processing speed (64). Encouraging children to engage in physical activities may be helpful in improving processing speed. Application of classroom accommodations by the school managements for children with ADHD like providing a quiet, structured environment with limited distractions to help them focus on the task at hand help improve to ease the consequences of low processing speed.

By incorporating play into therapeutic interventions, clinicians can create a more engaging and interactive environment for children, which can lead to better cognitive outcomes in the treatment of ADHD and related conditions. A recent systematic review of studies suggests that play therapy has a high effect size for the treatment of ADHD and other related symptomatology (65). The use of play therapy can also help improve children's processing skills by enhancing their verbal, tactile, and visual engagement through the selection of various toys and designing play scenarios.

Our study has limitations mainly due to its retrospective design. There are other potential contributors for the psychiatric comorbidity in children with ADHD, such as age of onset and severity of ADHD symptoms and ADHD presentation type (34, 66). However, we were not able to analyze the effect of those in our study. The comorbidities were very heterogeneous and there may be differences in their mechanisms related to processing speed. All the participants were instructed not to take their medications on the day of the test until the test is completed, however we were not able to control that objectively and participants may be using longacting medications with a wash-out period longer than 24 hours.

It is important for researchers and practitioners to have a comprehensive understanding of the characteristics associated with children with ADHD and other comorbid psychiatric diagnosis. This could lead to the development of more effective treatments which improve those children's intellectual,

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cognitive, and learning abilities as well as overall functioning and quality of life. The study findings highlight the importance of considering emotional processes in addition to cognitive assessments. The development of individualized interventions which are targeted to the enhancement of reduced PSI should be prioritized to alleviate comorbidity severities. It is important to address slow processing speed in children in order to minimize the functional consequences and support their overall wellbeing. Strategies such as those mentioned earlier, including cognitive training, physical exercise, play therapy and working memory training, may be helpful in improving processing speed and reducing the negative impact of slow processing speed on a child's life. Finally, in light of the current study findings, further research with longitudinal designs may also investigate whether children with lower PSI may be more likely to develop comorbidities.

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Decision-making under ambiguity in patients with social anxiety disorder

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SUMMARY

Objective: The study aimed to compare the decision-making functions of patients with social anxiety disorder (SAD) under ambiguity with healthy controls.

Method: Seventy-nine patients with SAD (47 with generalized subtype, and 32 with nongeneralized subtype) were included in the study. The healthy control group consisted of 72 individuals who were matched with the patient group in terms of age, sex, and education. Sociodemographic Data Form, Beck Depression Inventory (BDI), State-Trait Anxiety Inventory (STAI), Liebowitz Social Anxiety Scale (LSAS), Barratt Impulsiveness Scale-Short Form (BIS-15), and Iowa Gambling Test (IGT) were administered to all participants.

Results: The decision-making performance of patients with SAD was similar to healthy control group. In SAD subtypes, the generalized type performed poorly in the IGT compared with the nongeneralized subtype type. Participants with nongeneralized subtype increased their performance by choosing more advantageous decks after the first 20 card selections and showed a learning effect. Those with generalized type showed a learning effect only in block 5 and continued to choose from disadvantageous cards in the other blocks.

Discussion: Patients with SAD preferred advantageous decks like healthy control group and learned to avoid disadvantageous decks. The decision-making performance of the generalized type was impaired. The generalized subtype made choices that won in the short run but lost in the long run and did not benefit from feedback. We believe that this separation in decision-making processes among SAD subtypes will contribute to a better understanding of the types.

Key Words: Social anxiety disorder; ambiguity; decision-making; generalized subtype; nongeneralized subtype

INTRODUCTION

Social anxiety disorder (SAD) is a psychiatric disorder in which a person has a fear of being humiliated in social situations and being judged by others, and has a distinct and constant fear regarding this issue (1). The prevalence rates of SAD in various countries vary between 4-16% (2). SAD is associated with impairment in important areas of daily life such as professional/academic, relationships with others, and social activities (3). Major risk factors such as genetic predisposition, environmental and developmental factors, personality traits, insufficient social support, restricted social environment, and negatively perceived parenting style have been associated with the etiology of SAD (4–8). Epidemiologic studies reveal that the rate of SAD is high in women (9). However, the higher treatment-seeking rate among men can be attributed to the greater functional impairment they experience as a result of SAD (2,9).

Although the classification of subtypes of SAD remains controversial, it has been divided into two

DOI: 10.5505/kpd.2023.82713

Cite this article as: Demirci H, Pirdogan Aydin E, Kamazoglu BA, Ozer OA. Decision-making under ambiguity in patients with social anxiety disorder. Turkish J Clin Psych 2023; 26:282-292

The arrival date of article: 03.03.2023, Acceptance date publication: 16.06.2023

Turkish J Clinical Psychiatry 2023;26:282-292

subtypes: generalized and nongeneralized for diagnostic purposes (2,10,11). The generalized type of SAD includes people who are fearful of many social situations that require interpersonal relationships (2,9). The nongenaralized type includes only one or a limited number of people who experience fear in different social situations (12). The generalized type fears and avoids almost any social situation that requires interpersonal contact or that they think will be watched by others (12,13). The generalized type is usually earlier and shows familial transition (1,14,15).

In neuropsychological research, decision-making behavior is examined with two different paradigms as decision-making under risk and decision-making under ambiguity (16,17). In the decision-making atrisk paradigm, information about possible outcomes and information about reward-punishment probabilities is clear (17,18). In decision-making under ambiguity, the probability of reward-punishment is uncertain, and the prior information about the results is implicit (17). The decision-making task in uncertain situations is often tested using the Iowa Gambling Test (IGT) (19-21). This task is an experimental test that includes components such as uncertainty, reward, and punishment, simulating decision-making in real life (19). To be successful in this task, participants must implicitly understand the rules of the task based on the feedback they receive after the choices they make (17). Understanding implicitly means it is difficult for the participants to follow and remember their earnings and losses from the previous card selections (16,17). Instead, the participants must follow their emotions and prerequisite in accordance with the somatic marker hypothesis (SMH) (22,23). According to the somatic marker hypothesis, emotions guide decision-making when the outcome of one's choices regarding reward and punishment is uncertain (24). Emotions consist of somatic changes. These somatic states emerge in the decision-making process and work as an automatic alarm, marking specific options as advantageous and the left as disadvantageous (24,25). Somatic markers work like automatic alarms in uncertain situations, marking response options with an emotional signal (25). Automatic alerts protect against future harm before things go any further and enable accurate decision-making from fewer

options (22).

Many studies used the IGT task to evaluate decision-making disorders in psychiatric disorders (26-34). In these studies, poor performance findings in decision-making were obtained in patient groups. There are few studies in the literature evaluating decision making under uncertain situations in social anxiety. Some of these studies only included individuals with social anxiety variants who were not formally diagnosed (35,36). Another study in the literature included only participants with SAD (37). Decision-making behavior under ambiguous situations has not been previously studied between patients with SAD and healthy controls (HCs). It has been shown that IGT, which evaluates decisionmaking in uncertain situations, is sensitive to orbitofrontal/ventromedial prefrontal cortex and limbic system functioning (18,20,38,39). We think that evaluating the decision-making paradigm with a specific neuropsychological task sensitive to this region of the brain will contribute to research on the etiology of SAD. The primary aim of our study was to compare decision-making function under uncertain situations in patients with SAD with HCs. The secondary aim of our study was to investigate the differences in decision-making between generalized and nongeneralized types. Finally, we aimed to assess the relationship between decisionmaking and depression, anxiety, avoidance, and impulsivity.

METHOD

Participants and procedure

The investigation was performed with patients with SAD, all were diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria by two psychiatrists in the outpatient clinic of the Department of Psychiatry, Sisli Hamidiye Etfal Training and Research Hospital, University of Health Sciences in Istanbul, Turkey. The Comorbidities of patients were determined using the Structured Clinical Interview for DSM-5 (SCID-5-CV). The inclusion criteria for the study were as follows: being diagnosed as having SAD according to the DSM-5, being aged 18-50 years,

being at least a primary school graduate, and agreeing to participate in the study. The inclusion criteria for HCs were the same, except there was no current or lifetime history of any psychiatric disorder. Exclusion criteria of the study were intellectual disability, schizophrenia and other psychotic disorders, bipolar disorder, history of any neurologic disease, and alcohol or substance abuse. After the selection of the patient groups was made according to the purposeful sampling method, 72 people who were matched with the patient group in terms of age, sex, and educational status, were included in the study as the control group. Twenty-five of the patients with SAD had no comorbidities. Fortyseven patients with SAD had one or more comorbidities (adult separation anxiety n=5, agoraphobia n=2, anxiety disorder n=1, another defined anxiety disorder n=7, attention-deficit/hyperactivity disorder n=13, eating disorder n=1, generalized anxiety disorder n=3, major depressive disorder n=16, obsessive-compulsive disorder n=8, panic disorder n=1, skin picking disorder n=5, somatic symptom disorder n = 3, trichotillomania n = 4).

Psychiatrists who conducted the clinical interviews identified 47 of the 79 patients with SAD as having generalized type and 32 as having nongeneralized type. Those with anxiety/avoidance in two or more different social situations were considered as having the generalized type, and those with anxiety/avoidance in a single area were considered as having the nongeneralized type (40). Sociodemographic Data Form, Beck Depression Inventory (BDI), State-Trait Anxiety Inventory (STAI), Liebowitz Social Anxiety Scale (LSAS), Barratt Impulsiveness Scale-Short Form (BIS-15), and Iowa Gambling Test (IGT) were administered to all participants. After explaining the purpose and method of the study to the participants, their written informed consent was obtained. The study was conducted in conformity with the Declaration of Helsinki and was approved by the ethics committee of Sisli Hamidiye Etfal Teaching and Research Hospital, University of Health Sciences in Istanbul, Turkey (3615/2022).

Assessments

Sociodemographic Data Form: This detailed inter-

view form was prepared by the researchers for the study, evaluating the sociodemographic characteristics of the patients, the onset and course of the disease, their clinical status, and the clinical diagnosis process.

Structured Clinical Interview for DSM-5-Disorders-Clinician Version (SCID-5/CV): SCID-5/CV is a semi-structured interview guide that was developed to diagnose DSM-5 disorders. SCID-5 was developed by First et al. in 2015 (41) This guide can be administered by physicians or trained mental health professionals familiar with the DSM-5 classification and diagnostic criteria. Adaptation, validity, and reliability studies were conducted for Turkish society (42)

Beck Depression Inventory (BDI): The BDE was developed to determine the presence and severity of depressive symptoms in adults (43). The scale consists of 21 items, and each item is scored between 0 and 3. The total score ranges from 0-63. The high total scores obtained from the scale indicate severe depression. The cut-off point of the scale is 17. A validity and reliability study was conducted for use in the Turkish population (44).

State-Trait Anxiety Inventory (STAI): The STAI was developed by Spielberger et al. (45). The STAI consists of two separate scales with a total of 40 items. The state anxiety scale includes questions about how the person feels at a certain moment and under certain conditions. The trait anxiety scale, on the other hand, includes questions about how the person usually feels. The total score obtained from both scales varies between 20 and 80. High scores indicate high anxiety and low scores indicate low anxiety. A validity and reliability study was conducted for use in the Turkish population (46).

Liebowitz Social Anxiety Scale (LSAS): The LSAS scale, which evaluates the severity of fear and avoidance in social environments and situations requiring performance, was developed by Liebowitz (47). It consists of a total of 24 questions, 11 of which evaluate social situations and 13 questions that evaluate situations that require performance. For each situation, the individual's anxiety and avoidance levels are scored between 0 and 3.

The higher the score obtained, the worsening of social anxiety and avoidance. A validity and reliability study was conducted for use in the Turkish population (48).

Barratt Impulsiveness Scale-Short Form (BIS-15): The BIS-15 scale is a 15-item self-report scale that evaluates the impulsivity structure. Items are rated on a 4-point Likert-type scale (1=rarely/never; 2 = sometimes; 3=often; 4=almost always / always). It consists of three sub-dimensions: non-planning (BISnp), motor impulsivity (BISm), and attentional impulsivity (BISa). Higher scores are indicative of higher levels of impulsiveness. A validity and reliability study was conducted for use in the Turkish population (49).

Iowa Gambling Test (IGT): The IGT was developed to evaluate decision-making behavior under uncertain situations. (19,50). In this test, the participants are given an advance of 2000 TL as computer money at the beginning. Participants are instructed to make as much money as possible and lose as little money as possible during the test by making choices from four different decks of cards (A,B,C,D) displayed on the computer screen. They are informed that they can choose as much as they want from each deck and switch from one deck to the next. The participant chooses a total of 100 cards, but this information is not given to the participant. The decision-making behavior among the decks varies according to the reward and punishment obtained as a result of the card selected from each deck. These rewards and punishments are pre-programmed and known to the tester, but not to the participant. A and B decks are risky decks that make a lot of money but also lose a lot of money in the long run. C and D decks are advantageous and risk-free in the long run, with little gain and little loss. Participants are expected to learn this rule as the test progresses. In a selection of 100 cards, choosing more from decks A and B results in a net loss, while choosing more from decks C and D results in a net win. In the selection of 100 cards in total, the selections made from the advantageous decks (C and D) are subtracted from the selections made from the disadvantageous decks (A and B), and the advantageous decision performance during the IGT is calculated. A high score indicates good decision-making performance. A validity and reliability study was conducted for use in the Turkish population (51).

Statistical analysis

The SPSS version 20.0 for Windows software package (SPSS, Inc., Chicago, Illinois) was used for statistical analysis. Descriptive statistics, mean and standard deviation, were used for numerical variables, and categorical variables are reported as numbers and percentages. Comparisons of numerical variables in two independent groups were made using Student's t-test under normal distribution conditions, and the Mann-Whitney U test when normal distribution conditions were not met. A comparison of rates in independent groups was made using Chi-square Analysis. Analysis of covariance (ANCOVA) was used to compare the IGT blocks, and total scores by controlling age, education status, STAI, and BDI scores in paired groups. In cases where IGT scores did not meet normal distribution conditions, Quade's ANCOVA analysis was performed by transforming age, education status, STAI, BDI scores, and dependent variables into ordinal values. Pearson's correlation analysis was used when the correlations between variables were provided with normal distribution conditions, and when normal distribution was not achieved, Spearman's correlation analysis was used. Statistical alpha significance level was accepted as p < 0.05.

RESULTS

Social anxiety disorder versus health control

There were 151 participants, including 79 with SAD, and 72 HCs. Sociodemographic characteristics and clinical scale scores of the patient and control groups are compared in Table 1. There was no statistically significant difference between the patient and control groups in terms of age (p=0.554), sex (p=0.167), and education years (p=0.133). Depression and anxiety (STAI-1, STAI-2) scores of patients with SAD were significantly higher than in the HCs (p<0.001, Cohen's d =1.32, p<0.001, Cohen's d =1.31, and p<0.001, Cohen's d =1.62, respectively). LSAS-anxiety and LSAS-avoidance scores of patients with SAD were statis-

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|-----------------|-------------|------------|----------|---------|-------------|---------------|
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|-------------------------|-------------------------|------------------------|---------------------|---------|---------|-------|-------|
| Variables | SAD (n=79) ^a | HC (n=72) ^a | t, Z, x† | Р | F | Р | n2 |
| Age (yr) | 24.8-6.1 | 25.1-5.7 | 0.592 ^b | 0,554 | | | |
| Sex (Female), n (%) | 35(44.3) | 40(55.6) | 1,908° | 0,167 | | | |
| Education (yr) | 14.2-2.8 | 14.9-2.2 | -1,512 ^b | 0,133 | | | |
| BDI scale scores | 21.1-12.5 | 7.7–7 | -6.877 ^d | < 0.001 | | | |
| STAI-1 (state) | 46.6-11.3 | 33.2-9.1 | 7,971 ^b | < 0.001 | | | |
| STAI-2 (trait) | 55.9-11.8 | 38.2-10 | 9,859 ^b | < 0.001 | | | |
| LSAS-fear | 59.1-15.2 | 41.5-11 | 8,108 ^b | < 0.001 | | | |
| LSAS-avoidance | 55-15.8 | 37.1-8 | -7.406 ^d | < 0.001 | | | |
| BIS-15np | 11-3 | 9.2-2.4 | -3.508 ^d | < 0.001 | | | |
| BIS-15m | 10.7-3.1 | 8.7-2.4 | -3.961 ^d | < 0.001 | | | |
| BIS-15a | 10.7-3.5 | 8.6-2.3 | -3.967 ^d | < 0.001 | | | |
| BIS-15total score | 32.5-8.6 | 26.5-6 | 4,968 ^b | < 0.001 | | | |
| IGT-1 (1-20) | -2-4.4.3 | -2.2-4.3 | -0.115 ^d | 0,908 | 0,643 | 0,424 | 0,004 |
| IGT-2 (21-40) | - 0.5–4.2 | -0.2-3.6 | -0.578 ^d | 0,536 | 0,004 | 0,95 | - |
| IGT-3 (41-60) | -0.1-4.5 | 0.4-5.1 | -0.081 ^d | 0,935 | 0,015 | 0,902 | - |
| IGT-4 (61-80) | -0.4-5.1 | 0-5.7 | -1.142 ^d | 0,253 | 0,521 | 0,472 | 0,003 |
| IGT-5 (81-100) | 1.1-6.4 | -0.3-8.3 | -0.935 ^d | 0,34 | 0,617 | 0,433 | 0,004 |
| IGT-total score (1-100) | -2-15.3 | -2.4–16.3 | -0.203 ^d | 0,839 | 0,007 | 0,932 | - |

 Table 1. Demographic features, clinical data, impulsivity, and decision-making scores of the participants

Abbreviations: BDI: Beck depression inventory scale, BSIa: Barratt Impulsiveness Scale-Short Form- attentional impulsivity, BIS-15m: motor impulsivity, BIS-15np: non-planning, IGT: Iowa Gambling Test, Hc: Healthy control, LSAS: Liebowitz Social Anxiety Scale, SAD: Social anxiety disorder, STAI: State-Trait Anxiety Inventory

^aData expressed as mean – standard deviation, ^bStudent's test, ^cCh -Square test, ^dMann-Whitney U test.

tically higher than the control group (p<0.001, ANCOVA analysis (Table 1), (Fig 1).

Cohen's d =1.33, and p<0.001, Cohen's d =1.42, respectively) (Table 1).

Generalized type versus nongeneralized type

The BIS-15 total scores (p < 0.001, Cohen's d=0.81) BIS-15np (p<0.001, Cohen's d=0.66), BIS-15m (p < 0.001, Cohen's d = 0.72), and BIS-15a (p < 0.001, Cohen's d = 0.83) for SAD were higher than the HCs. Risk-taking behavior was defined as the total number of cards taken from advantageous and disadvantageous decks for each block. According to this, the IGT-total score, IGT-1, IGT-2, IGT-3, and IGT-4 performance of the SAD group was similar to the HCs. The IGT-5 score performance of the HC group was significantly worse than the SAD group (p=0.34, Cohen's d=0.19). However, when the education, age, depression, and anxiety scores of the patient and control groups were fixed and their IGT scores were compared, no difference was found according to the Quades

The comparison of sociodemographic data and test scores of patients with generalized type and nongeneralized type SAD is shown in Table 2. There was no statistically significant difference between subtypes in terms of age (p=0.219), sex (p=0.078), duration of education (p=0.286), and comorbidities (p=0.091). There was no significant difference between STAI-trait, BIS-15-total score, and subscales between the generalized type and the nongeneralized type. Although there was no significant difference between the two types concerning impulsivity, the nongeneralized type had higher impulsivity scores. BDI, STAI-state, LSAS-anxiety and LSAS-avoidance scores were significantly higher in the generalized type than in the nongenera-



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Fig.2. The Total Advantageous (C and D) and Disadvantageous (A and B) card selection in the generalized type, and the nongeneralized type

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| Table 2. Compariso | on of subtypes of SAD | | | | | | |
|-------------------------|---------------------------------|------------------------------------|---------------------|---------|--------|---------|-------|
| | | | | | ANCOVA | | |
| Variables | Generalized (n=47) ^a | Nongeneralized (n=32) ^a | t, Z, x† | p value | F | p value | n2 |
| Age (yr) | 24.1-5.4 | 25.8-6.9 | 1 ^b | 0,219 | | | |
| Sex (Female), n (%) | 17(36.2) | 18(56.2) | 3,111° | 0,078 | | | |
| Education (yr) | 14.2-2.8 | 14.9–2.2 | -1,068 ^d | 0,286 | | | |
| Comorbidity, n (%) | 35(14.5) | 18(56.2) | 2,862° | 0,091 | | | |
| BDI scale scores | 24.5-11.6 | 16.1–12.1 | -3.095 ^b | 0,003 | | | |
| STAI-1 (state) | 48.9-11.2 | 43.2-10.6 | -2.290 ^b | 0,025 | | | |
| STAI-2 (trait) | 57.9-11.6 | 52.8-11.6 | -1.937 ^b | 0,056 | | | |
| LSAS-fear | 64.4–14.6 | 51.5-12.9 | -4.050 ^b | < 0.001 | | | |
| LSAS-avoidance | 60.9-14.7 | 46.5-13.3 | -4.438 ^b | < 0.001 | | | |
| BIS-15np | 10.9-2.9 | 11.2-3.3 | -0.463 ^d | 0,643 | | | |
| BIS-15m | 10.6-2.8 | 11-3.5 | 0,591 ^b | 0,556 | | | |
| BIS-15a | 10.3-3.3 | 11.2-3.7 | 1,095 ^b | 0,277 | | | |
| BIS-15total score | 31.8-7.7 | 33.4–9.4 | 0,845 ^b | 0,401 | | | |
| IGT-1 (1-20) | -1.5-4.8 | -2.4-3.9 | -0.698 ^d | 0,485 | 2,237 | 0,139 | 0,028 |
| IGT-2 (21-40) | -0.8-4.3 | 0.06-4 | 0,948 ^b | 0,346 | 0,641 | 0,426 | 0,009 |
| IGT-3 (41-60) | -0.6-4.1 | 0.7-4.9 | 1,252 ^b | 0,214 | 1,79 | 0,185 | 0,024 |
| IGT-4 (61-80) | -1–5.4 | 0.4-4.5 | -1.645 ^d | 0,1 | 3,599 | 0,062 | 0,045 |
| IGT-5 (81-100) | 0.2-5.7 | 2.2-7.3 | 1,374 ^b | 0,174 | 1,989 | 0,163 | 0,027 |
| IGT-total score (1-100) | -4.6-14.7 | 1.7-14.8 | 2 ^b | 0,067 | 4,731 | 0,033 | 0,061 |

Abbreviations: BDI: Beck depression inventory scale, BSIa: Barratt Impulsiveness Scale-Short Form- attentional impulsivity, BIS-15m: motor impulsivity, BIS-15np: non-planning, IGT: Iowa Gambling Test, Hc: Healthy control, LSAS: Liebowitz Social Anxiety Scale, SAD: Social anxiety disorder, STAI: State-Trait Anxiety Inventory ^aData expressed as mean – standard deviation, ^bStudent's +test, ^cCh -Square test, ^dMann-Whitney U test.

lized type (p=0.03, Cohen's d =0.80, p=0.025, Cohen's d =0.53, p<0.001, Cohen's d =0.94 and, p < 0.001, Cohen's d =1.04, respectively). There was no significant difference in IGT-total score and sub-blocks between the generalized type and the nongeneralized type. However, the IGT-total score was significantly lower in patients with generalized type SAD in the ANOVA analysis when depression, anxiety, age, and education were controlled for (p=0.033, Cohen's d = -0.43) (Table 2), (Fig1,2).

In the generalized type, only Barratt-total and IGT-5 were significantly negatively correlated (r=-0.306; p<0.05). There was no significant correlation between Barrat's subscales and LSAS subscales and the IGT. In the nongeneralized type,

only BIS-15a, and IGT-2 were significantly negatively correlated (r = -0.400, p < 0.005). There was no significant correlation between the others.

DISCUSSION

In this study, we compared risk-taking and decision-making performance in patients with SAD under ambiguous situations with HCs. One of the main results of this study is that the decision-making performance of patients with SAD under uncertainty was similar to that of the HCs. Patients with SAD preferred advantageous decks like HC parti-cipants and learned to avoid disadvantageous decks (see Fig 3).



Fig.3: Decision-making between generalized and nongeneralized types. The mean net number of chosen cards (C+D) -(A+B) by generalized and nongeneralized types, across five blocks each consisting of 20 trials. Positive net scores reflect advantageous decisionmaking performance, while negative net scores reflect disadvantageous decision-making performance. 287

Somatic markers are regulated in the emotional circuits of the brain, specifically, in the ventromedial prefrontal cortex (vmPFC), and are suggested to aid decision-making in ambiguous situations (21,25). In ambiguous situations, somatic markers work like automatic alarms, marking available response options with an emotional signal (25). These auto-alarms enable accurate decision-making from fewer options (22). Somatic cues of good or bad choices enable people to make and maintain useful decisions (21). From this point of view, it can be argued that patients with SAD can develop somatic markers in this task.

It is noteworthy that patients with SAD outperformed healthy controls in the "conceptual" period (block 5) when the participants understood the reward/punishment differences between the IGT bundles and reached a fully conscious knowledge of the content of the task. This finding shows that patients with SAD comprehended the content of the task towards the end of the test and turned to advantageous decks. However, the same finding was not observed in healthy participants. During the IGT, as healthy participants learn the approximate frequency and magnitude of reward and punishment through trial and error, participants are expected to direct their preference to advantageous cards (52). In the IGT task, healthy participants were found to perform poorly (53). Normal adults who describe themselves as risk takers make more choices from disadvantaged decks than advantageous decks (20). The reason for the low performance of healthy participants during the IGT was explained by reasons such as excitement seeking, disinhibition, impulsivity, and lack of motivation (53-55). While stress encourages risk taking in individuals with low social anxiety, it causes risk aversion in individuals with high social anxiety (35). High negative affect was associated with greater avoidance of high loss decks, and high positive affect was associated with more selection than high gain decks (56). In addition, individuals with high trait anxiety were found to be associated with impaired decision making in IGT (57). Individuals with different trait anxiety may react in a certain way under stress and may differ from each other in their initial decision-making performance (57,58). The lack of difference between the patient group and the control group in our study may be due to the robust decision-making ability of patients with SAD or the poor performance of the HCs.

We found some important differences in decisionmaking strategies under ambiguous situations according to clinical subtypes of SAD. Patients with generalized-type SAD made more choices from disadvantaged and risky decks. They were more sensitive to immediate rewards rather than longterm gains, and their choice resulted in a net loss. The patients with the nongeneralized type, on the other hand, chose more advantageous packs in the long run, winning less and losing less, and their selections resulted in net profits. The decisionmaking behavior of patients with the generalized type can be thought of as taking immediate comforting action, such as avoiding, instead of thinking about the long-term disadvantageous consequences of avoidance, as in real life. In other words, the avoidance behavior of patients with common-type SAD can also be interpreted as not being able to make a long-term profit-loss analysis correctly because when their strategy in the task is a choice that will bring immediate reward, they make that choice and ignore future possibilities (Fig 2).

Poor performance in the IGT has also been associated with reverse learning (17,25) because disadvantageous decks (A and B) are clearly associated with higher payoffs at the start of the task. After a few tries, participants should learn that these decks are at a disadvantage because they lead to losses in the long run (17). Accordingly, successful performance in the IGT typically involves moving from risky decks to less risky decks that initially seem rewarding but are gradually associated with greater penalties (16). From this point of view, it can be said that the generalized type has weak reverse learning skills under uncertain situations.

To see the increasing learning effect of both subtypes in the gambling task, when the block net scores throughout the 5 blocks were examined, it was seen that the scores of the nongeneralized type increased above 0 from block 1. The nongeneralized type increased their performance by choosing more advantageous decks after the first 20 card selections and managed to show a learning effect. By contrast, the generalized type showed a learning effect only in the fifth block and continued to choose from disadvantageous cards in the other blocks. It is thought that a successful decision-making performance is related to different cognitive functions such as evaluating the loss-gain possibilities, making profit-loss analysis, keeping the decision in memory in the previous election, and using the feedback obtained after the elections (59). From this point of view, it is thought that the generalized type group could not benefit from feedback and did not have a learning effect (see Fig 3).

Patients with generalized type SAD were found to show more anxiety, poorer skills, and less positive thinking during behavioral tests (13,60). It was found that patients with the nongeneralized type showed more anticipatory anxiety and higher heart rate than the common type and controls in behavioral tests (13). In another study, the nongeneralized type showed a higher heart rate during behavioral testing than the generalized type (60). SMH, claims that somatic activation secretly drives decision-making (22). Skin conductivity responses such as heart rate and muscle tension are some of these somatic cues. According to this hypothesis, every behavioral possibility is associated with unconscious somatic responses evoked by its previous consequences (61). Somatic states evoked by emotions are associated with positive or negative outcomes, then reactivate this state through the somatosensory cortex, influencing decision-making (23). Impairments in this task in patients with generalized-type SAD may be related to an impairment in somatic activation.

SMH suggests that impairment in emotions and feelings negatively affects decision-making (21) because, in ambiguous situations, somatic markers are assumed to mark possible options with an emotional signal about the good or bad of the associated outcome (53). Studies have shown that patients with the common subtype and early-onset SAD exhibit more severe symptoms and greater behavioral inhibition (62). It has been found that patients with SAD of the generalized type are more sensitive to environmental threats, do not seek novelty, and show more behavioral inhibition than those with the nongeneralized type (63). Binelli et al. examined a group of patients with high social anxiety levels as harm avoidant, a low novelty-seeking cluster, and a novelty-seeking impulsive cluster. It was observed that the majority of the people in the first group showed behavioral suppression, tried to control themselves excessively, and avoided taking risks, whereas the other group was prone to risk-taking, and exhibited impulsive and aggressive behaviors (64). In a study conducted by Kashdan and Hofmann in 2008, patients with the generalized type of SAD were examined in two different subgroups, low novelty seeking and high novelty seeking. The first group was characterized by social anxiety and avoidance and low novelty seeking, and the second group was characterized by high novelty seeking tendencies. In this group, it was stated that there may be impulsive decision-making behavior in parallel with difficulty in emotion regulation, novelty seeking, and risk proneness (65). There are also criticisms suggesting that SAD should be seen as a continuum of severity, and that when social anxiety is controlled, the differences between subtypes disappear (66). We think that the findings in the decision-making processes of the subtypes in our study can contribute to the current discussions.

An interesting finding of our study was that there was a significant negative correlation between Barratt-total and IGT-5 in patients with generalized type. It may be possible to interpret this finding in the following way. Bechara et al. reached the following results in a study they conducted on the process of choosing from advantageous decks. Regardless of whether the participants chose from the A and B decks after the first 10 card selections, they defined this period as the pre-punishment period because they did not face any punishments. The pre-hunch period is when participants have yet to grasp the content of the task, choosing cards from the A or B decks and facing a few penal sanctions. When healthy participants can develop an idea that decks A and B are riskier when approaching about 50 cards, this has been described as the hunch period. The conceptual period is defined as when healthy participants consciously reach full knowledge of what is going on in the content of the task as they approach about 80 cards (50). It can be concluded in our study that the generalized type reached the conceptual period, becoming aware that something was wrong. They realized that they should not avoid social situations. However, high impulsivity can cause them to make disadvantageous decisions despite the knowledge that something is wrong.

The most important limitation of our study is the high rate of comorbidities in patients with SAD.

Studies show that there is a high rate of comorbid diagnoses in patients with SAD (67,68). Another limitation of our study is the low mean age of both the patient and healthy control groups. We can recommend repeating the study in a wider age range. Finally, the fact that we did not look at skin conductivity during the task can be considered another limitation. For both high and low trait anxiety, skin conductance responses before choosing advantageous cards were found to predict IGT performance (57). Future studies that evaluate decisionmaking along with skin conductivity to elucidate the effect of somatic markers on decision-making processes in patients with SAD and their subtypes may lead to further enlightenment.

CONCLUSION

In conclusion, according to the findings of our study, decision-making performance in patients with SAD is similar to that of healthy controls. The ability to make decisions under uncertainty of patients with the generalized subtype was found to be impaired compared with those with the nongeneralized subtype. This suggests that the deterioration in the generalized subtype may be related to the short-term winning but long-term losing choices and the inability to benefit from feedback. We believe that this differentiation in the decisionmaking processes of SAD subtypes will contribute

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to a better understanding of generalized and nongeneralized subgroups.

Acknowledgments

The authors are grateful to the patients with SAD and the healthy volunteers who participated in this study.

Conflict of Interest

The authors declare that they have no conflicts of interest.

Ethical Publication Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Assessment of suicide risk among newly diagnosed cancer patients

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SUMMARY

Objective: We aimed to assess clinical (type, grade, symptom, quality of life), demographical, and psychological (social support, anxiety, and depression) risk factors of suicidality among newly diagnosed cancer patients in Turkey. **Method:** 122 cancer patients within their first month of diagnosis were enrolled in the study. Sociodemographic Form, Suicide Probability Scale (SPS), Multidimensional Scale of Perceived Social Support (MSPSS), European Organization for Research and Treatment (EORTC) quality of life questionnaire (QLQ-C30), Edmonton Symptom Assessment System (ESAS), and Hospital Anxiety and Depression Scale (HADS) were given to the patients.

Results: There were no relationships between SPS scores and age, gender, having metastatic cancer, being religious, marital status, having health insurance or employment. The EORTC QLQ-C30 cognitive function (p=0.003, r=-0.267) and emotional function (p=0.006, r=-0.249) and social function (p=0.019, r=-0.212) were found to be negatively and weakly correlated with SPS. Among ESAS variables, only severe insomnia was significantly correlated with high SPS scores (p=0.012). There were no statistical significance between SPS scores and having anxiety (p=0.110) or depression (p=0.591). There was no statistically significant relationship between SPS and MSPSS scores.

Discussion: There have been no study published in the literature that assesses the correlation between suicide risk and a variety of clinical and sociodemographic characteristics among Turkish cancer patients who have just received a diagnosis. According to our results, special attention must be given to cancer patients with severe insomnia and poorer cognitive, emotional, and social functioning.

Key Words: Anxiety, depression, functioning, cancer, suicide

INTRODUCTION

A diagnosis of cancer may cause psychological distress which may negatively affect treatment compliance and life quality and may result in psychiatric disorders that may lead to suicide (1). The risk of suicide among cancer patients has been found 4.4 times that of the general population (2). Demographic risk factors for suicide among cancer patients in western countries are similar to those among the general population; higher in elderly, white, and unmarried males (2). However, suicide **DOI:** 10.5505/kpd.2023.48902 risk factors may show regional and cultural differences. For example, in Turkey, suicidal behaviors are lower in the elderly population (3). Additionally, suicide rates in Turkey are lower compared to western countries and similar to those of Muslim countries (3).

Although it is mostly detectable and preventable, the majority of suicides among cancer patients seems to occur within 1 month of their last medical visit (4). It would sometimes be challenging for oncology healthcare professionals, especially in

Cite this article as: Kilic OHT, Aksoy I, Varol U, Anil M, Alacacioglu A, Cetin AS. Assessment of suicide risk among newly diagnosed cancer patients. Turkish J Clin Psych 2023; 26: 293-299

The arrival date of article: 31.05.2023, Acceptance date publication: 09.01.2023

Turkish J Clinical Psychiatry 2023;26:293-299

newly diagnosed patients, to distinguish normative grief symptoms which are expectable after diagnosis. Unfortunately, suicide risk is highest in the initial period after diagnosis and oncology healthcare professionals' training and awareness on identifying suicide risk is reported to be lacking (5,6).

In the current study we aimed to assess clinical (type, grade, symptom, quality of life), demographical, and psychological (social support, anxiety, and depression) risk factors of suicidality among newly diagnosed cancer patients in Turkey.

METHOD

In this cross-sectional descriptive study, we included patients who have been newly diagnosed with cancer (within one month of diagnosis) and were admitted to Izmir Katip Celebi University Ataturk Research and Training Hospital Medical Oncology Clinic for treatment from June 2020 to March 2021. Among 286 patients admitted to the clinic, 122 newly diagnosed cancer patients agreed to participate in the study. The eligibility criteria for inclusion in the study were patients who were 18 years old or older, intended to undergo chemotherapy, and have been informed of their cancer diagnosis. Patients with mental retardation, cognitive disorder or an inability to comprehend Turkish language were excluded. The study protocol received an institutional review board approval (TPF-20H03) according to the provisions of the Declaration of Helsinki, and all participants provided informed consent.

Sociodemographic Data Form, Suicide Probability Scale (SPS), Multidimensional Scale of Perceived Social Support (MSPSS), European Organization for Research and Treatment (EORTC) quality of life questionnaire (QLQ-C30), Edmonton Symptom Assessment System (ESAS), and Hospital Anxiety and Depression Scale (HADS) were given to the patients.

Sociodemographic Data Form: In this form, there are 15 questions about sociodemographic data of

the patients prepared by the researchers including age, education, religion, employment, marital status, disease and treatment history, alcohol and drug consumption, and tobacco use. The Eastern Cooperative Oncology Group (ECOG) Performance Status score was also noted. ECOG score assesses the quality of life and degree of wellbeing in patients with cancer. ECOG 0 represents asymptomatic (fully active, able to carry on all predisease activities without restriction), ECOG 4 means bedbound (completely disabled, cannot carry on any self-care), and ECOG 5 is equal to death.

Hospital Anxiety and Depression Scale (HADS): HADS is a self-report scale developed by Zigmond and Snaith which is used to determine anxiety and depression levels (7). It consists of 14 questions, each of which is scored between 0–3. Anxiety and depression are evaluated with seven questions each. The lowest possible scores for depression and anxiety are 0, and the highest possible scores are 21. Higher scores indicate increased severity of anxiety or depression. The reliability and validity of the Turkish language version were examined by Aydemir et al. and Cronbach alpha coefficients for anxiety is 0.85 and for depression is 0.78 (8). Cutoff scores for Turkish society have been determined as 7 for anxiety and 10 for depression (8).

Suicide Probability Scale (SPS): This scale evaluates the risk of suicide in adolescents and adults and includes 36 items with responses on a 4-point Likert-type scale. High scores on the scale indicate a high probability of suicide. Turkish validity and reliability study was conducted by Atli et al. and Cronbach alpha coefficient is 0.89 (9).

European Organization for Research and Treatment quality of life questionnaire EORTC QLQ C30 (version 3.0): EORTC-QLQ-C30 (version 3) was translated and validated in the Turkish language by Hoopman et al. (10). It has been developed for patients' self-assessment. It is a "30-item cancerspecific questionnaire" designed for patient selfcompletion. It is organized into functional scales (physical function, role function, cognitive function, emotional function, social function), symptom scales (fatigue, pain, dyspnea, loss of appetite, insomnia, diarrhea, constipation, nausea–vomiting, and financial difficulties), and global health status. It also includes a single item assessing the overall quality of life. Cronbach alpha coefficient are all above 0.70 except cognitive function subscale which is 0.57 (10). The scale scores are transformed into a 0 to 100 scale. Therefore, a high score on the functional scale represents a high level of functioning; a high score on a symptom scale represents a high severity level of symptoms (11).

Edmonton Symptom Assessment System (ESAS): The ESAS scale was developed by Eduardo Bruera et al. to improve the management of care for patients with cancer (12). The main rule (golden rule) of the symptom assessment is based on the opinion of a patient regarding the severity of his/her symptoms (13). The ESAS is designed to assist in the assessment of nine symptoms that are common in patients with cancer: pain, tiredness, nausea, depression, anxiety, drowsiness, appetite, loss of well-being, and shortness of breath (there is also a line labeled as "Other Problems"). The patients were asked if, in addition to the nine listed symptoms, they have other symptoms. The additional symptoms reported by patients were as follows: (1) skin and nail changes, (2) mouth sores, and (3) hand numbness. The severity at the time of the assessment of each symptom was rated on a numerical scale from 0 to 10, with 0 meaning that the symptom was absent and 10 meaning the worst possible severity.

Multidimensional Scale of Perceived Social Support (*MSPSS*): It was developed by Zimet et al. and adapted into Turkish by Eker and Arkar (14, 15). Cronbach alpha coefficient is 0.89 in the Turkish version (15). This instrument evaluates the qualitative presence of social support. Each item is graded using a 7-point scale with Likert-type ratings. Totals of the subscale of the instrument vary between 4 and 28, while the total scores can be between 12 and 84. Higher scores indicate higher perceived social support. Accordingly, participants were grouped as "low social support" (12-48 points), "intermediate social support" (49-68 points), and "high social support" (69-84 points).

Statistical analysis

Survey results were analyzed with IBM SPSS 20.0 Statistics (IBM Corporation, New York, USA) package program. Categorical data were indicated by numbers (n) and percentages (%). The numerical data that met the parametric assumptions are shown with arithmetic mean \pm standard deviation $(mean \pm SD)$ and minimum-maximum (min-max)values; those that did not meet the parametric assumption were expressed with median and interquartile range (IQR). The parametric assumption was assessed by the Kolmogorov-Smirnov test. The Chi-square test was used to compare categorical data. Post-hoc Bonferroni correction was used to compare more than two groups. Mann-Whitney U test was used to compare two independent variables that did not meet the parametric assumptions, and the Kruskal Wallis test was used to compare more than two nonparametric variables. The relationship between the two groups was examined with Spearman's correlation analysis. p < 0.05 value was considered statistically significant.

RESULTS

Among 122 patients, 67 (54.9%) were women and 55 (45.1%) were men. The average age of the participants was $56,85 \pm 13,30$. Ninety-nine (81.1%) of the participants were married and 23 (19.9%) were single. 114 (93.4%) patients were religious whereas 8 (6.6%) were not. Ten (8.2%) of them did not have any health insurance and 100 (82%) patients were unemployed.

Seventy-two (59.0%) patients were receiving adjuvant chemotherapy while 50 (41.0%) patients were receiving chemotherapy due to metastatis. Most of the patients had ECOG 0 performance score (n=107; 87.7%). Primary cancer localizations were; 27 (22.1%) colorectal cancer, 40 (32.8%) breast cancer, 12 (9.8%) lung cancer, 8 (6.6%) gastric or esophageal cancer, 5 (4.1%) pancreatic cancer and 29 (23.8%) cancer of other primaries. There were not statistically significant relationships between SPS scores and age (p=0.225), sex (p=0.167), having metastatic cancer (p=0.174), being religious (p=0.662), marital status (p=0.257), having health insurance (p=0.470) or employment (p= 0.879)

| Table 1. SPS scores according to characteristics of the patients. | | | | | | | |
|---|-------------|---------------|------------|-------|--|--|--|
| | n (%) | SPS (mean-sd) | t/U values | р | | | |
| Age | | | | | | | |
| <65 | 82 (67.2%) | 85.04-9.57 | 1.176* | 0.242 | | | |
| <u>></u> 65 | 40 (32.8%) | 82.88-9.47 | | | | | |
| Marital Status | | | | | | | |
| Married | 99 (81.1%) | 84.62-8.93 | 0.679* | 0.257 | | | |
| Single | 23 (19.9 %) | 83.11-12.01 | | | | | |
| Sex | | | | | | | |
| Male | 55 (45.1%) | 83.45-10.91 | 0.275* | 0.167 | | | |
| Female | 67 (54.9%) | 82.74-9.43 | | | | | |
| Metastasis | | | | | | | |
| Yes | 50 (41%) | 85.13-10.48 | -0.762* | 0.174 | | | |
| No | 72 (59%) | 83.78-8.88 | | | | | |
| Religiosity | | | | | | | |
| Yes | 114 (93.4%) | 84.42-9.64 | 391.5** | 0.662 | | | |
| No | 8 (6.6%) | 83.09-8.58 | | | | | |
| Health Insurance | | | | | | | |
| Yes | 112 (91.8%) | 84.42-9.58 | 414** | 0.470 | | | |
| No | 10 (8.2%) | 81.69-8.78 | | | | | |
| Employment | | | | | | | |
| Yes | 22 (18%) | 83.45-10.01 | 1030.5** | 0.879 | | | |
| No | 100 (82%) | 83.09-10.15 | | | | | |
| Smoking | | | | | | | |
| Yes | 27 (22.1%) | 90.08-10.14 | 751** | 0.003 | | | |
| No | 95 (77.9%) | 82.87-8.83 | | | | | |
| Suicide thought last month | | | | | | | |
| Yes | 4 | 98.30-13.96 | 83.5** | 0.029 | | | |
| No | 118 | 83.69-8.92 | | | | | |
| Past suicide attempt | | | | | | | |
| Yes | 7 | 93.01-9.18 | 190.5** | 0.020 | | | |
| No | 115 | 83.81-9.35 | | | | | |

*Independent samplest-test, **Mann Whitney U test,

SPS: Suicide Probability Scale

(Table 1).

The EORTC QLQ-C30 physical function, role function, cognitive function, emotional function, social function subscale scores and global health status scores were 67.73±24.22, 73.80±29.91, 79.58 ± 23.80 , 75.35 ± 24.11 , 76.40 ± 26.78 , and 58.40 ± 26.34 respectively. Cognitive function (p= 0.003, r = -0.267) and emotional function scores (p=0.006, r=-0.249) were found to be negatively and weakly correlated with SPS scores. Social function (p = 0.019, r = -0.212) scores were found to be

| Table 2. Correlations | between | SPS | and | EORTC | ! |
|-----------------------|---------|-----|-----|-------|---|
| OLO-C30 subscales. | | | | | |

| QLQ-C50 subscales. | | |
|----------------------|---------------------------|-------|
| | Suicide Probability Score | |
| EORTC QLQ-C30 | r | P^* |
| Physical function | -0.108 | 0.238 |
| Role function | 0.00 | 0.997 |
| Cognitive function | -0.267 | 0.003 |
| Emotional function | -0.249 | 0.006 |
| Social function | -0.212 | 0.019 |
| Global health status | -0.009 | 0.920 |
| *0 1 1 | 1 . | |

*Spearman's correlation analysis.

SPS: Suicide Probability Scale, EORTC QLQ-C30: European Organization for Research and Treatment Quality of Life Questionnaire

negatively and weakly correlated with SPS scores. There were no statistically significant relationships between other function subscales of EORTC QLQ-C30 and SPS (Table 2).

With using Edmonton Symptom Assessment System, we compared symptom severity and suicidality. Only severe insomnia was significantly correlated with high SPS scores (p = 0.012). Other symptoms like pain, fatigue, nausea, constipation, anorexia, shortness of breath and well-being were not found to be related with suicide risk (Table 3).

According to the cut-off scores, 45.9% (n=56) and 18.9% (n=23) of the patients had depression and anxiety, respectively. There was not any statistical significance between SPS scores and having anxiety (p=0.110) or depression (p=0.591) (Table 4).

The average score of MSPSS were 69,80±14,19. There was no statistically significant relationship between SPS and MSPSS scores (p = 0.451).

| Table 3. Relation | onship between ESAS | and SPS scores | | | | |
|-------------------|-----------------------|-----------------------|---------------------------|-------------------------|--------|--|
| Symptom Severity | | | | | | |
| | None SPS (mean-sd) | Mild SPS (mean–sd) | Moderate SPS (mean-sd) | Severe SPS (mean–sd) | р | |
| Insomnia | 81.06-8.11* | 85.46-9.49 | 83.62-9.14 | 89.82-10,99* | 0.012* | |
| Pain | 84.86-9.20 | 82.12-7.71 | 84.02-10.35 | 87.37-11,32 | 0.237 | |
| Fatigue | 84.59-8.92 | 83.58-8.83 | 82.74-10.29 | 87.40-10,42 | 0.328 | |
| Nausea | 83.76-8.79 | 84.62-10.68 | 85.21-9.47 | 85.69-11.77 | 0.894 | |
| Constipation | 84.34-9.41 | 76.94-10.01 | 83.23-6.29 | 91.87-9.71 | 0.056 | |
| Anorexia | 84.28-9.77 | 84.14-8.72 | 83.90-9.04 | 85.17-11.16 | 0.971 | |
| Shortness of | 83.89-9.08 | 83.26-10.38 | 89.03-8,13 | 84.10-11.24 | 0.309 | |
| Breath | | | | | | |
| Well-being | 87.30-8.82 | 81.88-8.50 | 83.73-9.04 | 86.32-11,55 | 0.124 | |

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*The difference between none and severe sample groups ESAS: Edmonton Symptom Assessment System, SPS: Suicide Probability Scale

DISCUSSION

To the best of our knowledge, this is the first study that examines the association between suicidality and a wide range of demographical, clinical, and psychological factors among newly diagnosed cancer patients in Turkey. We found that having severe insomnia and lower cognitional, emotional, and social functioning is related to higher suicide probability. There was no correlation between suicidality and demographic or social factors among newly diagnosed cancer patients.

Previous studies investigating the associations between physical symptoms and suicidality among cancer patients reported that pain and anorexia enhance suicide risk (16,17). But we didn't find any correlation between suicidality and any symptom except insomnia. Unlike previous studies, we included only newly diagnosed cancer patients who applied to our outpatient clinic. Therefore, pain and lack of appetite may not be as severe as in hospitalized patients which may explain these contradictory results. Thus, only one-sixth of our patients had severe pain and only one-sixth had severe anorexia. Besides, we found that severe insomnia is related to increased suicidality. Consistent with our results, Qingyi et al. demonstrated significant associations between insomnia and suicidal ideation among Chinese patients with cancer (18). Insomnia is generally considered an independent risk factor for suicide. Because after psychiatric disorders and related symptoms are controlled, the risk of suicide continues as long as sleep problems persist (19). It is hypothesized that insomnia may have an indirect effect on suicidal behavior by altering endocrinological and immunological pathways (20). For example, the serotonergic system takes a role in the sleep-wake cycle and its dysfunction is related to suicidal behaviors. Furthermore, insomnia is related to cognitive impairments which is also a mediator for suicide (20). Therefore, clinicians should pay particular attention to the sleep quality of their patients; should screen their patients for sleep disturbances, assess the severity of the problem, and provide appropriate interventions.

It has been shown in many studies that cancer patients frequently experience functional limitations and changes in family and social roles, which lowers their life quality (21,22). Furthermore, lower quality of life has been shown to increase suicidality among cancer patients (23). Consistent with this data we found negative correlation between life quality in terms of cognitive, emotional, and social functioning and suicide probability. Evidence indicates that after diagnosis, cancer patients face significant psychological stress and individuals with poorer cognitive skills are more likely to experience suicidal ideation in response to stress (24,25). We can speculate that receiving a diagnosis of cancer may increase suicidality by increasing stress in patients with lower cognitive functioning in the short term but self-rating scales for cognitive function may have limitations and could be biased.

Cancer patients have an increased risk for depressive and anxiety disorders, affecting 20% and 10% of them, respectively (1). We found depression in almost half of the patients and anxiety in one-fifth. Compared to the literature, the high rates of anxiety and depression in our study may be due to the use of different diagnostic tools and patient group characteristics. In a recent study from Turkey that

 Table 4. Relationship between HADS and Suicide Probability

 HADS
 n (%)

| IIAD5 | II (%) | Suicide Probability | p |
|----------------|------------|---------------------|---------|
| | | (mean – sd) | |
| HADS-A | 23 (18.8%) | 91.70 - 10.04 | p=0.591 |
| <u>></u> 10 | | | |
| HADS-A | 99 (82.2%) | 82.62 - 8.62 | |
| <10 | | | |
| HADS-D > 7 | 56 (45.9%) | 85.60 - 10.55 | p=0.110 |
| HADS-D <7 | 66 (54.1%) | 83.26 - 8.54 | |

HADS: Hospital Anxiety and Depression

(A: Anxiety, D: Depression subscale)

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used the same tools with our study, the rates of depression and anxiety symptoms were reported similar to our results as 52.7% and 29.2% (26). Contrary to our hypothesis and previous studies, we found no correlation between suicide probability and having anxiety or depression according to HADS (27-29). This is maybe due to the risk of suicide varies depending on the nature of depressive/anxiety disease and other circumstances like the previous history of suicide, age, social status, religiosity, and spiritual beliefs (30,31). Although depression and anxiety disorder rates in Turkey are similar to western countries, suicide rates are much lower (32). This data indicates that suicide is a complex condition that cannot be simplified by diagnosis of psychiatric disorders.

We also did not find any correlation between suicidality and perceived social support which is inconsistent with previous studies (33). Compared to previous studies, we found higher perceived social support scores in our patients. This may indicate that patients have lower expectations from their family, friends, and significant others in the early period and their social support is higher compared to the later stages of the disease. Being an elder is a known risk factor for suicide in both the general population and among cancer patients but we didn't find any enhanced risk in this population. Living in an extended family for all generations thought to protect elderly from loneliness and psychological difficulties.

First and perhaps the most important limitation to our study is the recruitment process of patients; it is not clear whether the patients who refused to participate in the study were less or more prone to the suicide. Lack of motivation to participate may indicate the latter, therefore generalizability of our study is limited. Further limitations arise from the cross-sectional structure of the study, which may increase potential bias of self-reported scales. Also the low number of participants in the study limited our statistical ability to search for further associa-

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tions by means of regression analyses.

Further studies are needed to examine the potential mediating and moderating factors that may influence the relationship between suicide risk in patients with cancer. Also, further research is needed to develop reliable and valid screening tools for suicide risk in patients with cancer. Finally, future studies should consider using objective measures of cognitive function to validate the self-reported cognitive function scores.

CONCLUSION

There has been no study published in the literature that assesses the correlation between suicide risk and a variety of clinical and sociodemographic characteristics among Turkish cancer patients who have just received a diagnosis. According to our results, special attention must be given to cancer patients with severe insomnia and poorer cognitive, emotional, and social functioning. Suicide prevention needs to be considered as one of the main interventions to the patients diagnosed with cancer, especially in the first month of receiving the diagnosis. So that, oncology medical professionals must be adequately trained and be aware of the warning indicators of suicide when they first deliver the diagnosis.

Acknowledgements

The authors would like to thank Songul Uluc Ozaltas and all of the cancer patients who completed surveys in their one of the most stressful times.

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Turkish J Clinical Psychiatry 2023;26:293-299

Evaluation of dynamic thiol/disulfide balance and oxidative metabolism in patients with obsessive compulsive disorder

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SUMMARY

Objective: We aimed to compare Total Oxidant Level (TOL), Total Antioxidant Level (TAL), Oxidative Stress Index (OSI), Thiol/Disulfide levels, Plasma Malondialdehyde (MDA) levels in both plasma and erythrocyte patients with OCD and healthy controls.

Method: Our study included 47 patients with OCD and 49 healthy controls. Sociodemographic data form was applied to all participants, CGI and Y-BOCS were applied to the patient group. TAL and TOL measurements were made in both plasma and erythrocytes, and Malondialdehyde (MDA) and Thiol/Disulfide measurements were made only in plasma.

Results: TAL, TOL, OSI and MDA values in the plasma of the patient and control groups were compared, no statistically significant difference was found. However, erythrocyte TAS level was lower in the patient group (p<0.05) and OSI level was higher (p<0.05) in the patient group. While no difference was observed in plasma total thiol level in the patient group compared to the controls, plasma native thiol levels were significantly higher (p<0.001) and plasma disulfide levels were significantly lower (p<0.05).

Discussion: The high level of native thiol, an antioxidant molecule in plasma, in OCD patients can be interpreted as an effort to compensate for the decreased antioxidant capacity in erythrocytes. According to these results, we think that when evaluating oxidative stress parameters in psychiatric diseases such as OCD, it is important to study the thiol/disulfide ratio as well as the total oxidant capacity of the plasma, and it would be appropriate to measure these parameters not only in the plasma but also in the erythrocyte.

Key Words: Obsessive compulsive disorder, oxidative stress, thiol, disulfide, thiol/disulfide balance

INTRODUCTION

Obsessive-compulsive disorder (OCD) is a chronic psychiatric condition characterized by obsessions and/or compulsions, leading to significant functional impairment (1). Although genetic predisposition and neurobiological factors are believed to contribute to the etiology of OCD, its pathophysiology remains not fully elucidated (1,2). In recent years, oxidative free radical damage has been proposed as a potential etiological factor for OCD (3). Oxidative stress arises when there's an imbalance between the production and consumption of free radicals within an organism (4). This condition results in an increased formation of free radicals, impairment of the antioxidant defense mechanism, and consequently, tissue damage (4). It's known that the brain is sensitive to alterations in oxidative metabolism and possesses limited antioxidant capacity to tolerate oxidative stress (5,6). The identification of increasing neurodegenerative changes

DOI: 10.5505/kpd.2023.98853

Cite this article as: Yilmaz OF, Kartal F, Kartalci S. Evaluation of dynamic thiol/disulfide balance and oxidative metabolism in obsessive compulsive disorder patients. Turkish J Clin Psych 2023; 26: 300-308

The arrival date of article: 13.09.2022, Acceptance date publication: 17.01.2023

Turkish J Clinical Psychiatry 2023;26:300-308

in neuropsychiatric disorders has given rise to the notion that oxidative damage may be integral to the etiology of these conditions (5,6). However, data on the role of oxidative stress in the complex neurobiological underpinnings of OCD pathophysiology are both limited and inconsistent. While some studies report no difference in oxidative stress levels in OCD, others suggest an alteration favoring either antioxidants or oxidants (7-10).

Erythrocytes, or red blood cells, are among the most affected by oxidative stress in the body (5). The limited metabolism of erythrocytes makes them susceptible to effects like oxidative stress exposure (11). Therefore, evaluating erythrocyte intracellular oxidative stress parameters in such studies, alongside plasma oxidative stress parameters, could be of significant importance.

Thiols, major and frequently utilized antioxidants in plasma, play a critical role in preventing the onset of oxidative stress in cells. They achieve this functionality through their sulfhydryl (-SH) groups. Reactive oxygen species oxidize thiols in the environment, leading to the formation of disulfides. The dynamic thiol/disulfide balance is key in antioxidant protection, signal transmission, apoptosis, enzymatic activity, transcription factor regulation, and cellular signaling mechanisms (12). Evaluating the thiol/disulfide homeostasis is considered critically important in understanding the role of oxidative stress in the pathogenesis of diseases (12). Abnormal levels of thiol/disulfide balance have been demonstrated to be involved in the pathogenesis of various diseases (13,14,15). Literature does contain studies examining the relationship between the thiol/disulfide balance and certain psychiatric diseases (16,17,18). However, no study investigating the thiol/disulfide balance in adult patients diagnosed with OCD undergoing treatment has been encountered.

In our research, our primary objective was to evaluate oxidative stress parameters, specifically in the context of the thiol-disulfide balance, in adult patients diagnosed with OCD who were undergoing pharmacological treatment. In addition, besides samples taken from plasma, we aimed to assess parameters related to the oxidative system in erythrocytes, given their capacity to reflect cellularlevel changes. Thus, in both patients with OCD and healthy controls, we sought to compare levels of Total Oxidant Level (TOL), Total Antioxidant Level (TAL), Oxidative Stress Index (OSI), Thiol/Disulfide levels. and Plasma Malondialdehyde (MDA) levels in both plasma and erythrocytes. Furthermore, we hypothesized a potential relationship between the severity of obsessive-compulsive symptoms, levels of functionality, and the balance of thiol/disulfide along with oxidative markers. We believe that our study will contribute to the literature by providing data related to the thiol/disulfide balance and oxidative system parameters in both plasma and erythrocytes within the context of OCD.

METHOD

Our study sample comprised patients diagnosed with OCD and healthy controls who were matched with the patient group in terms of age and gender.

Based on the power analysis conducted, to compare the patient and control groups with a confidence level of 95% (alpha=0.05) and a power of 80% (beta=0.80), the required minimum sample size per group was calculated to be 41, assuming an effect size of 0.63.

Participants included in our study were aged between 18 and 65, had at least basic literacy, did not have any known chronic physical illnesses as verified by medical records and self-report, had no substance use disorders, and did not exhibit medical conditions such as rheumatological diseases, neurological diseases, severe obesity, pregnancy, vascular diseases, or history of traumatic brain injury. Moreover, participants who had been taking xanthine oxidase inhibitors (e.g., allopurinol, folic acid) or agents with antioxidant properties (e.g., vitamin E, vitamin C, N-acetyl cysteine) were excluded.

Between December 2020 and June 2021, 62 patients who presented to the outpatient clinic of a university hospital's psychiatry department and were diagnosed with OCD by a psychiatric specialist/assistant according to DSM-5 were evaluated for participation in the study (19). Eight patients were excluded due to incomplete survey responses, and seven were excluded due to the presence of concurrent psychiatric or chronic metabolic diseases determined after psychiatric assessment. Ultimately, 47 patients diagnosed with OCD without co-morbid psychiatric conditions were included in the study. All these patients were undergoing treatment with drugs from the Selective Serotonin Reuptake Inhibitor (SSRI) group. All the patients included in the study had been under pharmacotherapy for at least two years, but had recently presented to the outpatient clinic due to exacerbated OCD symptoms. The healthy control group consisted of 49 health workers from our hospital, none of whom had any psychiatric illnesses.

Ethical approval for this research was obtained from İnönü University Faculty of Medicine, Medical Ethics Committee with the decision number 19.02.2019/ 81. Informed consent was duly obtained from all participants.

Procedure

In our study, all participants were administered a Socio-demographic data form. Participants in the patient group were additionally assessed using the Clinical Global Impression Scale (CGI) and the Yale-Brown Obsessive Compulsive Scale (Y-BOCS). These evaluations were conducted by an interviewer, taking approximately 30-45 minutes. Subsequently, blood samples were collected from all participants.

Measurment Tools

Sociodemographic Data Form: A semi-structured interview schedule created by the researchers conducting the study, the Sociodemographic Data Form queries information regarding age, gender, marital status, education, smoking habits, and past substance use history (not currently using).

Clinical Global Impression Scale (CGI): The Clinical Global Impression Scale (CGI) is used to evaluate clinical progression across all psychiatric disorders (20). The scale comprises three sub-dimensions and sheds light on symptom improvements and severity. It's a semi-structured scale filled out during the interview. The first two sub-dimensions are in a seven-point Likert scale format, revealing overall improvement and severity of the disease. The last sub-dimension reveals the efficacy index, based on a four-point Likert scale.

Yale-Brown Obsessive Compulsive Scale (Y-BOCS): Y-BOCS is a scale developed to grade the quality and severity of OCD symptoms (21,22). Administered by the interviewer, it consists of 19 items; however, only the first ten items are used to determine the total score. The first five items assess obsessions, while items 6 to 10 evaluate compulsions. Each item is scored between 0 and 4, with total scores ranging from 0 to 40. The scale's validity and reliability in Turkish were studied by Karamustafahoğlu et al. in 1993 (23).

Measurement and Calculation of Variables Biochemical Analysis

Blood samples were taken from both the patient and control groups after 12 hours of fasting from the antecubital vein. Blood drawn into anticoagulant full blood tubes was centrifuged at 3,000 rpm for six minutes to collect serum. The erythrocyte pack's bottom phase was washed twice with saline, obtaining erythrocyte packets. Both plasma and erythrocyte packs were stored in storage tubes at -80°C until analysis. On the analysis day, samples were thawed, and measurements of MDA, TAL, TOL, total thiol, and native thiol were taken, and OSI was calculated.

Measurement of Total Antioxidant Level (TAL): TAL is a method that measures the intracellular and extracellular total antioxidant capacity of the body. The measurement of total antioxidant status was performed with a commercial kit (RelAssay Diagnostic, Turkey). This method relies on the principle that antioxidants in the sample convert ABTS radicals from a deep blue-green color to a colorless ABTS state (24). As specified in the kit, in an ELISA device set to 25 °C, 500 µL of reagent 1 (measurement buffer) and 30 μ L of serum were mixed, and the absorbance was measured at 660 nm. This mixture was incubated with 75 μ L of reagent 2 (colored ABTS solution) for 10 minutes, and subsequently, the absorbance was measured again at 660 nm to calculate TAL levels.

Measurement of Total Oxidant Level (TOL): TOL represents the cumulative value of oxidative stress in the body. The total oxidant level measurement was performed with a commercial kit (RelAssay
Diagnostic, Turkey). This method is based on the color difference resulting from the interaction between ferrous ion-chelator complexes being oxidized to ferric ions by the oxidants in the sample and a chromogenic substance in an acidic environment (25). As specified in the kit, in an ELISA device set to 25 °C, 500 μ L of reagent 1 (measurement buffer) and 75 μ L of serum were mixed, and the absorbance was measured at 530 nm. This mixture was incubated with 25 μ L of reagent 2 (prochromogen solution) for 10 minutes, and subsequently, the absorbance was measured again at 660 nm to calculate TOL levels.

Calculation of Oxidative Stress Index (OSI): The Oxidative Stress Index (OSI) was determined using the Total Oxidant Status (TOL)/Total Antioxidant Status (TAL) formula (26).

Measurement of Plasma Malondialdehyde (MDA): Level MDA level was measured in plasma. MDA, one of the final products of lipid peroxidation, serves as an indirect indicator of oxidation. MDA measurement was conducted according to the method of Uchiyama et al. (27). MDA levels were measured by reading the color change resulting from the supernatant's reaction with thiobarbituric acid at 95 °C in the n-butanol phase using a spectrophotometer at 535 and 520 nm.

Measurement of Thiol/Disulfide Levels: Thiol-disulfide was evaluated from serum samples. The thioldisulfide level (native thiol (-SH) - disulfide (-S-S-)) was determined using a commercial kit (RelAssay Diagnostics, Mega Med, Gaziantep, Turkey). The commercial kit method initially involves the conversion of disulfide bonds in serum samples to functional thiol groups with sodium borohydride (NaBH4). Subsequently, a method using formaldehyde and reductive sodium borohydride prevents the reduction of 5,5'- dithiobis-(2nitrobenzoic) acid (DTNB) (28). This method inhibits potential disulfide bond formation. Sulfite amounts were calculated as natural thiol/total thiol, disulfide/total thiol, and disulfide/natural thiol percentages.

The dynamic thiol/disulfide balance and the oxidation end product MDA were only measured in plasma, while parameters reflecting total oxidant and antioxidant statuses, namely TAL, TOL, and OSI, were compared both in plasma and erythrocytes.

Statistical Analyses

Data obtained in the study was analyzed using SPSS 22.0 (Statistical Package for the Social Sciences). Data were presented as mean (standard deviation) and number (percentage). The Kolmogorov-Smirnov test was used for testing normal distribution. For data that followed a normal distribution, parametric tests were applied, whereas non-parametric tests were used for data that did not conform to a normal distribution. The chisquare test was applied for the comparison of categorical sociodemographic data between groups. The t-test was used for the comparison of numerical data between two groups. Correlations between data, which exhibited a normal distribution, were determined using the Pearson Correlation Coefficient test. A significance level of p<0.05 was established for evaluations.

RESULTS

The statistical analysis of descriptive data related to the sociodemographic characteristics of the participants included in the study is presented in Table 1.

Table 1: Comparison of the data related to the descriptive statistics of the participants' sociodemographic characteristics

| | 40; | Patients (n:47) | Control (n:49) | Р | |
|-----------------------------|-------------------|-----------------|-------------------|---------|--|
| Age (Mean±SD) | | 31.10±12.08 | 29.61±7.27 | 0.463 | |
| Conder (n/9%) | Male | 23 (%48.9) | 24 (%49) | 0.009 | |
| Gender (11/50) | Female | 24 (%51.1) | 25 (%51) | 0.998 | |
| | Married | 14(%29.8) | 21(%42.9) | | |
| Marital Status | Single | 28 (%59.6) | 27(%55.1) | | |
| | Divorced | 5 (%10.6) | 1(%2) | 0.130 | |
| | Yes | 16(%34) | 10(%20.4) | 0 1 2 2 | |
| Smoking | No | 31(%66) | 39(79.6) | 0.155 | |
| | Primary Education | 8(%17) | 0 (%0) | | |
| Educational Status | High School | 10(%21.3) | 8(%16.3) | 0.006 | |
| Educational Status | University | 27(%57.4) | 41(%83.7) | 0.000 | |
| | Other | 2(%4.3) | 0(%0) | | |
| Contraction and Contraction | Country | 2(%4.3) | 1(%2) | | |
| Residental Status | City | 43(%91.5) | 48(%98) | 0.154 | |
| | Other | 2(%4.3) | 0(%0) | | |
| 0 | Employee | 13(%27.7) | 28(%57.1) | 0.004 | |
| Occupational Status | Unemployee | 34(%72.3) | 21(%42.9) | 0.004 | |
| Harring a shild | Yes | 14(%29.8) | 15(%30.6) | 0.020 | |
| riaving a child | No | 33(%70.2) | 34(%70.4) | 0.930 | |
| Substance Use | Yes | 1(%2.1) | 0(%0) | 0.205 | |
| History | No | 46 (%97.9) | 49(%100) | 0.305 | |

Mean±SD: Mean=Standart Deviation, Chi-square test, significant p value <0.05

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Table 2. Minimum, maximum and mean source of participant: in Parliant: group from the V-BOC's and CGI

| | Min-Mas. | Mean+SD |
|-------------------|----------|---|
| V-BOES-Obsective | 1-20 | 11.04±4.31 |
| Y-BOCS-Computtion | 3-20 | 9.59±4.74 |
| Y-BOCS-Total | 6-30 | 22,55+8,42 |
| CGI | 5-14 | 8.70+2.04 |
| | | the second second second second second second second second second second second second second second second se |

MasMar, Mananan Maranan, Masa-10, Masa-Yondar Devenior, Yala-Brews (Deanter, Computers Scale (T-2005) , Charal Girbai Inprocess Scale (CG)

The mean score for the Y-BOCS obsession subscale of the patient group is 13.04 ± 4.27 , and for the Y-BOCS compulsion subscale, it's 9.89 ± 4.74 . The overall mean score for Y-BOCS is 22.93 ± 8.42 . The average score patients obtained from CGI is 8.70 ± 2.04 (Table 2).

When comparing the patient and control groups in terms of plasma TAL, TOL, OSI, and MDA values, no statistically significant difference was observed (p>0.05). It was determined that the OSI level in erythrocytes, one of the oxidative stress markers, was higher in the patient group compared to the control group (p<0.05). Among the antioxidant markers, it was found that the erythrocyte TAL level in patients was lower than that in the control group (p<0.05) (Table 3).

Upon examining data related to plasma thiol-disulfide levels, while no significant difference was observed between patient and control groups regarding total thiol levels, which is an antioxidant marker, it was determined that the native thiol level in plasma was higher in the patient group (p < 0.001). The plasma disulfide level, an oxidative stress marker, was found to be lower in patients compared to the control group (p < 0.05). Consequently, in this study, the ratio of disulfide/total thiol and disulfide/native thiol, which are oxidative stress markers, was significantly lower in the patient group compared to the healthy controls, while the native thiol/thiol ratio, an antioxidant marker, was found to be significantly higher (p < 0.05) (Table 3). It was determined that the plasma TAL level measured in the patient group was inversely weakly correlated with the Y-BOCS subscales and total score (p < 0.05). A positive weak correlation was observed between the plasma TOL level and the illness duration (p<0.05) (Table 4).

Table J. Comparison of the participants' TAL, TDS, OSL MDA, Tetal Third, and Native Third levels in planars and arythraction between groups

| | Patients (nei7) MeantsD ^{ae} | Control (no45) MeandSD | 9 | p |
|---------------------------|---|------------------------------|--------|-------|
| TAL-Brythrocytei | 0.3550.02 | 0.1650.02 | 2.896 | 0.645 |
| TOC-Erythronyte | 5,7150,95 | 5.80±0.86 | -0.505 | 0.616 |
| OSI- Brythracyte | - 56.7522.50 | 34,9752,73 | 3.673 | 0.032 |
| MDA Plasma | 3.9010.42 | 2.2410.47 | 0.740 | 0.461 |
| TOL-Placing | 1 1210 50 | 1.3310.96 | -0.895 | 0.323 |
| TAL-Plairea | a \$3x0.57 | 0.6610.14 | -L 778 | 0.079 |
| OSI-Platma | 2,7241.67 | 2.57±1.00 | 0.434 | 0.680 |
| Planno-Total Thiol | 205,92522,33 | 294.67125.12 | 5.632 | 0.106 |
| Placeus-Nutliee Thiol | 231.24335.45 | 200 31138 30 | 4.167 | 0.000 |
| Planna-Disuffita | 37.29115.39 | 47.12£18.94 | -2.784 | 0.995 |
| Mative Thiol/ Total Thin! | 0.7550.09 | 0.6550.11 | 3.558 | 0.901 |
| Disa The Total Third | 9.3250.04 | 0.1550.05 | -3.555 | 0.001 |
| Disa lite/Mative Thiol | 0.5610.00 | 0.27±0.25 | -2.651 | 0.609 |

Mean-SD: Mean-Smaller Deviation, Independent unigsle vites, utgutätisar pivalue +0.01, TAL. Total Antipoidant Level Secures: TOL: Total Opidiar Level/OSI: Opidation Specylader, MDA: Malondaldebyte

DISCUSSION

One of the significant findings of our research is that in patients diagnosed with OCD, compared to controls, the ratio of reduced thiol (native thiol/total thiol), which is an indicator of the antioxidant system, is high. In contrast, the thiol oxidation-reduction ratio (disulfide/native thiol) and oxidized thiol ratio (disulfide/total thiol), indicators of the oxidative system, are low. To our knowledge, based on the literature review, there is no research examining thiol-disulfide levels in adult OCD patients. In a study conducted only in the child and adolescent group, it was reported that, contrary to our data, the plasma oxidized thiol ratio and thiol oxidation-reduction ratios were significantly higher in the OCD patient group not taking pharmacological treatment than in the control group (29). One possible reason for this difference may be that the patients included in our study were using pharmacological treatments. Another possible reason might be that, during childhood when the disease starts, disulfide levels trend higher due to an increase in oxidative stress, whereas in adulthood, possibly due to the chronic nature of the illness, a potential compensatory mechanism might lead to a decrease in plasma disulfide levels and an increase in native thiol levels.

In the adult period, there are studies examining the thiol/disulfide balance in psychiatric disorders other than OCD. Based on the results of studies conducted in patients diagnosed with Schizophrenia, Heroin Use Disorder, and Anxiety

| | | TOL- Erythrocytes | TAL- Erythrocytes | OSI- Erythrocytes | Plasma- MDA | TOL-Plaima | TAL-Plasma | OSI- Plasma | Plasma- Total Thiol | Plasma- Native Thiol | Plaima- Disulfide | Native Thiol/Total Thiol | Disulfide/Tot al Thiol | Disulfide/Nat ive Thiol |
|------------------------|---|----------------------|----------------------|----------------------|----------------|------------|------------|----------------|------------------------|-------------------------|----------------------|--------------------------------|---------------------------|----------------------------|
| CGI | R | -0,009 | 0,018 | -0,070 | -0,090 | 0,154 | -0,232 | 0,210 | -0,079 | -0,195 | 0.110 | -0.153 | 0.153 | 0.190 |
| | P | 0,953 | 0,907 | 0,642 | 0,549 | 0.302 | 0,117 | 0,157 | 0,597 | 0,189 | 0,463 | 0,304 | 0,304 | 0,201 |
| Y-BOCS- 1 obsession | R | 0,224 | 0,252 | -0,088 | -0,113 | 0,071 | -0,444(**) | 0,274 | 0,027 | -0,214 | 0,240 | -0,270 | 0.271 | 0.284 |
| | P | 0,130 | 0,088 | 0,554 | 0,451 | 0,638 | 0,002 | 0,063 | 0,856 | 0,148 | 0,104 | 0,066 | 0,066 | 0,053 |
| Y-BOCS- compulsion | R | 0,242 | 0,197 | 0,078 | -0,114 | 0,031 | -0,302(*) | 0,109 | -0.068 | -0,160 | 0,087 | -0.119 | 0,119 | 0.122 |
| | P | 0,101 | 0,184 | 0,602 | 0,444 | 0,838 | 0,039 | 0,466 | 0,652 | 0,283 | 0,550 | 0,425 | 0,425 | 0,413 |
| Y-BOCS- Total | R | 0,246 | 0,237 | -0,007 | -0,118 | 0,053 | -0,388(**) | 0,197 | -0,023 | -0,188 | 0,162 | -0.194 | 0.194 | 0.204 |
| | P | 0,096 | 0,108 | 0,963 | 0,430 | 0,724 | 0,007 | 0,183 | 0,877 | 0,205 | 0,276 | 0,191 | 0,191 | 0,170 |
| Illness Duration | R | 0,071 | 0,145 | -0,157 | 0,042 | 0,316(*) | -0,117 | 0,221 | -0,126 | -0,175 | 0,041 | -0.094 | 0.094 | 0,057 |
| (ren) | P | 0,636 | 0,331 | 0,292 | 0,779 | 0,030 | 0,433 | 0,135 | 0,397 | 0,238 | 0,786 | 0,531 | 0,531 | 0,702 |

Table 4. Correlation of the patients' levels of TAL, TOL, OSI, MDA, Total Thiol and Native Thiol in erythrocytes and plasma and CGI, Y-BOCS, illness duration

Pearson correlation test ,** p<0.01 * p<0.05, Yale-Brown Obsession-Compulsion Scale (Y-BOCS), Clinical Global Impression Scale (CGI), TAL: Total Antioxidant Level, TOL: Total Oxidant Level, OSI: Oxidative Stress Index, MDA: Malondialdehyde,

Disorder, an increase in oxidative parameters is generally reported when examining the thiol/disulfide balance (17,18,30-33). In a study conducted in bipolar disorder, antioxidant parameters were found to be higher in patients in the manic phase compared to patients in remission and healthy controls (16). Another study reported high antioxidant markers regardless of the clinical stage of the disease (34). In a study with a sample consisting of patients diagnosed with bipolar disorder and unipolar depression, plasma oxidative stress parameters were found to be significantly higher in both patient groups (35). In a study conducted in depression patients not taking pharmacological treatment, antioxidant parameters related to plasma thiol disulfide hemostasis were found to be high, and oxidative stress parameters were low compared to the control group (36). In summary, the literature shows conflicting data regarding the thiol/disulfide balance in psychiatric disorders. Possible reasons for these conflicting results might be that the studies were conducted during different stages of the diseases, medication use that might affect the thiol/disulfide balance, and/or the presence of accompanying psychiatric or physical illnesses. The results of our study can be interpreted as indicating a shift towards the reducing side, the native thiol, of the thiol/disulfide balance as a compensatory mechanism to offset increased oxidative stress in OCD. In conclusion, when considering other oxidative stress pathways along with dynamic

thiol/disulfide homeostasis, it's conceivable that there might be a more complex interaction related to oxidative stress in OCD.

In patients diagnosed with OCD, the TAL level inside the red blood cells was found to be lower and the OSI value higher compared to the control group. No difference was found between the patient and control groups in terms of TOL value. Therefore, these results indicate that the high OSI, which is the TOL/TAL ratio, originates from a decrease in the total antioxidant capacity, i.e., TAL level. When studies evaluating psychotropic drug use, smoking, and patients with psychiatric diagnoses other than OCD are examined, there are studies reporting that antioxidant parameters in materials obtained from plasma are higher, oxidative stress parameters are lower, or there is no difference between variables compared to healthy controls (37.38). In children and adolescents with OCD who do not receive medical treatment and do not have a comorbid disease, plasma antioxidant markers were found to be lower and oxidation markers higher compared to controls (39).

In our study, we observed no difference in the oxidative system indicators in plasma. When comparing the results of previous studies, it can be inferred that the discrepancy between the results might be due to different measurement techniques, the type of material examined (red blood cells, plasma, serum, etc.), the use of psychotropics, different age groups, sampling at different stages of the disease, different ethnic origins, lifestyle, and dietary features. While the general consensus in the literature suggests that the plasma antioxidant capacity is low in OCD (37), (40), we could not observe this result in the plasma of patients diagnosed with OCD. However, we did identify significant differences in the oxidative stress parameters inside the red blood cells. When evaluating these different findings related to oxidative values in plasma and red blood cells in OCD patients together, it can be interpreted that changes in oxidative stress markers might start within the red blood cells. Considering the interaction of red blood cells with metabolism throughout the body, and even in the brain, it can be suggested that this situation might be related to neurophysiological changes in OCD.

In our study, when we examined the plasma MDA levels, which are an index of lipid peroxidation, we found no significant difference between the patient and control groups. In a study conducted with patients diagnosed with schizophrenia, it has been reported that, consistent with our results, there was no significant difference between the patient and healthy control groups in terms of plasma MDA levels (41). However, there are also studies reporting that the plasma MDA level in patients diagnosed with OCD is higher than the healthy control group (3,41). The lack of difference in plasma MDA levels in our study can be seen as a consistent result, given that while we detected differences in other oxidative stress parameters at the erythrocyte level, we did not detect any at the plasma level.

In our research, we also examined the relationship between the oxidation markers we evaluated and the average scores taken from Y-BOCS, CGI, and the duration of the disease. We found a statistically significant weak inverse relationship between the severity of obsessive-compulsive symptoms and plasma TAL level and a weak same-direction relationship between the duration of the disease and the TOL level. Selek et al. interpreted the shift in oxidative balance towards the antioxidant side in OCD patients as a rebound phenomenon or an indicator of chronicity (37). Additionally, in the same study, it was suggested that long-term exposure to the disease might have increased antioxidant mechanisms or, alternatively, the treatment might have activated antioxidant mechanisms. According to our results, the decrease in TAL levels as obsessive-compulsive symptom severity increases and the increase in TOL levels as the duration of the disease increases supports the inference that oxidative balance might be more affected by chronicity rather than disease severity.

One of the strengths of our study is that it is the first to evaluate the thiol/disulfide balance along with oxidative stress parameters such as MDA, TAL, TOL, OSI in adult patients diagnosed with OCD receiving pharmacological treatment. Another strength is our examination of oxidative stress parameters at both plasma and erythrocyte levels to reduce inconsistency related to the examined material. A main limitation of our study is its cross-sectional nature. Participants were ensured not to use antioxidant agents, and factors affecting the oxidative system were tried to be excluded by ensuring they don't have neurological, genetic, or chronic medical diseases. However, significant limitations include not excluding the effects of psychotropic drugs used by patients, nutrition, exercise status, and Body Mass Index. Although the inclusion of smokers is also a limitation of our study, the fact that there is no significant difference in smoking rates between the groups can be considered an advantage. In the study, patients from the OCD group who applied to our outpatient clinic were included; hence, the results from community screening studies might differ. As a homogeneous patient group was chosen in our study, the potential effects of other psychiatric comorbidities on the results could not be investigated.

CONCLUSION

We believe that our study's significance lies in it being the first study to investigate the Thiol/Disulfide level in adult patients with OCD (Obsessive-Compulsive Disorder). Unlike other reported systemic diseases, the dynamic thiol/disulfide homeostasis in patients diagnosed with OCD may be related to mechanisms such as increased anti-oxidative compensations in response to oxidative stress. Since our study is cross-sectional, even though a cause-and-effect relationship cannot be clarified, it might be suggested that underlying possible mechanisms be longitudinally researched in future studies.

When evaluating the results of our study, we found that the plasma TAL and TOL values in patients with OCD were not different from the control group. However, we determined that the erythrocyte TAL level was lower in the OCD patient group, while the OSI ratio was higher. Looking at the literature, in OCD, plasma oxidative stress markers usually show high oxidant levels and low antioxidant levels (40). Contrary to the general opinion when we examined the thiol-disulfide parameters, we determined that the antioxidants were high. The high level of native thiol, an antioxidant molecule in plasma, in patients with OCD, can be interpreted as an effort to compensate for

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the decreasing antioxidant capacity within erythrocytes. In light of these results, we believe that when evaluating oxidative stress parameters in psychiatric diseases like OCD, in addition to plasma total oxidant capacity, studying the thiol/disulfide balance is crucial. Moreover, it could be said that measuring these parameters not only in plasma but also within erythrocytes would be appropriate.

Conflicts of interest: The authors declare that they have no conflict of interest.

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Earthquake and mental health of healthcare workers: A systematic review

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SUMMARY

This systematic review aims to examine the psychological effects of earthquakes on healthcare workers and the related variables influencing these psychological effects. This study includes 11 research articles that assessed the psychological effects of earthquakes on healthcare workers by categorizing them under various mental health outcomes. Through keyword searches in databases, it was observed that healthcare workers experienced posttraumatic stress disorder, burnout, depression, stress, and decline in quality of life. Factors affecting the mental health of healthcare workers after earthquakes include gender, professional and earthquake-related factors, personality traits, social support, coping strategies, psychological resilience, and meeting personal needs. The review study provides important clues for interventions that could reduce negative mental health effects on healthcare workers following earthquakes.

Key Words: Earthgauke, healthcare workers, psychological health, mental health, post-traumatic stress

INTRODUCTION

On 6 February 2023, devastating earthquakes hit Turkey and Syria. According to the Moment magnitude scale, on 6 February 2023, two earthquakes with a magnitude of 7.7 centred in Pazarcık in Kahramanmaraş province and two earthquakes with a magnitude of 7.6 centred in Elbistan occurred. On 20 February 2023, there was another earthquake with a magnitude of 6.4 centred in Samandağ. As a result of these earthquakes, according to official figures, at least 48448 people lost their lives in Turkey and at least 8476 people in Syria; more than 129 thousand people were injured and about 14 million people were affected by the DOI: 10.5505/kpd.2023.70845

earthquake. Following these earthquakes, which caused severe damage in 11 provinces, it was noted that nearly 17,000 aftershocks occurred (1,2). Our country, which is located in the earthquake zone, has experienced earthquakes of similar magnitude of 7.8 and 7.5 in Gölcük (Kocaeli) and Düzce in 1999, and 7.9 in Erzincan in 1939, causing many casualties and property damage (3).

Earthquakes are unforeseeable, abrupt and unmanageable natural occurrences. It is deemed a social tragedy that has a considerable impact not only on the inhabitants in the earthquake-stricken area but also the search and rescue teams who travel to the location to provide assistance in different

Cite this article as: Schlikoglu S, Yilmaz Karaman IG, Yastibas Kacar C, Canakci ME. Earthquake and mental health of healthcare workers: A sistematic review. Turkish J Clin Psych 2023; 26:309-318

The arrival date of article: 30.05.2022, Acceptance date publication: 19.09.2023

Turkish J Clinical Psychiatry 2023;26:309-318

areas, public officials who volunteer or work officially, and individuals who work for non-governmental organisations (4,5). Following seismic activity such as earthquakes, individuals who are directly exposed to the event and those who receive detailed information about it second-hand, even if they do not witness or experience it themselves, as well as the teams operating in the affected area, may suffer from traumatic stress symptoms that arise after the trauma. These symptoms are classified as secondary traumatic stress or vicarious traumatization and parallel the experiences of primary trauma survivors (6,7). The medical personnel who arrived in the region following the earthquake bore witness to the traumas suffered by locals and encountered several unfavourable conditions. Post-traumatic mental health issues can be observed in healthcare workers who were present during the earthquake, as well as those who arrived to respond. Health workers who offer services to people exposed to trauma have been studied using various concepts that differ from those explored for those who experienced the earthquake. These include compassion fatigue, secondary traumatic stress, indirect trauma, and burnout, as documented in reference 8.

Before a disaster, healthcare professionals who live in the affected area not only serve as rescuers but are also affected by the disaster themselves, unlike those arriving to offer support. Local healthcare workers often face the loss of family and friends and may not have the opportunity to communicate with their loved ones. Following the 2010 Yushu earthquake, a study revealed a higher incidence of post-traumatic stress disorder (PTSD) in local health workers in comparison to those who had travelled to provide support. The cause of this disparity remains unclear (9). Similarly, another study found that therapists exposed to the earthquake suffered increased levels of burnout and lower levels of personal accomplishment compared to nonexposed therapists (10). Zhen et al. (11) revealed that nurses who experienced earthquakes reported considerably elevated levels of PTSD and depression symptoms within one year when compared to unexposed nurses. The results were objective and supported by the study's findings.

In addition to the urgent treatment of serious

injuries during disasters, it has been noted that these events can worsen acute and chronic physical and psychological conditions in individuals, resulting in greater demand for healthcare services (12). Healthcare workers providing emergency medical services in disaster zones may face additional pressures and are at risk of experiencing secondary traumatisation due to exposure to graphic images, including corpses, severe injuries, blood, and difficult circumstances (13). Furthermore, healthcare workers have been found to suffer psychological disorders more frequently than the general population in disaster situations (14). Failure to accept the risk of fulfilling one's duty, being apart from one's family, daily needs' inadequacies and experiencing mental exhaustion have adverse effects on mental health (15).

Healthcare professionals frequently work under demanding circumstances and are required to make essential clinical decisions on the ground. In addition to coping with personal losses, financial hardships and housing damages stemming from the disaster, they may also be exposed to a range of issues linked to weakened infrastructure caused by earthquakes, increased risk of endemic disease transmission, extended work hours, staff deficits, physical exhaustion, anxiety, burnout and even chronic unpredictable effects like PTSD (16).

Although post-traumatic stress symptoms do not occur uniformly in all individuals, some may be asymptomatic. Furthermore, other individuals may suffer from various psychological issues, including suicide, anxiety disorders, and substance use disorder, as well as conditions such as short-term adjustment disorder, PTSD, or major depressive disorder, after experiencing trauma (17,18,19,20,21). Risk factors for PTSD are divided into two categories: those related to the traumatic event and those related to the individual exposed to trauma. It is important to note that identifying these risk factors can be helpful in preventing PTSD. The most serious risk factor associated with the event is the trauma's severity, type, and duration (22). Risk factors related to the traumatised individual include being female, having a history of traumatic experiences, coping mechanisms, and the level of depression. Meanwhile, youth, low socioeconomic and educational levels, singleness, widowed or

divorced status, and a personal or family history of psychiatric illness are identified as risk factors for PTSD (23). Living at the centre of a disaster, suffering personal losses, being part of the initial response team, and having limited work experience are all factors that markedly impact the mental well-being of healthcare workers involved in rescue efforts. However, there are several protective factors for PTSD, including having received professional mental health education before, advanced age, male gender, professional experience, and social support from family and friends (9,26,27,28).

Mental health conditions have a detrimental impact on the daily lives of healthcare professionals. Burnout, already prevalent among healthcare workers in their routine work, is even more common in the context of disaster response (30). Research suggests that burnout affects 30% to 70% of healthcare workers (30,31). Studies conducted after the Great East Japan earthquake suggest that burnout, which has a detrimental effect on healthcare workers' work and daily life, could also lead to various mental health issues, notably PTSD (32, 33, 34).

As a result, there are many studies showing that healthcare workers working in various social disasters such as earthquake, nuclear accident, fire, tsunami, COVID-19 are negatively affected mentally (29,32). PTSD, depression, anxiety, and substance abuse are the main mental problems experienced (20). Various factors that increase or reduce the risk of mental health problems among healthcare workers are believed to exist. Identifying and understanding these factors is crucial for improving the mental health practices within this workforce. When examining the relevant literature, it is clear that while there are indeed review studies regarding the effects of diverse social disasters on healthcare workers, these studies can only be linked to one specific psychopathology, such as PTSD (20), and the correlation with different social traumas (35). As such, it has been noted that there is a paucity of review studies that directly concentrate on the mental wellbeing of healthcare professionals working in earthquake-prone areas and aftermath zones. It is crucial to assess the mental wellbeing of healthcare professionals who have a vital role in providing immediate and lasting medical care in earthquake situations, particularly in our earthquake-prone country. Initial findings indicate that healthcare workers experienced psychosocial challenges following the earthquakes that occurred in Turkey on 6 February 2023 (36).

Therefore, the present review intends to examine the impact of the earthquake on the mental wellness of healthcare professionals and the contributing factors influencing their mental health.

METHODS

The primary aim of the investigation was to assess the impact of the earthquake on the psychological well-being of healthcare professionals.

Search Strategy

The current review study utilized the Web of Science and PubMed databases. The analysis followed the PRISMA criteria (37) to ensure a systematic approach. To search both databases, keywords such as "healthcare worker," "health personnel," "medical responder," "earthquake," "mental health," and "psychological health" were employed.

Selection of Studies

The systematic review employed inclusion criteria, including that the study: a) had been published from 2003 to present, b) had healthcare professionals as the sample, c) was quantitative in methodology, d) analysed the impact of the earthquake on the mental health of healthcare professionals, and e) was composed in English or Turkish. Exclusion criteria consisted of the following: a) publications prior to 2003, b) studies failing to involve healthcare workers as individual participants or not analyzing data relevant to healthcare workers separately, c) studies devoid of any mental health outcome, d) types of studies other than original research such as case reports, reviews and metaanalyses, e) simultaneous occurrence of another disaster with the earthquake.

A total of 523 studies have been acquired through the specified keywords. The remaining 471 studies



underwent separate screening by two independent researchers following removal of repeated studies. Subsequently, a third researcher scrutinised the selected studies, identifying discrepancies in the decisions made. All identified studies were then deliberated upon by three researchers until a consensus was achieved by mutual agreement. The entire process of study selection is depicted in the PRISMA flowchart (Figure 1).

RESULTS

After applying the inclusion and exclusion criteria, we analysed 11 studies for our systematic review. We summarised our findings in Table 1.

The included studies were published between 2010 and 2022, and the number of participants ranged from 63 to 1527. Two studies were longitudinal, and nine were cross-sectional. The seismic events linked to mental health outcomes in this investigation comprise the 2008 Sichuan-Wenchuan earthquake (4 studies), the 2009 L'Aquila earthquake (2 studies), the 2010 Yushu earthquake, the 2014 Ludian earthquake, the 2015 Nepal Earthquake, the 2018 Taiwan Haulien earthquake, and the 2020 Malatya-Elazığ earthquake. The data collection processes for the studies encompassed a broad time interval, ranging from 3 weeks to 11 years after the earthquake.

Outcome variables concerning the mental health of healthcare workers following the earthquake were investigated. Seven studies focused on posttraumatic stress, 2 studies investigated burnout, 2 stu-dies looked at the decline in quality of life, 1 study explored psychological stress and 1 study analysed depression. In terms of mental health outcomes following the earthquake, the impact of psycholo-gical resilience was investigated in 1 study.

Post Traumatic Stress Disorder

The review predominantly focused on PTSD amongst healthcare workers. The research reported varying rates of PTSD, with prevalence ranging between 3.2% and 30%. Notably, psychosocial and demographic factors were identified as influencing post-traumatic stress levels. Researchers recorded a decrease in PTSD over time following the earthquake (38), and previous experience of an earthquake was found to offer some protection against traumatic stress (28). Furthermore, the study revealed that individuals who suffered from water and food shortages during their earthquake relief efforts (39) and those who provided rescue services in their own community (9) reported higher PTSD scores. The analysis of occupational factors indica-ted that nurses (9,11) and those who were hospitalized during the initial post-earthquake period (40) had a higher level of posttraumatic stress. Female gender (9, 40, 41), an anxious disposition (28), neurosis (39), and a medical and psychological illness background (38) are factors associated with an increased risk for PTSD. Analysis of psychosocial variables showed that failing to maintain regular communication with friends and family during the rescue mission (39) and being separated from family members following the earthquake (40) were positively correlated with more severe post-traumatic stress symptoms. The study revealed that healthcare workers who employed passive coping strategies, including

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| Table 1. Analyses of | n sample, method and findings of the s | tudies included in the review | (N=11) | n |
|--|--|---|--|--|
| Authors | Characteristics | Sample characteristics and size | Mental health variables analysed: | Results |
| | | | Measurement tools | |
| Cansel & Ucuz, 2022 | Cross-sectional 2020 Malatya-Elazig earthquake | Physicians, nurses, midwives, health officers, emergency medical | Post-traumatic stress: Post Earthquake Trauma Determination Scale | Thinking that a family member would die in the earthquake and anxious temperament traits were associated with higher levels of post-traumatic stress symptoms. Previous earthquake experience was found to be protective against high trauma reactions. |
| | Data collection 3 weeks after the earthquake | technicians | Temperament: TEMPS-A Temperament Scale | 25.8% of health workers had severe post-traumatic stress symptoms (PTSD) |
| | | N=201 | | |
| Guo et al., 2022 | Cross-sectional | Physicians and nurses | Psychological Resilience: Connor-Davidson | After eleven years, exposure to disasters was not significantly associated with resilience. |
| | 2008 Wenchuan earthquake | N=1527 | Psychological Resilience Scale | Those working in large hospitals reported higher levels of resilience. |
| | Data collection 11 years after the | | | Being female, having higher levels of education, being employed longer and having higher |
| | earthquake | | Post-traumatic growth: Posttraumatic Growth Inventory | postraumatic growth scores were associated with greater resilience. |
| Nieh et al., 2020 | Longitudinal 2018 Tayvan Haulien earthquake | Physicians, nurses, emergency medical technicians | Post-traumatic stress: Davidson Trauma Scale | After one month, 17.5% of emergency workers met the criteria for PTSD. After seven months, this rate fell to 3.2%. |
| | Data collection 1 and 7 months | | | Predictors of PTSD were a history of medical illness and a history of psychiatric illness. |
| | after the earthquake | N=63 | | Those with PTSD were less willing to serve as health workers in the future in the event of a disaster. |
| Mattei et al., 2017 | Cross-sectional | Physicians, nurses, health care support staff | Burnout: Maslach Burnout Scale | 23.4% of health workers had high levels of burnout. |
| | 2009 L Aquila earthquake | •• | | Hostile relationships with colleagues, direct exposure to earthquakes, moderate or high levels of stress predicted high levels of burnout. |
| | Data collection 6 years after the earthquake | N=284 | Psychological stress: General Health Questionnaire (GHQ-12) | |
| Schenk et al., | Cross-sectional | Medical rescue teams | Post-traumatic stress: Impact of Events Scale - | Seventeen per cent of the participants had PTSD symptoms above the threshold. |
| 2017 | 2008 Wenchuan earthquake | | E-ma | Experiencing water and food shortages was associated with PTSD. |
| | Data collection 14 and 17 months | N=337 | Form | PTSD symptoms were more severe in those who were injured during rescue missions, those |
| | after the earthquake | | Coping: 20-item Simple Coping Style Questionnaire | who did not communicate regularly with family and friends during the mission, those who resorted to passive coping, and those with neurotic personality traits. |
| | | | Personality traits: Eysenck Personality Questionnaire-Revised Short Form | |
| Kang et al., | Cross-sectional | Medical rescue teams | Post-traumatic stress: PTSD Checklist | The overall prevalence of PTSD was 21.8%, 28.6% in local rescue teams and 18.2% in |
| 2015 | 2010 Yushu earthquake | | Civilian Version | support teams. |
| | Data collection 8 months after the earthquake | N=303 | Quality of life: World Health Organisation Quality of Life Scale-Short Form (WHOQoL- | The prevalence of PTSD was higher among those aged 40-50 years, women, Tibetans, nurses, those who had been in serious danger, those who had witnessed injuries to other rescue team members, those who had witnessed severely danaged houses, and those who had felt guilty about the injury or death of another person. |
| _ | | | DKEP) | The most important predictor of quality of life was the PTSD score. |
| Shrestha, 2015 | Cross-sectional | Physicians, nurses, paramedics, and student | Post-traumatic stress: Posttraumatic Stress Disorder Checklist for DSM 5 - PCL-5 | 21.9% of health workers met the criteria for PTSD. PTSD scores were higher among women, those who were hospitalised in the first period after the disaster, those who |
| | 2015 Nepal earthquake | volunteers | | witnessed death and injury, those who were separated from their families during the earthquake, and those whose working hours were extended. |
| | Data collection 2 months after the | | | 59% reported a decrease in their ability to function at work and at home. Being female and |
| | caruquake | N=64 | | being a nurse were risk factors for loss of social and occupational functioning. |
| Tang et al., 2015 | Cross-sectional 2014 Ludian earthquake | Medical rescue teams | Health-related quality of life: Short Form-12 Quality of Life Scale | Poor mental health was associated with non-military status, younger age, female gender, exposure to hazards in the line of duty, and lower levels of education. |
| | Data collection 1 month after the earthquake | N=349 | | |
| Valenti et al., | Longitudinal | Autism therapists | Burnout: Maslach Burnout Scale | The burnout scores of those exposed to the earthquake at 1 and 2 years were higher than |
| 2014 | 2009 L Aquila earthquake | - | | those of autism therapists who did not experience the earthquake. |
| | | | | |
| | Data collection 1 month before, 1 year after and 2 years after the earthquake | N=64 | | |
| Zhen et al., | Data collection 1 month before, 1 year after and 2 years after the earthquake Cross-sectional | N=64 Nurses | Post-traumatic stress: Traumatic Stress | According to psychometric tests, PTSD was found in 30% and depression in 27.1% of the |
| Zhen et al., 2012 | Data collection 1 month before, 1 year after and 2 years after the earthquake Cross-sectional 2008 Wenchuan earthquake | N=64 Nurses | Post-traumatic stress: Traumatic Stress Symptom Scale | According to psychometric tests, PTSD was found in 30% and depression in 27.1% of the participants who had worked in the earthquake zone, while PTSD was found in 10.2% and depression in 9.7% of the nurses who had not been exposed to the disaster. |
| Zhen et al., 2012 | Data collection 1 month before, 1 year after and 2 years after the earthquake Cross-sectional 2008 Wenchuan earthquake Data collection 1 year after the | N=64 Nurses N=446 | Post-traumatic stress: Traumatic Stress Symptom Scale Depression: Traumatic Stress Symptom Scale | According to psychometric tests, PTSD was found in 30% and depression in 27.1% of the participants who had worked in the earthquake zone, while PTSD was found in 10.2% and depression in 9.7% of the nurses who had not been exposed to the disaster. Mental health problems were more common among younger nurses. |
| Zhen et al., 2012 | Data collection 1 month before, 1 year after and 2 years after the earthquake Cross-sectional 2008 Wenchuan earthquake Data collection 1 year after the earthquake | N=64 Nurses N=446 | Post-traumatic stress: Traumatic Stress Symptom Scale Depression: Traumatic Stress Symptom Scale | According to psychometric tests, PTSD was found in 30% and depression in 27.1% of the participants who had worked in the earthquake zone, while PTSD was found in 10.2% and depression in 9.7% of the nurses who had not been exposed to the disaster. Mental health problems were more common among younger nurses. Earthquake-related anxiety was more common among nurses who had participated in rescue operations for the first time. |
| Zhen et al., 2012 Wang et al., | Data collection 1 month before, 1 year after and 2 years after the earthquake Cross-sectional 2008 Wenchuan earthquake Data collection 1 year after the earthquake Cross-sectional | N=64 Nurses N=446 Healthcare workers (no | Post-traumatic stress: Traumatic Stress Symptom Scale Depression: Traumatic Stress Symptom Scale Post-traumatic stress: Impact of Events Scale - | According to psychometric tests, PTSD was found in 30% and depression in 27.1% of the participants who had worked in the earthquake zone, while PTSD was found in 10.2% and depression in 9.7% of the nurses who had not been exposed to the disaster. Mental health problems were more common among younger nurses. Earthquake-related anxiety was more common among nurses who had participated in rescue operations for the first time. PTSD was found in 19% of health care workers. |
| Zhen et al., 2012 Wang et al., 2010 | Data collection 1 month before, 1 year after and 2 years after the earthquake Cross-sectional 2008 Wenchuan earthquake Data collection 1 year after the earthquake Cross-sectional 2008 Sichuan earthquake | N=64 Nurses N=446 Healthcare workers (no details provided) | Post-traumatic stress: Traumatic Stress Symptom Scale Depression: Traumatic Stress Symptom Scale Post-traumatic stress: Impact of Events Scale - Revised | According to psychometric tests, PTSD was found in 30% and depression in 27.1% of the participants who had worked in the earthquake zone, while PTSD was found in 10.2% and depression in 9.7% of the nurses who had not been exposed to the disaster. Mental health problems were more common among younger nurses. Earthquake-related anxiety was more common among nurses who had participated in rescue operations for the first time. PTSD was found in 19% of health care workers. Being female, being injured, having lost loved ones, and experiencing severe fear during |
| Zhen et al., 2012 Wang et al., 2010 | Data collection 1 month before, 1 year after and 2 years after the earthquake Cross-sectional 2008 Wenchuan earthquake Data collection 1 year after the earthquake Cross-sectional 2008 Sichuan earthquake Data collection 3 months after the earthquake | N=64 Nurses N=446 Healthcare workers (no details provided) N=343 | Post-traumatic stress: Traumatic Stress Symptom Scale Depression: Traumatic Stress Symptom Scale Post-traumatic stress: Impact of Events Scale - Revised Form | According to psychometric tests, PTSD was found in 30% and depression in 27.1% of the participants who had worked in the earthquake zone, while PTSD was found in 10.2% and depression in 9.7% of the nurses who had not been exposed to the disaster. Mental health problems were more common among younger nurses. Earthquake-related anxiety was more common among nurses who had participated in rescue operations for the first time. PTSD was found in 19% of health care workers. Being female, being injured, having lost loved ones, and experiencing severe fear during the event were associated with the severity of PTSD. |

smoking, alcohol consumption and erratic eating, experienced higher levels of PTSD (39). This is the only study on coping strategies.

Depression

One of the studies included in the review analysed depression and found that the depression rate was 27.1% among nurses who were exposed to an earthquake in their evaluations one year later (11). The same study observed that the most prevalent depressive symptoms experienced by nurses were reluctance and lack of energy. Additionally, 8.6% reported having suicidal thoughts. The study emphasised that working in the earthquake epicentre and experiencing previous disasters were important factors contributing to psychological distress, such as depression (11).

Psychological Distress

As part of the review, a study analysed psychological stress levels using the Patient Health Questionnaire. The research found that 20.4% of healthcare workers experienced pathological psychological stress six years after the earthquake. Interestingly, physicians reported experiencing greater psychological stress than other healthcare workers (31).

Burn-out

Six years after the earthquake, 23.4% of healthcare professionals reported experiencing high levels of burnout (31). It was found that sociodemographic variables like age, gender, and marital status were not associated with burnout. However, direct exposure to the earthquake, the presence of hostile relations with colleagues, and high stress levels were identified as factors related to burnout (31). In a separate investigation, it was found that autism therapists who encountered the earthquake had more significant burnout scores than individuals who did not experience it (10).

Impairments in Life Quality

Two studies in the review focused on healthcare

worker quality of life after the earthquake. The researchers found a serious decline in their quality of life (9). Risk factors for worse quality of life included being young (42), female (9,42), and untrained in medical rescue teams (42). Experiencing danger during the mission and not being military personnel also negatively impacted quality of life (42). In Kang et al.'s (2015) study, the emergence of PTSD was identified as a crucial factor impacting quality of life (9).

Resilience

A study investigated the lasting impacts of earthquakes on healthcare workers, specifically their levels of psychological resilience and posttraumatic growth 11 years after the Wenchuan earthquake. Results indicated that exposure to the earthquake did not have a long-term effect on psychological resilience. However, when controlling for earthquake exposure, sociodemographic factors, and posttraumatic growth scale score, exposure to the earthquake had a significant association with psychological resilience (27). Psychological resilience was found to be greater in female participants, those with a higher level of education, and those with more professional experience. The study also found that posttraumatic development positively influences psychological resilience. Moreover, the research determined that posttraumatic development is not associated with earthquake exposure (27).

DISCUSSION

The purpose of this systematic review was to investigate the impact of the earthquake on the mental well-being of healthcare professionals and to identify the factors that contribute to mental health issues. This review aims to provide insight into the mental health implications of disasters on healthcare workers. The authors reviewed two databases and included 11 research articles meeting the review criteria. Healthcare practitioners who participated in the earthquake response and its subsequent aftermath were found to have suffered from symptoms of post-traumatic stress disorder (PTSD), depression, psychological stress, and burnout, resulting in a decline in their quality of life. Furthermore, a study investigated the potential protective effects of psychological resilience and post-traumatic growth. The majority of the studies included in this review highlighted the hazards of PTSD in healthcare workers. The present review study categorised the factors influencing mental health into personal and environmental factors and scrutinised their correlation with each mental health condition in detail.

The investigation examined the ties between sociodemographic variables and PTSD, and determined that age was a significant factor affecting the development of PTSD amongst medical rescue teams, with PTSD prevalence escalating as age increased (9). However, studies indicate that age is not a determining factor in the development of PTSD (38,39,40,41). Mental health scores were found to increase in healthcare workers with advancing age (42), with young and middle-aged female nurses being at a higher risk for mental symptoms following disasters (11). It is believed that variations in current physical condition, prior exposure to trauma and psychological training contribute to this trend (9). Valenti et al.'s study excluded gender comparison as the majority of healthcare workers were women (10).Furthermore, research has indicated that the occurrence of PTSD and burnout among healthcare workers does not differ significantly based on their gender (27,31,38).

When examining the correlation between marital status and PTSD, psychological resilience, and burnout in healthcare professionals, research indicates that there is no meaningful difference between married and unmarried workers (28,31, 39,41,42). Nevertheless, one investigation revealed that the cognitive sub-score of the post-earthquake trauma scale was greater in married healthcare workers. This outcome is attributed to cognitive impacts such as the concern of losing one's child and feeling of responsibility (28). While some research indicates that employees with a high level of education are less vulnerable to the psychological impact of earthquakes (11,27), other studies suggest that education is not a significant factor for trauma (9,38,41). One study has shown that medical rescue teams with lower education levels have a higher chance of experiencing deterioration in their mental health (42). Additionally, occupation has been identified as a crucial variable affecting the incidence of PTSD. Nurses often engage in emotional labour when providing medical care, which entails spending extended periods of time with patients. This can result in increased feelings of guilt in the event of any errors. Additionally, it is important to acknowledge the impact of gender, given the majority of nurses are women and the potential negative consequences of gender roles on female healthcare workers' mental health in the post-disaster period (9). Another study revealed that physicians had significantly higher emotional burnout scores than allied health personnel, particularly (31). Guo et al. conducted a study that concludes that nurses possess a higher ability to cope with stress in comparison to doctors (27). There are also studies demonstrating that being a doctor or a nurse does not associate with PTSD (38,40,42). In general, the evaluation of the relationship between sociodemographic variables and mental health drew attention to contradictions in research findings. These results suggest that further research on demographic variables is necessary to assess the impact of earthquakes on the mental health of healthcare workers.

Exposure to earthquakes was found to have no lasting effects on health workers in terms of psychological resilience and post-traumatic development (27). Wang et al. found no significant association between witnessing death and PTSD in healthcare workers (41). A possible reason for this may be the normalisation of death in the professional practice of healthcare workers. However, the same study found that the intensity of the first fear and the severity of PTSD symptoms increased in direct proportion. When the earthquake experience was analysed, it was found that those who experienced serious danger during rescue operations (9,39), those who worked in the first hours of the earthquake had higher levels of PTSD (9,39,40) and those who were on rescue duty for the first time had more anxiety (41). These findings suggest that psychological resilience can be enhanced by qualified psychoeducation received prior to the earthquake, consistent with the views of Kang et al. and that the recruitment of individuals with resilient personalities to rescue work is an important protective factor against trauma (9). Similarly, Cansel and

Ucuz emphasised the importance of the relationship between personality structure and trauma, finding that healthcare workers with depressive, cyclothymic and anxious personalities were exposed to more severe trauma (28). Anxious individuals were found to have exaggerated reactions to distressing events and were unable to adapt (39). In addition to personality, chronic illness and psychiatric illness in the healthcare worker were found to be important predictors of the development of PTSD (38). It was concluded that some personality traits, chronic illness and psychiatric illness are important factors for health care workers to experience traumatic stress.

Another environmental factor that emerged from the research included in the review is the social support and quality of life that health workers received after the earthquake. Cansel and Ucuz found that receiving help and support from family and friends was not related to the level of trauma, and attributed this to the fact that the participants survived the earthquake with little material damage and experienced occupational deformation against traumatic events (28). This may be explained by the low severity of the earthquake and the level of destruction it caused. Another study showed that large hospitals provided more adequate social and resource support than small hospitals, and that workers in large hospitals had higher levels of psychological resilience (27). At the same time, PTSD has been found to impair the social and occupational functioning of workers. According to the studies, the fact that the personal needs of healthcare workers are not met and that they have inadequate resources and psychosocial support increases the stress of individuals after the earthquake and negatively affects their functionality.

Another variable that stands out in studies examining earthquakes and the mental health of health workers is burnout. One study of health workers found that direct exposure to the earthquake was associated with high levels of burnout. At the same time, workers' perceptions of high workload and poor relationships with colleagues were identified as risk factors for the development of burnout (31). It has been highlighted that teamwork, social support and cooperation between colleagues play a protective role against burnout; therefore, the importance of regular monitoring of health workers and developing preventive strategies is emphasised (10,31). In addition, administrative support has been found to be negatively related to emotional burnout and positively related to personal accomplishment (10). Studies agree that factors such as high workload and inadequate social support contribute to burnout.

Earthquakes have a negative impact on the mental health of health workers, who are one of the first groups to work in the disaster area. To this end, the relevant literature has carried out cross-sectional and longitudinal studies aimed at identifying the mental health problems of health workers and examining the variables associated with mental health. As a result of the studies examined in our review, it has been observed that healthcare workers experience PTSD, depression, psychological distress, burnout, deterioration in quality of life, as well as experiences such as psychological resilience and post-traumatic development. Studies on the effects of variables such as age, marital status and education level on PTSD have varied in the impact of earthquakes on mental health, and in relation to gender, it has been observed that predominantly women experience more PTSD. Although the impact of occupational factors such as being a doctor or nurse on mental health differed, factors such as working hours were found to be important for experiencing burnout. In general, earthquakerelated factors such as being exposed to the earthquake, being in the earthquake for the first time, being injured and witnessing severe damage were found to have a negative impact on mental health.

In addition to socio-demographic variables and earthquake-related factors, social support, coping strategies, personality traits, previous chronic illnesses and the presence of psychiatric illnesses were also found to affect the mental health of health workers. Ineffective coping strategies, such as smoking and substance abuse, were found to be a predictor of poor mental health (38). Anxious personality traits and lack of resources and social support lead to poor quality of life and impaired functioning. It has also been observed that the mental health of health workers is significantly affected in earthquakes that cause social trauma. In this direction, it is important that psychosocial interventions for health workers should aim to improve negative mental health problems such as PTSD and burnout. It is recommended that psychosocial support and rehabilitation programmes be organised to strengthen resources such as social support, effective coping strategies and solidarity.

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