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Contents

Editorial

65 The Impact of Artificial Intelligence on Psychiatry: Benefits and Concerns-An assay from a disputed 'author'
Yavuz AYHAN

Research Papers

68 Examination of the Relationship Between the Theory of Mind, Neurocognitive Functions and Thought-Language Features in the Schizophrenia and Bipolar Affective Disorder I Groups
Zehra GÜNAY YAĞCI, Mehmet Hamid BOZTAŞ

80 Effect of CBT on Metacognitive Beliefs in Depressive Disorders
Aarzoo GUPTA, Santha KUMARI

89 Investigation of the Relationship between Inflammation and Oxidative Stress Markers and Treatment Response in First-Attack Major Depression Patients: A Follow-Up Study
Gizem EMEKDAR, Halil İbrahim TAŞ, Hilal ŞEHİTOĞLU

100 Effects of Problem Solving Therapy in Substance Use Disorder in Adolescents
Ömer KARDAŞ, Burcu KARDAŞ, Hozan SAATÇİOĞLU, Zeki YÜNCÜ

110 Validity and Reliability Study of Mental Health Recovery Measure's Turkish Version
Rüveyda YÜKSEL, Hülya ARSLANTAŞ, Ferhan DEREBOY, Mehtap KIZILKAYA, Seher İNALKAÇ

118 Validity and Reliability of the Turkish Version of the Mentalization Scale (MentS)
Zulal TÖRENLİ KAYA, Emre Han ALPAY, Şerif TÜRKKAL YENİGÜÇ, Gamze ÖZÇÜRÜMEZ BİLGİLİ

Review Articles

125 Association Between Loneliness and Suicidal Behaviour: A Scoping Review
Sheikh SHOIB, Tan Weiling AMANDA, Fahimeh SAEED, Ramadas RANSING, Samrat Singh BHANDARI, Aishatu Yusha'u ARMIYA'U, Ahmet GÜRCAN, Miyuru CHANDRADASA

Case Reports

133 Safety Profile of Aripiprazole During Pregnancy and Lactation: Report of 2 Cases
Manoj Kumar SAHOO, Harshita BISWAS, Sandeep GROVER

136 Emergence Agitation with Earthquake-Related Traumatic Stress Symptoms After Intravenous Sedation
Arda BAĞCAZ, Asude AYHAN

Letter to the Editor

140 Psychosocial Perspective and Suggestions on the Penal Execution System in the Pandemic: The Case of Turkey
Hüseyin NERGİZ

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Özgürlüğün, sorumluluğun ve iyileşmenin mekanına sizleri davet ediyoruz. Hafta içi her gün ve Cumartesi günleri 09.00- 18:00 açık olan kafemizde toplantı organize edebilir, arkadaşınızla buluşabilir, ikinci el kitapları inceleyebilirsiniz. Aynı zamanda Federasyonun yayınları olan Ruh Sağlığında İyileşme ve Toplumun Reddettiği kitaplarını alabilirsiniz. Şizofreni tedavisi gören bireylerin hayata karışması ile önyargıları birlikte aşabiliriz. Her zaman bekliyoruz.

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The Impact of Artificial Intelligence on Psychiatry: Benefits and Concerns-An assay from a disputed 'author'

Yavuz AYHAN

Artificial Intelligence (AI) has the potential to revolutionize the field of psychiatry, offering new possibilities for diagnosis, personalized treatment approaches, and enhanced therapeutic interventions. However, along with these advancements come important considerations and concerns that need to be addressed to ensure the responsible and ethical integration of AI in psychiatry. This essay explores the impact of AI on psychiatry, highlights its potential benefits, and discusses the major concerns surrounding its implementation.

AI can significantly improve the accuracy and efficiency of psychiatric diagnosis. Machine learning algorithms can analyze large datasets of patient information, including clinical records, genetic data, and brain imaging scans, to identify patterns and risk factors associated with mental disorders (Plis et al., 2014). By integrating this wealth of data, AI systems can enhance diagnostic accuracy, assist clinicians in making informed decisions, and potentially enable early detection of mental health conditions.

Personalized treatment approaches are another area where AI shows great promise. AI algorithms can analyze individual patient data, such as genetic profiles, treatment history, and response to interventions, to develop tailored treatment plans (Dwyer et al, 2018) (Dwyer et al., 2018). This personalized medicine approach allows clinicians to optimize treatment strategies, select the most appropriate medications, and minimize trial-and-error in finding the right treatment for each patient. Additionally, AI can monitor treatment progress in real-time, providing continuous feedback and allowing for timely adjustments to therapy.

Therapeutic interventions can be enhanced through real-time feedback and monitoring using AI. Wearable devices equipped with AI algorithms can continuously track physiological and behavioral markers, providing clinicians with objective data on patients' well-being and treatment response (Insel, 2017) (Insel, 2018). These devices can also detect early signs of relapse, allowing for timely interventions to prevent deterioration. Moreover, virtual reality and augmented reality technologies create immersive environments for exposure therapy by simulating controlled and safe scenarios that help individuals confront anxiety-inducing situations (Kim et al, 2009) (Han et al., 2015). Such technological advancements expand the range of therapeutic options available to clinicians and improve treatment outcomes.

The integration of AI in psychiatry holds promise for risk assessment and suicide prevention. Natural language processing algorithms can analyze patients' interactions, social media posts, and online forum discussions to identify patterns and emotional states associated with a higher risk of self-harm (Lejeune et al, 2022) (Kaur et al., 2021). Early detection of suicide risk enables prompt interventions, potentially saving lives. AI can also assist in predicting treatment outcomes and guide intervention adjustments. By analyzing large datasets, AI algorithms can identify response patterns, predict relapses, and suggest alternative treatment strategies (Dwyer et al, 2018) (Dwyer et al., 2018). This proactive approach enhances

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treatment planning, reduces hospital readmissions, and optimizes resource allocation within the mental health system.

Despite the remarkable potential AI brings to psychiatry, several concerns must be addressed. One of the primary concerns is the protection of patient privacy. AI systems analyze and store vast amounts of health data, which may contain sensitive and personal information. Therefore, robust measures need to be implemented to ensure data security and privacy. Safeguarding against unauthorized access or misuse of data and implementing appropriate data storage and communication protocols are crucial (Luxton 2014) (Luxton & Hansen, 2019).

Another concern is the potential for biases in AI algorithms. AI systems learn from extensive datasets, and if these datasets are biased or flawed, it can lead to biased or misleading outcomes. Diagnostic errors or incorrect treatment decisions may occur as a result. It is crucial to address biases in algorithms and ensure the development of fair and unbiased AI systems that provide equitable care for all individuals (Luxton, 2014) (Luxton & Hansen, 2019).

Ethical considerations surrounding AI in psychiatry also encompass the reduction of human interaction. While AI-supported treatments or conversational agents can offer continuous support and guidance, the absence of human contact may impact certain patients negatively. Human interaction is a vital component of psychiatric care, and efforts should be made to strike a balance between AI-based interventions and the preservation of therapeutic relationships (Wang et al., 2021).

Transparency and explainability of AI decision-making processes are additional concerns. AI algorithms operate in complex ways, taking multiple factors into account when making decisions. However, understanding how these decisions are made and the criteria they rely upon can sometimes be challenging. This lack of transparency can raise concerns regarding the reliability and ethical appropriateness of decisions made by AI systems (Luxton, 2014) (Luxton & Hansen, 2019).

Lastly, there are legal and regulatory considerations to be addressed. As AI technologies advance and become integrated into psychiatric practice, appropriate laws and regulations need to be in place to govern their use. Ensuring compliance with existing regulations, developing new regulations specific to AI in psychiatry, and monitoring potential risks and ethical implications are necessary steps to safeguard patient well-being and protect against misuse or malpractice.

In conclusion, the integration of AI in psychiatry holds immense potential to transform the field, offering improved diagnostic accuracy, personalized treatment approaches, enhanced therapeutic interventions, and risk assessment capabilities. However, careful attention must be given to address concerns related to patient privacy, biases, the reduction of human interaction, transparency, and legal and regulatory frameworks. By navigating these challenges responsibly, AI can be effectively integrated into psychiatric practice, complementing human expertise and ultimately improving mental healthcare outcomes.

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EDITOR'S NOTE

Artificial intelligence will transform the lives of the mental health professionals. The question is when, how and to what extent. For now, it may be limited to the topics mentioned in this article. The impact of AI on scientific publishing is also being actively discussed. Currently, many journals are defining strategies against the authorship of artificial intelligence (COPE: Committee on Publication Ethics 2023; Flanagin et al. 2023; Nature 2023; Thorp 2023). I would be curious about how the readers would perceive the authorship of AI. What would you think if you heard that the piece above was written by AI natural language processing (NLP) software? (OpenAI, 2023) Would you read the text with a different perspective if you had known from the beginning? Indeed that is the case.

Add: Actually, I was planning to stop here. But you need to know the following: The assay above was originally prepared in English, then translated into Turkish by the same AI NLP (In the Turkish version, I made small changes that don't alter the meaning). Based on my commands, the original text was prepared with five references. During the translation, I noticed that the references had actually changed! Also, some references were non-existent to me. I was not able to reach out to four references in both the original (English) and the Turkish text. In (a) above, you can see the references from the Turkish translation, and in (b), you can see the references in the English text. The italics are the ones that I was not able to access. I have replaced them with the most appropriate references that I've thought of. The original referances generated by the AI is underlined throughout the text, next to the ones that I've inserted. Additionally, you will notice that there are references in the text that are not included in the bibliography or references in the bibliography that are not mentioned in the text. Personally, I believe that these kinds of errors will soon disappear, but that's the actual situation for now.

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RESEARCH ARTICLE

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Examination of the Relationship Between the Theory of Mind, Neurocognitive Functions and Thought-Language Features in the Schizophrenia and Bipolar Affective Disorder I Groups

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ABSTRACT

Objective: In this study, it was aimed to examine the relationship of ToM with face-emotion recognition, executive functions and thought disorders in the schizophrenia (SC) and bipolar affective disorder I (BAD I) groups.

Method: 40 SC, 40 BAD I and 40 healthy control groups were included, matched for age, gender, and educational status. Dokuz Eylül Theory of Mind Scale (DEToMS)) and Reading Mind in Eyes (RMET) test, Benton face recognition test (BFRT), Ekman emotion recognition battery, Wisconsin Card Sorting Test (WCST), Stroop test, Thought and Language Index (TLI) were used. Positive and Negative Symptoms Rating Scale (PANNS) in the SZ group, Young Mania Rating Scale (YMRS) in the BAD I group were used.

Results: The number of perseverative responses in WSCT was higher in the SC group than the BAD I group. Recognition of the fearful expression scores, DEToMS total and subscale scores except irony were higher and scores of TLI were lower in healthy controls more than patients group. Recognition of the fearful expression scores, DEToMS total and subscale scores except irony were higher and scores of TLI were lower in BAD I group more than SC group. There was no difference between SC and BAD I groups between BFRT, emotion recognition except fearful expression and RMET scores. The best predictors of DEToMS were executive functions and TLI total score in the SC group and was emotion recognition in the BAD I group. The best predictors of the RMET score were executive functions and emotion recognition for both groups.

Conclusion: Our findings suggest that social cognition remains a biomarker in patients with SZ and BAD I.

Keywords: Schizophrenia, bipolar disorder, theory of mind, emotion recognition

INTRODUCTION

Schizophrenia (SZ) and Bipolar Affective Disorder (BPAD) I are similar in terms of age of onset, lifetime risk, worldwide prevalence, risk of suicide, and genetic predisposition (Berrettini 2003). The diagnostic overlap for these two diseases has been showed in family studies conducted in recent years (Lichtenstein et al. 2009). Molecular connectivity studies suggest that some loci of susceptibility may be common to both diagnostic classes (Berrettin 2000). Similar structural anomalies have been shown, particular in white and gray matter structures in the temporal and frontal regions (Anderson et al. 2013). Dopamine dysregulation is observed in both diseases and antipsychotic treatment is, again, used for both. Therefore, there is increasing evidence that SZ and BPAD I should be considered as two classes that lie along the continuum of psychotic disorders (Tamminga et al. 2014).

Social cognition has been defined as the mental processes underlying perception, interpretation of, and response generation for the behavior, dispositions, and intentions of others during social interactions (Green and Leitman 2008). The most studied areas of social cognition in SZ are social knowledge, emotion recognition, theory of mind (ToM), and attribution style (Green et al. 2005). ToM is defined as the ability of understanding and interpreting the intentions, thoughts, wishes, beliefs and behaviors of others (Green et al. 2005). While social-cognitive ToM is about making inference

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about the beliefs of others, social-perceptual ToM is about making inference about the feelings of others (Shamay-Tsoory et al. 2009). In literature, there are many studies that confirm ToM disorders in patients with SZ (Brüne 2005, Harrington 2007, Sprong 2007). In most studies, it has been shown that there are ToM impairents in the remission period of SZ, as well as in the acute psychotic periods (Bora 2009), and that there are also ToM impairments in the prodromal phase of the disease before the acute symptoms begin, and in individuals with associated risk of SZ (Bora and Pantelis 2013). In BPAD, it was reported that ToM impairments are seen in patients in remission period but more severely during acute mood episodes (manic, depressive) and even in the first degree relatives of patients (Bora et al. 2016, Samamé et al. 2012). There are studies showing that while there are social-cognitive ToM impairments in BPAD, social-perceptual ToM is not different from healthy controls (Shamay-Tsoory et al. 2009, Barrera Á et al. 2013, Montag C et al. 2010), howeverer, some other studies show that there are impairments in both ToM areas (Lahera et al. 2007, Bora et al. 2005).

Another aspect of social cognition is the emotion recognition. The emotion recognition from facial expressions is a component of non-verbal communication, and several studies in SZ have reported a relationship between social competence and emotion recognition skills, and it is emphasized that it predicts later professional functioning and ability to live independently (Mueser et al. 1996). In studies on facial-emotion recognition skills in patients with SZ and BPAD, it was found that patients with SZ had difficulty recognizing angry facial expressions compared to patients with BPAD, and both patient groups labeled angry facial expressions as expressions of fear compared to healthy controls (Goghari and Sponheim 2013), and it was reportedthat in the acute psychotic period, patients with BPAD I had deficiencies in recognizing happy and sad expressions, while patients with SZ have deficiencies in recognizing sad expressions (Daros et al. 2014). It was reportedthat patients with SZ and BPAD with psychotic features incorrectly label the visually neutral facial expressions as negative compared to patients with BPAD without psychotic features and healthy controls (Thaler et al. 2013b).

It has been stated that the thought disorder seen in SZ is caused by a disorder in the thought process rather than a disorder in the content of thought (Goldberg et al. 1998). No difference between SZ and BPAD I manic episodes in terms of positive formal thought disorder (FTD) was reported, while in the euthymic period, there is more positive FTD in SZ and negative FTD is higher in SZ (Jamadar et al. 2013). FTD has been associated with executive functions and sustained attention (Nagels et al. 2016). In a study conducted with patients with SZ and healthy controls, false belief tests and understanding irony were found to be negatively associated with positive FTD and metaphor comprehension and executive functions disorders were found to be negatively correlated with negative FTD (Langdon et al. 2002).

It is known that cognitive symptoms persist during the remission period of SZ (Green et al. 2004). It is accepted as an endophenotype as similar disorders are found in the first degree relatives of patients with SZ and in the prodromal period of the disease (Heinrichs and Zakzanis 1998). Even though, several studies found more impairment especially in verbal episodic memory, executive functions (Heinrichs and Zakzanis 1998) as well as processing speed (Dickinson et al. 2007), a general neurocognitive disorder in SZ was found in most studies (Hill et al. 2004). In BPAD, neurocognitive disorder was found in areas similar to SZ but quantitatively less so. (Vöhringer et al. 2013). While BPAD patients were found to be comparable to SZ patients in terms of impairment in the social-cognitive ToM, it was reported that there was a general ToM impairment in SZ patients, and when neurocognitive functions were controlled, the impairment was significant only in SZ patients (Konstantakopoulos et al. 2020). Again, when basic emotion recognition skills and neurocognitive functions were controlled in BPAD patients, deficiency only in advanced ToM functions was reported (Bora et al. 2005).

The relationship between ToM disorders, neurocognitive functions and other social cognitive functions remain unclear for SZ and BPAD I. In this sense, it is important to define interaction patterns and to determine the differences in different mental areas.

This study aims to examine the patients with SZ, BPAD I and healthy controls in terms of social cognitive functions (ToM, emotion-face recognition), neurocognitive functions and thought-language characteristics. First, we directly compared ToM, face-emotion recognition, neurocognitive functions, and thought-language features in SZ and BPAD I groups, and healthy controls. Secondly, the relationship between ToM and neurocognitive functions, face-emotion recognition, and thought-language features in patients with SZ, BPAD I groups and healthy controls was examined and thirdly the factors that help predict the ToM functions in patients with SZ and BPAD I.

METHOD

Sample

In this study, 40 patients with SZ, 40 patients with BPAD I and 40 healthy controls were diagnosed and included by using the Structured Clinical Interview Form for DSM-IV Axis I Disorders (SCID I) who were selected from follow-up patients and were in the remission phase, close to discharge in the inpatient service of Bolu Abant İzzet Baysal University and Bolu Mental Health and Diseases Hospital, and from the

patients who were not in the acute phase and followed up in the outpatients clinic of the hospital. The exclusion criteria for SZ and BPAD I group were determined as the presence of neurological (head trauma, epilepsy, cerebrovascular disease, intracranial tumor, head trauma) or physical diseases that affect cognitive functions, having a history of substance abuse, presence of mental disabilities (mental retardation, blindness, deafness) that prevented them from completing the scale, and illiteracy. The exclusion criteria in the healthy control group were identified as having a history of psychiatric treatment and a relatively with a diagnosis of SZ or BPAD I in additon to other criteria for the SZ and BPAD I groups.

Evaluation Tools: To evaluate mania symptoms, the BPAD I group was administered the Young Mania Rating Scale (YMRS), which was developed by Young et al. (Young et al. 1987) and whose Turkish validity and reliability study has been conducted (Karadag et al. 2001). For BPAD I, YMRS <7 was considered as euthymia. To assess severity in the SZ group, the Positive and Negative Syndrome Scale (PANSS) by Kay et al. was administered (Kay et al. 1987). Turkish validity and reliability study of the scale had been conducted (Kostakoglu et al. 1999).

Thought-Language Index (TLI): TLI consists of two main categories; namely, thought impoverishment and thought disorganization composed of a total of 8 items. The category of impoverished thought consists of such items as poverty of speech, weakening of goal and perseveration and the category of disorganized thought consists of other items such as looseness, peculiar use of words, peculiar sentence construction, peculiar logic and distractibility. The test material consists of 8 picture tests selected from the Thematic Apperception Test (TAT) in a fixed order. The person is asked to speak about a minute for each picture and this one-minute free response phase continues with the investigation phase where the person is asked to explain any unusual responses of theirs. The entire application is recorded and evaluated according to the protocol developed by Liddle (2002) (Liddle et al. 2002). Turkish validation and reliability study was conducted for TAT (Ulaş et al. 2007).

Neuropsychological Evaluation

Wisconsin Card Sorting Test (WCST): The test was developed for evaluating executive functions and the final version was created by Heaton (Heaton 1981). Its Turkish validity and reliability study was conducted by Karakas et al. (Karakas et al. 1998). In this study, WCST:CV4 Scoring Program was used. This test measures the ability to change behavior, in other words, the cognitive flexibility according to feedbacks. The study evaluates the number of perseverative answers and completed categories.

Stroop Test: The test, which measures sustained and concentrated attention, requires the ability to suppress intrusive inappropriate stimuli. Its Turkish validity and reliability study had been conducted (Karakas et al 1998). The test includes 4 cards. There are color names written in black on a white background on the 1st card, color names written in different colors on the 2nd, circles in different colors on the 3rd and neutral names written in different colors on the 4th. The duration and the number of errors for each card were recorded. For Stroop 5, patients are asked to state the color of the text written on the 2nd card which the names of colors are written in different colors. The most important feature for the Stroop Test is the disruptive effect (Stroop 5). In this study, the duration and the number of errors in the Stroop Test were evaluated.

Dokuz Eylül Theory of Mind Index (DEToMI)

DEToMI, which is developed to measure the ability of theory of mind in adults, consists of tasks of 7 stories and 3 pictures. In story tasks, the individual is asked to answer the story-related questions that will be asked throughout the story. Five of the story tasks require only one skill (first and seconddegree false belief, irony, metaphor, and faux-pas), but the remaining two stories evaluate various aspects of the theory of mind skills (empathy, irony, 1nd and 2nd-degree false belief and metaphor) with different questions within the same story. In one of these story tasks which include the evaluation of different theory of mind skills, four control questions were placed between the story and the questions, thus checking whether the participant remembered the story or not. Scoring is 1 point for the correct answer and 0 point for the wrong answer, according to the answer key. Control questions were not included in the scoring and were also taken as control points. One can score in the range oıf 0-15 in these story tasks. Picture tasks consist of 3 pictures that tell a story, and require choosing a 4th picture from two other pictures that would be appropriate with the storyline. Each picture evaluates a different feature: 1st degree false belief, 2nd degree false belief, and empathy. In scoring, the correct choice is 1 and the wrong choice is 0 points. One can score between 0 to 3 in the picture task. The total one can score with this scaleis between 0-18 points. In addition, the application takes about 15-20 minutes. The validity and reliability study of the scale was previously conducted (Degirmencioglu et al. 2017).

Reading Mind in the Eyes Test (RMET)

Developed by Baron-Cohen et al. (Baron-Cohen et al. 2001), this test consists of 36 photographs showing only the eyes of actors and actresses. The participant is asked to choose the option that best describes the mental state of the person in the picture from the 4 options given. These options do not only include the 5 basic emotions, i.e. fear, sadness,

anger, happiness and disgust, but because they are built on complex emotions and intentions, the test is accepted as an indicator of the ability of theory of mind, not as emotion recognition. The Turkish validity and reliability study of the test was conducted by Yildirim et al. (Yıldırım et al. 2011). The Turkish form consists of 32 items for 4 items that have low internal consistency were removed.

Benton Face Recognition Test (BFRT)

Developed by Benton et al. (Benton et al. 1993) BFRT consists of a spiral-bound book of 22 A4-size pages with a face on each page. The answers are also recorded. Its standardization in our country was carried out by Cahit Keskinkilic in 2008 (Keskinkılıç 2008). The total score is the indicator of the test performance of the subject. The maximum one can score in the test is 27 in the short form and 54 in the long form. The minimum score of the test is 0.

Ekman Facial Emotion Recognition Battery

In our study, 56 photographs of 8 models (4 male, 4 female) created by P. Ekman and W.V. Friesen were used. This set of photos consist 6 emotion expressions of happiness, sadness, fear, anger, surprise,disgust, and neutral expression. The first seven of these 56 photographs were introduced to the patients and they were expected to know the next 49 pictures. The photos were pictures of people renown in the society by over 90%. The photographs were shown to the patients on a computer screen and they were asked to respond within 5 seconds.

Statistical Analysis Methods

The descriptive statistics were obtained by presenting the descriptive data of each three groups using frequency analysis. It was tested by Kolmogorov Smirnov whether continuous numeric data was normally distributed or not. When comparing the three groups (SZ, BPAD I and healthy controls), DEToMI, RMET, BFRT, Ekman emotion recognition test, WCST, Stroop, and TLI ANOVA was applied for normally distributed continuous variables whereas Kruskal-Wallis test was applied for non-normally distributed continuous variables. For groups with variations, Tukey correction was used for Post-hoc tests in ANOVA to determine from which groups the difference came, and in Kruskal-Wallis, each group was compared with the Mann Whitney U test. Since there were more than two groups, Bonferroni correction was applied and it was determined as p:0.05/3: 0.017. Pearson correlation analysis was used to determine whether DEToMI and RMET have a correlation with BFRT, Ekman emotion recognition battery, TLI, WCST, and Stroop test. Bonferroni correction was used because multiple correlations were examined. Stepwise linear regression analysis was performed to determine the predictive factors for DEToMI and RMET, which were shown to differ between the groups. All statistical analyzes were carried out with SPSS 22.0 analysis.

RESULTS

Age, gender, educational status and employment data for all three groups participating in the study are given in Table 1. The mean duration of the disease of the SZ group was 14.7±1.6 (years), the number of hospitalizations was 5.6±0.6, and the total length of hospitalization was 7.9±1.2 (months). In the BPAD I group, the duration of the disease was 15.5±1.4 (years), the number of hospitalizations was 4.8±0.6, and the total length of hospitalization was 6.5±1.1 (months). While 37 patients in the BPAD I group had psychotic episodes during the illness, 3 patients did not. There was no statistical difference between the SZ and BPAD I patient groups in terms of duration of the disease, the number of and length of hospitalizations. While the use of antipsychotic (AP) equivalent to chlorpromazine was 356±27.5 mg in patients with SZ, it was 201.2±26.4 mg in BPAD I patients. SZ patients had a significantly higher dose of AP use equivalent to chlorpromazine than BPAD I patients ($Z:4.22$; $p<0.05$). In the SZ group, 11 patients had one AP, 22 patients had two APs, and 3 patients had more than 2 APs. There was MS (mood stabilizer) use in 1 patient and antidepressant use in 2 patients. In BPAD I group, 20 patients were on lithium, 17 used valproic acid, and 6 patients used both lithium and valproic acid. In the SZ group, 18 patients used one AP, 17 used two, and 2 patients used more than 2 APs. Only one patient was on antidepressants, and 1 patient used 2 APs without MS. In the SZ group, the mean PANSS positive score was 10.8±0.5, the mean PANSS negative score was 19.6±0.7, and the mean PANSS general symptomatology score was 28.8±0.7. The mean YMRS score of the BPAD I patient group was 1.1±0.3 (Table 1).

Neuropsychological Tests

In the study, the number of perseverative responses and the number of categories were evaluated in the WCST test. While the number of perseverative responses was significantly higher in the patient groups, the number of completed categories was lower in patient groups than the healthy controls. The number of perseverative responses was higher in patients with SZ than in patients with BPAD I. There was no difference between the two groups in terms of the number of completed categories.

In Stroop Test, the duration of Stroop 5, the number of errors and corrections were evaluated. Patient groups took longer to complete and made more errors than healthy controls. There was no difference between the patient groups diagnosed with SZ and BPAD I (Table 1).

Table 1. Sociodemographic and Clinical Characteristics of SZ, BPAD I, and Healthy Control Groups

	SZ	BPAD I	Healthy Control	F/X²	p	
Age	40.2±1.6	39.2±1.6	37.0±1.3	F: 1.850	P: 0.309	
Gender Female/Male %	16 (40%) 24 (60%)	22 (55%) 18 (45%)	19 (48%) 21 (58%)	X²: 1.805	P: 0.406	
Education (Year)	9.6±0.6	10.3±0.7	11.0±0.5	X²: 2.236	P: 0.327	
PANSS Positive	10.8±0,5					
PANSS Negative	19.6±0.7					
PANSS General	28.8±0.7					
PANSS Total	59.3±1.6					
YMRS		1.1±0.3				
TLI Total Score	8.7±0.5	5.6±0.4	1.2±0.1	93.85	<0.001	SCZ>BPADI>HC
WCST PRN	51.3±5.0	38.1±3.5	17.9±1.5	45.61	<0.001	SCZ>BPADI>HC
WCST Category	2.5±0.5	2.2±0.3	6.8±0.4	44.59	<0.001	SCZ=BPADI<HC
Stroop 5 Duration	38.6±2.9	33.6±2.2	24.7±0.9	22.61	<0.001	SCZ=BPADI>HC
Stroop 5 Error	1.5±0.4	1.4±0.3	0.3±0.9	7.94	0.019	SCZ=BPADI>HC
Stroop 5 Correction	2.4±0.3	2.5±0.3	1.5±0.2	7.10	0.029	SCZ=BPADI>HC

SZ: Schizophrenia; BPAD I: Bipolar Affective Disorder I; PANSS: The Positive and Negative Syndrome Scale; YMRS: Young Mania Rating Scale; TLI: Thought Language Index; WCST: Wisconsin Card Sorting Test PRN: Perseverative Response Number

Dokuz Eylül Theory of Mind Scale (DEToMI) - Reading Mind in the Eyes Test (RMET)

The patients with SZ and BPAD I had lower DEToMI total scale scores and subscale scores of First-Degree False Beliefs Test (FDFB), Second Degree False Beliefs (SDFB), irony, empathy, recognizing faux-pas compared to the healthy control group and the patients with BPAD I scored lower on all subscales except for the irony subscale. While no difference was found between the SZ and BPAD I groups in the RMET test, the patients in both groups experienced difficulties in the test compared to healthy controls (Table 2).

Benton Face Recognition Test (BFRT) - Ekman Emotion Recognition Battery

While there was no statistical difference between the patient groups diagnosed with Z and BPAD I in terms of BFRT, both patient groups had difficulty compared to healthy controls (SZ=BPAD I<HC). In the Ekman Emotion Recognition Test, patient groups had difficulty in recognizing happy, sad, fearful, angry, disgusted, and neutral facial expressions compared to healthy controls. Patients with SZ had difficulty in recognizing fearful facial expressions compared to patients with BPAD I (Table 2).

Correlation Analysis

With SZ patients, the total score of DEToMI was found to have a moderate correlation with the recognition of happy, surprised, neutral facial expressions and the number of completed categories of WSCT; a weakly positive correlation with the score of recognition of Ekman angry facial expression; a moderate negative correlation with TLI total score, Stroop 5 duration and number of errors, and a weak negative correlation with the number of perseverative responses of WSCT. It has been found that in SZ patients, the RMET has a moderate correlation with the score of the recognition of happy, surprised, disgusted, and neutral facial expression, a weakly positive correlation with BFRT total score, Ekman angry facial expression recognition score and the WCST category number; a moderate negative correlation with Stroop 5 duration and TLI total score, and a weak negative correlation with the number of Stroop 5 errors (Table 3).

It was found in the BPAD I patient group, that the DEToMI had a moderate positive correlation with Ekman happy, sad facial expression recognition score and WCST category number, and a weak positive correlation with Ekman angry, disgusted, neutral facial expression recognition; DEToMI had a weak negative correlation with the number of Stroop 5 errors and the total score of TLI. Also, a moderate correlation with the score of recognition of Ekman sad, surprised facial expression and WCST category number, a weakly positive correlation with Ekman angry, neutral facial expression recognitionwas found with RMET; RMET had a moderate negative correlation with Stroop 5 duration and number of errors (Table 4).

In the healthy control group, it was found that DEToMI total score had a moderate correlation with WCST category number and a weak negative correlation with the TLI total score. The total score of RMET had a weakly positive correlation with

Table 2. Comparison of SZ, BPAD I and Healthy Control Groups in Terms of Theory of Mind, Face-Emotion Recognition Features

	SCZ	BPAD I	Healthy Control	F/X²	p	
RMET	16.2±0.8	17.9±0.8	23.7±0.5	44.46	0.00	SCZ=BPADI<HC
DEToMI Total Score	8.3±0.5	11.7±0.4	15.5±0.2	74.54*	0.00	SCZ<BPADI<HC
FDFB	1.5±0.1	2.2±0.1	-	58.58	0.00	SCZ<BPADI<HC
SDFB	1.5±0.1	2.0±0.1	2.8±0.1	33.63	0.00	SCZ<BPADI<HC
Irony	0.9±0.2	1.5±0.2	2.1±0.2	14.67	0.01	SCZ=BPADI<HC
Metaphor	0.7±0.1	1.0±0.1	1.5±0.1	25.02	0.00	SCZ<BPADI<HC
Empathy	3.6±0.2	4.3±0.1	4.9±0.5	30.77	0.00	SCZ<BPADI<HC
NFP	-	0.2±0.1	0.6±0.1	38.85	0.00	SCZ<BPADI<HC
Benton Face Recognition	20.9±0.4	20.8±0.3	23.3±0.2	32.34	<0.001	SCZ=BPADI<HC
Ekman Happy	6.7±0.1	6.8±0.9	-	4.07	0.019	SCZ=BPADI<HC
Ekman Sad	3.8±0.3	4.0±0.3	5.2±0.3	17.56	<0.001	SCZ=BPADI<HC
Ekman Fear	2.2±0.2	2.9±0.2	3.7±0.2	17.45	<0.001	SCZ<BPADI<HC
Ekman Angry	4.9±0.3	5.5±0.2	6.5±0.9	13.45	<0.001	SCZ=BPADI<HC
Ekman Surprise	5.5±0.3	6.0±0.2	6.6±0.1	7.13	0.001	SCZ=BPADI<HC
Ekman Disgusted	4.7±0.4	4.6±0.3	6.0±0.1	7.11	0.001	SCZ=BPADI<HC
Ekman Neutral	4.6±0.4	5.7±0.3	6.6±0.1	11.06	<0.001	SCZ=BPADI<HC

SCZ: Schizophrenia; BPAD I: Bipolar affective disorder I; RMET: Reading the Mind in the Eyes Test; DEToMI: Dokuz Eylül Theory of Mind Index; FDFB: First-degree false belief; SDFB: Second-degree false belief; NFP: Noticing the faux-pas (p<0.05)

Table 3. Correlation of DEToMI and RMET Total Score with Benton Face Recognition, Ekman Emotion Recognition Battery, WCST Category Number, WCST Perseverative Response Number, Stroop Duration, and Error Number in the SZ Group

		Benton Total	EH	EF	ES	ED	EN	WCST Category	WCST P R N	Stroop 5 duration	Stroop 5 error	TLI Total
DEToMI	r	0.289	0.509*	0.375	0.487*	0.282	0.535**	0.511**	-0.372	-0.535*	-.453	-0.539*
	p	0.071	0.001	0.017	0.001	0.078	0.000	0.001	0.018	0.000	0.003	0.000
RMET	r	0.333	0.618*	0.350	0.462	0.466	0.464	0.399	-0.150	-0.589**	-0.341	-0.444
	p	0.036	0.000	0.027	0.003	0.002	0.003	0 .011	0.354	0 .000	0.031	0.004

DEToMI: Dokuz Eylul Theory of Mind Index; RMET: Reading the Mind in the Eyes Test; EH: Ekman Happy; EF: Ekman Fear; ES: Ekman Surprise; ED: Ekman Disgust; EN: Ekman Neutral; WCST: Wisconsin Card Sorting Test; PRN: Perseverative Response Number TLI: Thought Language Index

Ekman surprised facial expression recognition; a moderate negative correlation with TLI total score, and a weak negative correlation with Stroop 5 duration (Table 5).

Regression Analysis

In order to understand which variables predicted the DEToMI total score in the patient group with SZ, family history of psychiatric disease, BFRT total score, Ekman happy, fearful, angry, disgusted, surprised, neutral, TLI total score, WCST correct number, number of completed categories, number of perseverative answers were included in the linear regression model as variables. The stepwise linear regression analysis showed that the total TLI score, the number of categories completed in the WCST, and the number of Stroop 5 corrections explained 56% of the variance (Table 6). When the same variables were included in the linear regression model, it was shown that Ekman happy and the duration of Stroop 5 test explained 51% of the variance for the total RMET score (Table 7).

In the BPAD I patient group, for the predictor factors of DEToMI and RMET total score, family history of psychiatric disease, Benton total score, Ekman happy, fearful, angry, surprised, disgusted, neutral, TLI total score, WCST correct number, number of perseverative answers, number of completed categories, Stroop 5 duration, and Stroop 5 number of corrections were included in the regression model. The stepwise linear regression analysis showed that for the total score of DEToMI, Ekman happy and neutral explained 31% of the variance (Table 8), for the total score of TLI, the number of WCST completed categories, Ekman surprised, and Stroop 5 duration explained 45% of the total variance (Table 9).

Table 4. Correlation of DEToMI and RMET Total Score with Benton Face Recognition, Ekman Emotion Recognition Battery, WCST Category Number, WCST Perseverative Response Number, Stroop Duration, and Error Number in BPAD I Group

		Benton Total	EH	ES	EF	ES	ED	EN	WCST Category	WCST P R N	Stroop 5 duration	Stroop 5 error	TLI Total
DEToMI	r	0.118	0.437	0.411	0.320	0.087	0.368	0.359	0.406	-0.243	-0.291	-0.346	-0.351
	p	0.470	0.005	0.008	0.044	0.595	0.019	0.023	0.009	0.131	0.068	0.029	0.026
RMET	r	0.228	0.048	0.417	0.353	0.429	0.291	0.374	0.501*	0.076	-0.483*	-0.611**	-0.164
	p	0.157	0.768	0.008	0.026	0.006	0.069	0.018	0.001	0.639	0.002	0.000	0.313

DEToMI: Dokuz Eylul Theory of Mind Index; RMET: Reading the Mind in the Eyes Test; EH: Ekman Happy; ES: Ekman Sad; EF: Ekman Fear; ES: Ekman Surprise; ED: Ekman Disgust; EN: Ekman Neutral; WCST: Wisconsin Card Sorting Test; PRN: Perseverative Response Number; TLI: Thought Language Index

Table 5. Correlation of DEToMI, RMET Test Scores, WCST Category Number, WCST Perseverative Response Number, Stroop 5 Duration and Stroop 5 Error Number, TLI Total Score in the Healthy Control Group

		Ekman Surprise	WCST Category	WCST P R N	Stroop 5 duration	Stroop 5 error	TLI Total
DEToMI	r	0.204	0.500**	-0.273	-0.250	-0.105	-0.373
	p	0.206	0.001	0.089	0.120	0.519	0.018
RMET	r	0.324	0.562**	-0.333	-0.385*	-0.081	-0.508**
	p	0.041	0.000	0.036	0.014	0.618	0.001

DEToMI: Dokuz Eylul Theory of Mind Index; RMET: Reading the Mind in the Eyes Test; ES: Ekman Surprise; WCST: Wisconsin Card Sorting Test; PRN: Perseverative Response Number; TLI: Thought Language Index

Table 6. Regression Analysis of the Predictors of DEToMI Total Score in the SZ Group (N:40)

Variable	B	SEB	β	95 CI%		p
				Lower Limit	Upper Limit	
Model 1						
Constant	13.845	1.472		10.866	16.824	0.000
TLI Total Score	-0.628	0.159	-0.539	-0.950	-0.305	0.000
Model 2						
Constant	15.302	1.382		12.501	18.102	0.000
TLI Total Score	-0.590	0.142	-0.506	-0.878	-0.302	0.000
Stroop 5 Correction Number	-0.730	0.221	-0.404	-1.177	-0.283	0.002
Model 3						
Constant	12.883	0.147		9.884	15.881	0.000
WCST Completed Category Number	0.429	0.140	0.360	0.144	0.714	0.004
Stroop 5 Correction Number	-0.724	0.199	0.400	-1.129	-0.320	0.001
TLI Total Score	-0.439	0.138	0.377	-0.718	-0.160	0.003

Model 1 R^2: 0.290 ; F:15.54
Model 2 R^2: 0.452 ; F: 10.94
Model 3 R^2: 0.565 ; F: 15.59 ; P<0.001 CI: Confidence Interval, DEToMI: Dokuz Eylul Theory of Mind Index; WCST: Wisconsin Card Sorting Test; TLI: Thought Language Index

DISCUSSION

In this study, it was shown that patients with both SZ and BPAD I had weaker ToM skills compared to healthy controls. While no difference was found between patients with SZ and BPAD I in terms of RMET test, it was shown that patients with SZ were weaker in terms of first- and second-degree false belief, understanding metaphor, empathy skills, and recognizing faux-pas, which are the subscales of DEToMI. There was no difference between the two groups in terms of recognition of irony. While literature distinguishes between social-perceptual ToM and social-cognitive ToM it was reported that false belief tests represented social-cognitive ToM, and faux-pas recognition and irony comprehension represented social-perceptual ToM (Shamay-Tsoory et al. 2007). In our study, finding no difference in the RMET

Table 7. Regression Analysis of the Predictors of RMET Total Score in the SZ Group (N:40)

Variable	B	SEB	β	95 CI%		p
				Lower Limit	Upper Limit	
Model 1						
Constant	-20.278	7.562		-35.587	-4.969	0.011
Ekman Happy	5.444	1.124	0.618	3.169	7.720	0.000
Model 2						
Constant	-5.723	8.236		-22.410	10.965	0.492
Ekman Happy	3.950	1.118	0.448	1.683	6.216	0.001
Stroop 5 duration	-0.118	0.037	-0.399	-0.193	-0.042	0.003

Model 1: R^2:0.382; F: 23.4
Model 2: R^2:0.512 ; F:19.3 p<0.001 CI: Confidence Interval RMET: Reading the Mind in the Eyes Test

Table 8. Regression Analysis of the Predictors of DEToMI Total Score in the BPAD I Group (N:40)

Variable	B	SEB	β	95 CI%		p
				Lower Limit	Upper Limit	
Model 1						
Constant	-1.411	4.412		-10.343	7.521	0.751
Ekman Happy	1.935	0.647	0.437	0.626	3.245	0.005
Model 2						
Constant	-3.963	4.229		-12.531	4.605	0.355
Ekman Happy	1.912	0.603	0.432	0.691	3.134	0.003
Ekman Neutral	0.475	0.183	0.353	0.104	0.846	0.014

Model 1 R^2:0.191; F:8.96
Model 2 R^2:0.315; F:8.52 p<0.001 CI: Confidence Interval BPAD I: Bipolar Affective Disorder I; DEToMI: Dokuz Eylul Theory of Mind Index

Table 9. Regression Analysis of the Predictors of RMET Total Score in the BPAD I Group (N:40)

Variable	B	SEB	β	95 CI%		p
				Lower Limit	Upper Limit	
Model 1						
Constant	15.379	0.980		13.395	17.364	0.000
WCST Completed Category Number	1.159	0.325	0.501	0.502	1.816	0.001
Model 2						
Constant	9.301	2.641		3.949	14.653	0.001
WCST Completed Category Number	0.986	0.313	0.426	0.351	1.620	0.003
Ekman Surprise	1.080	0.440	0.332	0.189	1.972	0.019
Model 3						
Constant	14.126	-3.167		7.703	20.549	0.000
WCST Completed Category Number	0.706	0.315	0.305	0.067	1.345	0.031
Ekman Surprise	1.037	0.413	0.319	-1.875	-0.199	0.017
Stroop 5 duration	-0.118	0 .048	-0.328	-0.020	-0.216	0.019

Model 1 R^2: 0.251; F: 12.75
Model 2 R^2: 0.356; F: 10.23
Model 3 R^2:0.448; F: 9.74 p<0.001 CI: Confidence Interval, BPAD I: Bipolar Affective Disorder I; RMET: Reading the Mind in the Eyes Test; WCST: Wisconsin Card Sorting Test

test and the irony comprehension task, which is one of the DEToMI subtasks, indicates that there was no difference in social-perceptual ToM. There was a difference between the two groups in the task of recognizing faux-pas, but it was reported in literature, that this task represents two mental states; the cognitive component (understanding that the person speaking should not say it) and the perceptual component (empathic understanding that the hearer will feel humiliated or upset) (Frith and Frith CD 2003). Therefore, the findings of our study can be interpreted as there is no difference between BPAD I and SZ in terms of social-perceptual ToM, and the SZ group experienced more difficulties in terms of social-cognitive ToM. In a study, neurocognitive skills, social-perceptual, social-cognitive ToM, and attribution style were examined in patients with SZ and BPAD, and it was shown that patients with BPAD had a social-perceptual ToM impairment comparable to SZ, while social-cognitive ToM was better in BPAD patients. In this study by Donohoe et al. (2012), Hinting test was used for cognitive ToM, RMET was used for perceptual ToM and BPAD I and BPAD II were included in the BPAD group (Donohoe et al. 2012). Our study is consistent with the findings of that study. Only BPAD I group is included in our study in order to avoid possible confounding factors of the BPAD II group. In another study, which included patients with a diagnosis of SZ, psychotic and non-psychotic BPAD I, two factors, socio-emotional processing and ToM, were found effective in social cognition. It was also found that socio-emotional processing differentiated SZ and psychotic BPAD I patients from BPAD I and healthy controls. It was suggested that the ToM factor can differentiate patients with SZ, psychotic and non-psychotic BPAD I from healthy controls (Thaler et al. 2013). Similar to this study, Ekman's emotion recognition battery and RMET test were able to differentiate the patient group from healthy controls in our study. Social cognitive functions were able to differentiate psychotic BPAD I patients from non-psychotic ones. In our study, psychotic BPAD I group was predominantly included, therefore BPAD I patients may be closer to the SZ group. In a study which clinically stable BPAD(I/II) and SZ patients and healthy control groups were included and in which social cognition and neurocognition (non-social cognition) were evaluated, it was found that the BPAD patients were not different from healthy controls in social cognition tests and SZ patients were worse than BPAD and healthy controls in both social cognition and neurocognition. It was also reported that there was more loss in neurocognitive skills in BPAD group compared to social cognition, and more loss in social cognitive skills in SZ group (Lee et al. 2013). In our study, unlike the study mentioned above, the BPAD group had impairments in both neurocognition and social cognition compared to controls, this finding may be related to the difference in the BPAD I sample. Unlike that study, the fact that a group of patients with predominantly BPAD I diagnosis showed a similar pattern with SZ patients may be an indication that the two diseases are two diagnostic classes lying along a continuum rather than being separate diseases. Bora et al. (2016) conducted a study in Turkey by using the latent class analysis involving BPAD I and SZ patient groups and an HC group in remission, where the groups were compared in terms of executive functions and ToM. In this study, it was shown that the SZ group experienced more difficulties than the BPAD I group in terms of RMET, hinting test, and the number of completed categories of WCST, and the two patient groups were found to be similar in terms of the Stroop Test (Bora et al. 2016). In this study, a total of 4 classes were obtained, and it was reported that while there were more patients with BPAD I in the group without disorders in both functions, the majority of the group with disorders in both domains, with more ToM impairment, consisted of patients with a diagnosis of SZ. Although ToM and executive functional performance of 16 of the patients included in the study were similar to healthy controls, 60% of the patients exhibited similar cognitive profiles and the two diseases were largely similar in terms of ToM and executive functions, which is consistent with the findings in our study group. In addition, in the study, it was reported that 16 patients had similar ToM and executive functional performance with the HC group. It was also reported that in the patient group, there were more BPAD I patients, higher level of education and PANNS negative scores were less. In addition, when the patient groups included in the study were examined, it is seen that the BPAD patients were in remission for at least 4 months, and the SZ patients were in clinical remission for at least 3 months whereas the inpatients in our patient group were from those who were in remission phase. This might be another reason why our findings are different.

Parallel to our findings, many studies examining ToM skills in patients with SZ reported that impairment in all subtypes of ToM (verbal/visual, social-cognitive/social-perceptual) persisted during the remission period (Sprong et al. 2007, Bora et al. 2007, Herold et al. 2002). On the other hand, patients diagnosed with BPAD I, who responded to treatment in the acute period, and were close to discharge and who are outpatients in the remission period, had ToM impairments compared to healthy controls. This finding is consistent with the previous studies. In a meta-analysis investigating ToM impairments in BPAD, it was reported that ToM disorder persists during remission, w more prominent during relapse, and that there was no difference between remission and subsyndromal symptoms, as well as that neurocognitive symptoms and especially manic symptoms were associated with ToM impairments (Bora et al. 2016). In some studies, comparing BPAD and healthy controls, no difference was found between the two groups in social-perceptual ToM, while social-cognitive ToM impairement

were found in BPAD I patients (Shamay-Tsoory et al. 2009, Montag et al. 2009, Barrera Á et al. 2013). The findings in these studies are different from our study, but it is believed that this may be related to the heterogeneity of the sample taken and the inclusion of predominantly psychotic BPAD I group in our study.

In our study, no difference was found between the patients with SZ and BPAD I in terms of face recognition evaluated by BFRT whereas the recognition ability of both patient groups were less than healthy controls. In the emotion recognition task evaluated with Ekman battery, while there was no difference in facial expressions other than fearful facial expressions between the patients with SZ and BPAD I, they were found to experience more recognition difficulties than healthy controls. The fearful facial expression was more difficult to be recognized by the SZ group than in the BPAD I group. Previous studies showed that SZ patients had an impairment in facial identification tasks evaluated by BFRT (Addington and Addington 1998, Bortolon et al. 2015, Penn et al. 2000). There are several studies showing problems in distinguishing facial expressions in patients with BPAD I compared to healthy controls, but no difference was found in facial recognition tasks compared to healthy controls in these studies (Addington and Addington 1998, Getz et al. 2003, Bozikas et al. 2006). This finding is inconsistent with our study, but it is thought that it can be related to more heterogeneous inclusion of the BPAD group (Addington and Addington 1998) and the inclusion the patients in relapse (Getz et al. 2003). In a functional imaging study conducted during emotion recognition and identity recognition tasks in BPAD I patients, increased activity was seen in medial prefrontal cortex (mPFC) and amygdala in both tasks in BPAD I patients compared to healthy controls. In healthy controls, a decrease in mPFC was seen during these tasks. The increase in activity in these regions, which are related to self-referential and social information processes, differentiated the BPAD I patients healthy controls in the facial identification processes (Keener et al. 2012).

The SZ group had more difficulty in recognizing fearful facial expression than the BPAD I group. It has been previously reported that patients with SZ had difficulties in recognizing the expression of fear as a negative expression. Eye regions are involved more in recognizing expressions of fear compared to others (Morris et al. 2009). In addition, it is known that the eye region is processed faster in fearful expressions than in other expressions, and this supports that fear is related to preconscious processing. Since patients with SZ do not establish eye contact, it is expected that they will have difficulty in recognizing fearful expressions, which is consistent with our study. It was reportedthat patients with SZ have decreased amygdala activity, especially when they look at fearful faces. In an Event-Related Potential study focuisng on the differentiation of neutral and fearful facial expressions in patients with SZ, it was found that patients with SZ and HC groups differentiated neutral and fearful facial expressions in the early stages of facial processing. It was also reported that, unlike controls, there is an amygdala activity in SZ during the recognition of fearful expressions in the later period compared to neutral faces, which is associated with clinical symptomatology (Martin et al. 2005). There was no difference in expressions other than fearful facial expressions between patients with SZ and BPAD I, which is consistent with previous studies with patients with SZ and BPAD I (Thonse et al. 2018, Daros et al. 2014).

SZ and BPAD I patient groups performed worse than healthy controls in terms of both positive and negative FTD. The SZ group was worse than the BPAD I group in terms of negative FTD. Neurocognitive and neuroimaging studies have shown that negative FTD is different from positive FTD. It is reported that while positive FTD is associated with a decrease in the language-related areas of Broca and Wernice, since negative FTD is associated with the medial frontal and orbitofrontal cortex, and the impairment in visual-motor tasks evaluating attention is associated with negative FTD, with not positive FTD, negative FTD is mostly associated with negative symptoms (Roche et al. 2014). Since the patient group in our study was included from a clinically-stable patient population, who were mostly outpatients and close to discharge, negative FTD may have been found to be worse in SZ patients than in BPAD I patients. In our study, a correlation was found between ToM and TLI total scores, which is consistent with the previous finding where thought and language disorders predicted ToM (Greig et al. 2004). However, the number of studies in this area is not sufficient.

The factors predicting social-perceptual and social-cognitive ToM showed different patterns in the SZ and BPAD I groups. The best predictors of DEToMI total score were the executive functions and TLI total score in the SZ group whereas in BPAD I group, Ekman happy and neutral facial expression recognition were the best predictors. This differentiates SZ and BPAD I even if they show predominantly psychotic symptoms. The best predictors of RMET were the Stroop 5 test correction number and the recognition of Ekman happy facial expression in the SZ group whereas in BPAD I group, the recognition of Ekman happy and surprised faces and Stroop 5 test duration were the best predictors. This finding is consistent with the finding that the executive functions predicted ToM in studies examining neurocognitive predictors of social cognition in patients with SZ in remission (Mehta et al. 2014, Fernandez-Gonzalo et al. 2013). In a study examining the relationship between social-cognitive and social-perceptual ToM and executive functions in patients with SZ in remission, the Stroop test was reported to be the best predictor of RMET, similar to the SZ group in our study (López-Navarro 2018). In a study that included

BPAD I patients in the euthymic period and healthy controls, in which Hinting test, RMET, Benton Face Recognition Test, emotion recognition and neurocognitive tests were applied, it was found that face recognition, emotion recognition and psychomotor speed were the predictive of RMET; whereas the number of WCST perseverative errors was a predictor for the Hinting test. (Bora et al. 2005)

Limitations of the study: While choosing the sample in our study, people who did not have clinical mental retardation were included, but there may be differences in the intelligence level, which may have created differences in understanding of and responding to these tests. The BPAD I group included in our study had predominantly psychotic features. More reliable results can be obtained by including different groups such as BPAD I and BPAD II. In the study, YMRS was used for manic attack symptoms in the BPAD I group, but the depressive episode was not evaluated. Since the study is cross-sectional, the predictors determined by linear regression analysis should be supported by longitudinal studies.

As a result, we showed that SZ and BPAD I patient groups received significantly worse results in social-perceptual ToM and social-cognitive ToM than healthy controls. While BPAD I patients had similar social-perceptual ToM impairments to SZ patients, they performed better in social-cognitive ToM skills than SZ patients. In addition, the executive functions and formal thought disorders are the best predictors of DEToMI in SZ patients whereas in patients with BPAD I, it is emotion recognition. Emotion recognition and executive functions were the best predictors of social-perceptual ToM assessed by RMET in both patient groups. Although the patients with SZ and BPAD I were similar to each other in terms of facial recognition and recognizing facial expressions other than fearful, they were found to have impairments compared to healthy controls. The healthy controls are the best in recognizing fearful expressions with which patients with SZ had the most difficulty.

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RESEARCH ARTICLE

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Effect of CBT on Metacognitive Beliefs in Depressive Disorders

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ABSTRACT

Metacognitive beliefs operate through cognitive attentional syndrome, where attention concentrated on negative automatic thoughts results in rumination. This perseverative thinking style manifesting in the form of rumination and worry intensifies depression. This study aims to assess the effect of cognitive behaviour therapy (CBT) on metacognitive beliefs, symptom severity, quality of life, and functionality. A pre-post study design comparing CBT-alone and CBT-with-medication was employed using purposive sampling to recruit 40 participants diagnosed with depressive disorders. All the participants received 10 sessions of CBT. Pre and post assessment measures were Beck Depression Inventory-II, Metacognitive Questionnaire-30, World Health Organization Quality of Life- Brief, and Global Assessment of Functioning. Paired t-test analysis revealed significant difference on outcome measures in both groups. Between-subject analysis revealed that the CBT-alone group was not significantly different in terms of improvement than CBT-with-medication group even when confounding variables were statistically controlled by way of testing analysis of covariance and propensity score match (nearest neighbour match).

Keywords: Cognitive behaviour therapy, metacognition, depressive disorders, metacognitive beliefs, depression, quality of life.

INTRODUCTION

Depressive disorders are recurrent or episodic with stressors often triggering individual episodes. Various grades of depression severity have been graded as mild, moderate, and severe (World Health Organization 1982). It calls for clinical judgment to determine such grades of severity as per number, type, and severity of symptoms the individual presents. Lifetime prevalence estimates of mood disorders are 20.8% and the median age of onset is 30 years (Kessler et al. 2005). A study conducted in India proclaimed that the overall prevalence of depression was 15.1% and, it affected females (3.0%) more than males (2.4%). Additionally, 13.7% lifetime prevalence for psychiatric morbidity was among those aged between 40-49 years, predominantly affected by psychotic, mood and neurotic and stress-related disorders (Gururaj et al. 2016, WHO 2017).

Beck's cognitive triad is a cardinal cognitive feature of depressive disorders (Freeman et al. 1990), with reference to dysfunctional thoughts about self, the others, and future that could worsen the course of or hamper recovery from a depressive episode. Any stressor can activate dysfunctional thoughts during recovery, making complete remission rare (Halvorsen et al. 2014). According to the metacognitive belief model, it is not the thinking per se but the way an individual relates to these thoughts that cause or maintain depression. Metacognitive beliefs tend to operate through cognitive attentional syndrome (CAS), where attention is concentrated on negative automatic thoughts (NATs) fostering rumination; and rumination supplements NATs (Halvorsen et al. 2014, Normann et al. 2014), worsening the depressive state. Wells classified these dysfunctional metacognitive beliefs such as positive beliefs about worry, negative beliefs about uncontrollability and danger of worry, cognitive confidence, need for control, and cognitive self-consciousness (Wells 2009). The positive metacognitive beliefs breed rumination evaluating it as a coping mechanism that could lead to paramount harmful social and interpersonal consequences. Later, these consequences generate negative metacognitive beliefs about rumination (inducing worry and uncontrollability) inducing decreased cognitive confidence among individuals in depressive states (Halvorsen et al. 2014, Papageorgiou and Wells 2003).

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Metacognition, therefore, can be understood as an information processing system that monitors, interprets, evaluates and regulates content, and content organization processes (Flavell 1979, Papageorgiou and Wells 2003). An individual in the state of depression centres attention on NATs and continues to ruminate about negative experiences, events or emotions. This perseverative thinking style, inclusive of rumination and worry, gives rise to depression (Halvorsen et al. 2014).

CBT is an evidence-based therapy (EBT) for NATs and a gold-standard treatment to address NATs through cognitive restructuring, which consequently reduces relapses and improves functioning (Halvorsen et al. 2014). The third wave therapies, namely, the metacognitive therapy and acceptance and commitment therapy, manipulate dysfunctional thoughts (Jelinek et al. 2017), and metacognitive beliefs using increased attentional flexibility through mindfulness (Evans et al. 2008, Hofmann et al. 2010) whereas CBT addresses the very content of thoughts and not the dysfunctional metacognitive beliefs about these thoughts. Hence, interrogating the effect of CBT on dysfunctional metacognitive beliefs will be pivotal as well as to understand whether or not techniques such as guided imagery act as a mindfulness-based intervention. The researchers did not come across any Indian studies related to the effect of CBT on metacognition or dysfunctional metacognitive beliefs. The current study might be first in such direction attempting to enhance the understanding that existing mental health service delivery (CBT) in depressive disorders will be beneficial in addressing new aspects of human cognition (metacognitive beliefs).

METHOD

The study employed an experimental research design controlled by grouping, comparing pre-post intervention findings within and between groups (Singh 1998). Forty participants diagnosed with depressive disorder as per ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines (ICD10 CDDG) by WHO 1982 were recruited from the outpatient department (OPD) of Psychiatry of a government tertiary care hospital located in an urban area. The purposive sampling method was used to recruit the participants (Singh 1998). CBT group comprised of participants receiving only CBT whereas CBTM group had participants receiving CBT along with anti-depressants, i.e., selective serotonin reuptake inhibitor (SSRI). Twenty participants were recruited in each group as per the inclusion/exclusion criteria.

Inclusion and Exclusion Criteria

Participants between 20-45 years of age of both sexes, with a minimum 10 years of formal education, having a clinical diagnosis of depressive disorder were included. Whereas those with psychiatric co-morbidities, severe depression, suicidality, clinical evidence of intellectual disability, or suffering from any terminal illness, neurological conditions, history of head injury, or having received electro-convulsive therapy (ECT) or any evidence-based psychotherapy currently or in last 6 months, practicing yoga/meditation/art of living currently or those to have done so in last 6 months were excluded.

Measures

Mini-International Neuropsychiatric Interview (MINI 7.0.2)

It is a short structured diagnostic interview developed by Sheehan and colleagues for DSM-III-R and ICD-10 psychiatric disorders. It assesses the 17 most common psychiatric disorders and has good reliability and validity when compared to other structured diagnostic interviews. Inter-rater reliability depicted thru kappa coefficients ranged from 0.88 to 1.0 and test-retest reliability with kappa coefficients values ranging between 0.76 and 0.93 (Lecrubier et al. 1997).

Beck Depression Inventory (BDI-II)

It assesses severity of depression, including a 4-point 21-item Likert scale with a scoring range from 0 to 3. The total maximum score can reach 63 requiring 5 to 10 minutes to complete (Beck et al. 1996). The internal consistency of BDI-II is reported around 0.9 and retest reliability between 0.73 to 0.96 (Wang and Gorenstein 2013)

Metacognitive Questionnaire (MCQ30)

It assesses the metacognitive model of psychological disorders. It includes 30 items, which are rated on a 4-point Likert scale from 1 to 4. The subscales assessing metacognitive beliefs include positive belief about worry, negative beliefs about the uncontrollability of thoughts & danger, beliefs about the need to control thoughts, cognitive confidence, and cognitive self-consciousness. It takes around 25 to 30 minutes to complete. The internal consistency of total score as well as of sub-scales using Cronbach's alpha ranged from 0.72 to 0.93 (Wells and Cartwright-Hatton 2004).

World Health Organization Quality of Life- Brief (WHOQOL-BREF)

It is a 26-item shorter version of the WHOQOL-100 with four domains on quality of life: (i) physical; (ii) psychological; (iii) social relationships and (iv) environment. It enquires about the quality of life in the 'last 2 weeks' rated on a 5-point (0-5) scale. The scale is useful for clinical settings with a high patient load as it takes only 5-8 minutes to complete (Saxena et al. 1998). Cronbach's alpha values were 0.85 for psychological health, 0.73 for physical health, 0.73 for social relationships, 0.68 for environment (Oliveria et al. 2016).

Table 1. Course of Cognitive Behaviour Therapy (CBT) Module in Depressive Disorders

Ss	Goal of Session	Content of Sessions
1	Psychoeducation	Informative model of psychoeducation - imparting information on symptoms and dysfunction, prevalence, course and treatment options. Homework assigned to read brochures or pamphlets on depression. Summarize and terminate the session. Explaining relationship among conation-affect-cognition (CAC). Conduct pre-assessment.
2	Initiate CBT	Recap with CAC. Feedback on homework and continue psychoeducation. Seeking consent for CBT. Goal setting. Deliver session of guided imagery (GI). Activity scheduling facilitated by environment. Homework - regular practice of GI and maintain record of activities followed. Summarize and terminate the session.
3	Introduce DTR	Review homework of previous session. Psychoeducation continues by explaining – rumination and negative automatic thought affecting mood and behaviour. Introduce dysfunctional thought record (DTR). Homework – GI practice, activity scheduling continued and to maintain DTR. Summarize and terminate.
4	Cognitive errors	Review homework of previous session. Discuss barriers in DTR, if any. Psychoeducation continued using DTR and its content to strengthen understanding of CAC. Discuss cognitive errors. Homework – GI practice, activity scheduling continued and to maintain DTR. Summarize and terminate.
5	Identify and label cognitive errors	Review homework of previous session. Identify cognitive errors in DTR and label. Homework – GI practice, activity scheduling and to maintain DTR. Summarize and terminate.
6	Cognitive restructuring	Review homework of previous session. Identify cognitive errors in DTR and label. Use cognitive techniques to challenge the cognitive errors. Homework – GI practice, activity scheduling continued, to maintain DTR and label cognitive errors in DTR. Summarize and terminate.
7	Cognitive restructuring	Review homework of previous session. Cognitive restructuring continued. Homework – GI practice, activity scheduling and practice challenging in new column in DTR. Summarize and terminate.
8	Cognitive restructuring	Review homework of previous session. Recognize barriers and techniques used in challenging of thoughts. Cognitive restructuring continued. Homework – GI practice, activity scheduling and continue challenging of thoughts in new column in DTR. Summarize and terminate.
9	Termination	Review homework of previous session. Strengthen cognitive restructuring. Introduce termination of the study.
10	Termination	Review homework on cognitive restructuring. Summarize CBT process. Post-assessment carried out.

Ss: Sessions.

Global Assessment of Functioning (GAF)

It is Axis V of the internationally accepted Diagnostic and Statistical Manual of Mental Disorders, fourth edition text revision (DSM-IV-TR). It scores the severity of psychopathology and the degree of psychological, social, and occupational functioning on a 10-point interval scale. It is a generic measure of how a patient is doing than a diagnosis-specific scoring system (Kaplan and Sadock 1998).

Intervention

A module of ten CBT sessions was adapted incorporating various techniques for the study (Freeman et al. 1990, Somers and Querée 2007). The authors of the study finalised the content of 10 sessions. Table 1 schematizes the 10 sessions of intervention. CBT sessions were delivered by the first author, a licensed clinical psychologist with a working experience of more than 10 years, and pharmacological treatment was prescribed by the psychiatrist.

Procedure

The study has been approved by the Ethics Committee of the Institution. The psychiatrists referred the patients of depressive disorders to psychotherapy to the behaviour therapy unit of the department. The researcher approached consecutive patients to seek consent to participate following the Helsinki Declaration (World Medical Association 2013). The researcher recorded the socio-demographic and clinical details of those who consented. Those included as per defined criteria were administered MINI 7.0.2 for ruling out comorbid psychiatric disorders and for objective assessment of depressive disorders. Those who fulfilled the criteria either major depressive episode (MDE) or recurrent depressive disorder (RDD) criteria and had no psychiatric comorbidities were included. Likewise, the researcher administered BDI-II, and those to score between 14-28 suggesting mild to moderate depression were also included (Smarr and Keefer 2011). Those with severe depression (score >28) were excluded and referred to psychotherapy. Once recruited in the study, those who have been referred only for CBT were assigned to the CBT group whereas those prescribed with SSRI were assigned to the CBTM group. The note was out in the file to keep the treating team informed. Each participant was pre-assessed for measures and – MCQ 30, and WHOQOLBref and GAF was carried out.

The researcher introduced every participant to CBT sessions once pre-assessment was complete. At the end of the 10th session of CBT, post-assessment was carried on measures: BDI-II, MCQ-30, WHOQOLBref and GAF. The study terminated and the participants continued to seek services in the OPD (Figure 1).

Data Analysis

Data was analysed using software for statistics and data science Stata/IC version 16. Descriptive statistics were computed for sociodemographic and clinical variables and scores of outcome measures. The difference between the two groups was computed using mean comparison tables; chi-square test for discrete variables and t-tests for continuous variables. The method of last observation carried forward (LOCF) was used for statistical analysis of the missing data of dropouts. Pre-post differences within groups were analysed using paired t-tests and independent t-test were used to compare the two groups. The analysis of covariance (ANCOVA) was used to control confounding variables such as diagnosis, number of episodes of depression, and the duration of illness. Propensity score matching was employed to overcome the limitation of purposive sampling by comparing each case to its nearest neighbour match (Austin 2011). Cohen's *d* determined the effect size of these changes in response to the intervention (Sawilowsky 2009).

RESULTS

Descriptive Statistics of Sociodemographic and Clinical Variables in Two Groups

The descriptive statistics was computed for sociodemographic and clinical variables. The two groups were matched on age, sex and education with no statistically significant ($p>0.05$) difference (see Table 2). However, the two groups differed significantly on clinical variables, namely, diagnosis, the duration of illness and the number of episodes. There was no significant difference in participation of therapy sessions.

Within-group Analysis of CBT and CBTM

The pre-post difference in scores on the outcome measures was very significant except for cognitive self-consciousness. Besides, CBTM group significant change in cognitive confidence. Cohen's *d* (see Table 3) unveiled larger effect size in CBTM group on negative beliefs about uncontrollability and danger of worry (d=1.33) value ranging from 0.33 to 4.15 indicating small to huge effect-range.

Between-group Analysis of CBT and CBTM

There was meaningful difference on positive belief about worry; physical health and global functioning whilst there was no significant difference as regards other measures (see Table 4). Disparities in clinical variables weakened the findings so ANCOVA was computed (see Table 5). The controlling of confounding variables, namely; diagnosis, duration of illness and number of episodes, also panned out meagre outcomes implying that CBT and CBTM produce parallel outcomes, which was verified when participants in groups were compared with their nearest match (see Table 5).

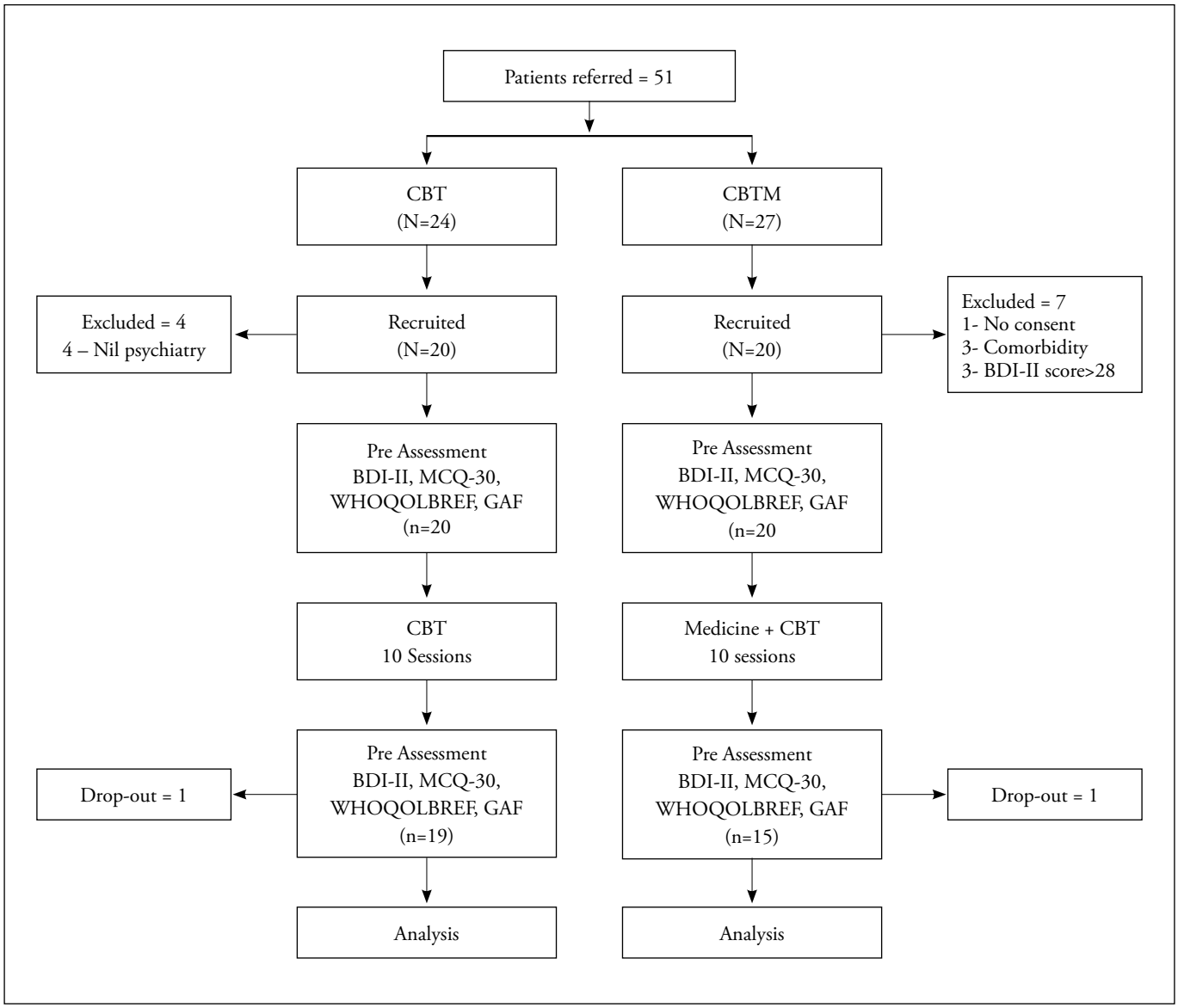

Figure 1. CONSORT diagram for participants throughout the study.

Table 2. Characteristics of Participants in Two Groups

Variable		CBT		CBTM		p
		M ± SD	Frequency (%)	M ± SD	Frequency (%)	
Age		28 ± 9.26	-	30.6 ± 9.21	-	0.379
Education (years)		15 ± 1.52	-	14.45 ± 1.67	-	0.283
Sex	Female	-	13 (65.0)	-	12 (60.0)	0.744
	Male	-	7 (35.0)	-	8 (40.0)	
Diagnosis	MDE	-	14 (70.0)	-	6 (30.0)	0.011*
	RDD	-	6 (30.0)	-	14 (70.0)	
Episodes	0	-	14 (70.0)	-	6 (30.0)	0.033*
	1	-	4 (20.0)	-	7 (35.0)	
	2	-	2 (10.0)	-	7 (35.0)	
Severity	Mild	-	9 (45)	-	5 (25)	0.185
	Mod	-	11 (55)	-	15 (75)	
DOI (Months)		26.2 ± 22.04	-	50.9 ± 31.79	-	0.006**
Number of sessions		9.8 ± .89	-	8.85 ± 2.08	-	0.069

p<0.05, **p<0.01, ***p<0.001, M: Mean, SD: Standard deviation, %: Percentage, MDD: Major depressive disorder, RDD: Recurrent depressive disorder, Mod: Moderate, DOI: Duration of illness.

Table 3. Outcome Measures at Pre-Post Treatment Differences Within-Groups (df=19)

Measure		CBT (n=20)							CBTM (n=20)						
		Pre-treatment		Post-treatment		t	p	d	Pre-treatment		Post-treatment		t	p	d
		M	SD	M	SD				M	SD	M	SD			
BDI-II		20.95	4.83	7.25	5.38	9.38	0.000***	2.68	21.75	3.81	10.95	7.27	7.12	0.000***	1.86
MCQ	Total	62.55	16.69	51.65	2.52	3.97	0.000***	0.76	54.9	15.67	45.45	13.65	4.67	0.000***	0.64
	POS	10.45	4.58	8.75	2.71	2.47	0.023*	0.45	8.5	3.24	7.1	1.86	3.39	0.003**	0.53
	NEG	15.65	4.29	12.25	3.61	5.79	0.000***	0.86	17.15	2.94	12.15	4.44	5.98	0.000***	1.33
	CC	10.2	3.47	8.6	2.87	2.71	0.014*	0.50	9.25	4.81	8.45	4.28	1.33	0.198	0.17
	NC	11.55	4.46	9.1	2.57	2.47	0.023*	0.67	9.15	3.28	7.8	3.43	2.38	0.028*	0.40
	CSC	14.7	4.88	12.95	4.63	1.82	0.083	0.37	11.4	4.75	10.45	4.39	1.56	0.135	0.21
QOL	PH	20.3	3.93	26.4	2.83	7.46	0.000***	1.78	19.6	3.27	23.7	4.29	5.00	0.000***	1.07
	PSY	14.85	3.60	20.45	3.19	8.45	0.000***	1.65	13.8	3.53	18.2	4.74	6.21	0.000***	1.05
	SR	8.9	1.62	10.15	1.35	3.05	0.006**	0.84	8.15	1.31	9.4	1.73	4.47	0.000***	0.81
	ENV	29.4	4.26	30.8	4.20	2.64	0.016*	0.33	25.2	5.19	27.5	5.09	3.38	0.003**	0.45
GAF		59.45	5.81	84.45	6.23	13.4	0.000***	4.15	57.55	5.74	73.85	5.13	12.58	0.000***	3.00

*p<0.05,**p<0.01, ***p<0.001, M: Mean, SD: Standard deviation, BDI-II: Beck Depression Inventory, MCQ30: Metacognition Questionnaire, POS: Positive belief about worry, NEG: Negative beliefs about uncontrollability and danger of worry, CC: Cognitive confidence, NC: Need for control, CSC: Cognitive self-consciousness, QOL: World Health Organization Quality of Life Brief, PH: Physical, PSY: Psychological, SR: Social relations, ENV: Environmental, GAF: Global Assessment of Functioning.

Table 4. Outcome measures at pre-post treatment differences between groups (N=40, df =38)

Measures		M (SD) CBT	M (SD) CBTM	Mean Difference	Standard Error Difference	t	p	d
BDI-II		7.25 (5.38)	10.95 (7.27)	3.7	2.02	1.83	0.075	0.58
MCQ	Total	51.65 (11.26)	45.45 (12.74)	6.2	3.96	1.57	0.125	0.50
	POS	8.75 (2.71)	7.1 (1.86)	1.65	0.73	2.24	0.030*	0.71
	NEG	12.25 (3.61)	12.15 (4.44)	0.1	1.28	0.08	0.938	0.02
	CC	8.6 (2.87)	8.45 (4.28)	0.15	1.15	0.13	0.897	0.04
	NC	9.1 (2.57)	7.8 (3.43)	1.3	0.96	1.36	0.183	0.43
	CSC	12.95 (4.63)	10.45 (4.39)	2.5	1.43	1.75	0.087	0.55
QOL	PH	26.4 (2.83)	23.7 (4.29)	2.7	1.15	2.35	0.024*	0.74
	PSY	20.45 (3.19)	18.2 (4.74)	2.25	1.28	1.76	0.086	0.56
	SR	10.15 (1.35)	9.4 (1.58)	0.75	0.49	1.53	0.134	0.48
	ENV	30.8 (4.20)	27.5 (5.09)	3.3	1.48	2.23	0.031*	0.71
GAF		84.45 (6.23)	73.85 (5.13)	10.6	1.80	5.87	0.000***	1.86

*p<0.05,**p<0.01, ***p<0.001, M: Mean, SD: Standard deviation, BDI-II: Beck Depression Inventory, MCQ30: Metacognition Questionnaire, POS: Positive belief about worry, NEG: Negative beliefs about uncontrollability and danger of worry, CC: Cognitive confidence, NC: Need for control, CSC: Cognitive self-consciousness, QOL: World Health Organization Quality of Life Brief, PH: Physical, PSY: Psychological, SR: Social relations, ENV: Environmental, GAF: Global Assessment of Functioning

Table 5. Outcome measures at pre-post treatment differences between groups

Measure		ANCOVA			PSM-NNM		
		F	R^2	p	Coef	z	p
BDI-II		1.03	0.44	0.463	0.37	0.16	0.877
MCQ	Total	0.59	0.31	0.867	2.35	0.56	0.574
	POS	0.65	0.33	0.818	0.48	0.59	0.556
	NEG	0.73	0.36	0.747	1.11	0.85	0.395
	CC	0.60	0.32	0.854	1.13	1.41	0.157
	NC	0.43	0.25	0.960	0.59	0.50	0.619
	CSC	1.10	0.46	0.409	1.02	0.62	0.538
QOL	PH	0.87	0.40	0.606	3.60	2.96	0.003**
	PSY	1.06	0.45	0.445	1.54	1.23	0.220
	SR	1.16	0.47	0.364	0.80	1.24	0.215
	ENV	1.24	0.49	0.315	2.17	1.45	0.147
GAF		2.90	0.69	0.010*	9.72	3.67	0.000***

*p <.05, **p <.01, ***p <.001, ANCOVA: Analysis of covariance, PSM-NNM: Propensity score matching using nearest-neighbour match, BDI-II: Beck Depression Inventory, MCQ30: Metacognition Questionnaire, POS: Positive belief about worry, NEG: Negative beliefs about uncontrollability and danger of worry, CC: Cognitive confidence, NC: Need for control, CSC: Cognitive self-consciousness, QOL: World Health Organization Quality of Life Brief, PH: Physical, PSY: Psychological, SR: Social relations, ENV: Environmental, GAF: Global Assessment of Functioning

DISCUSSION

CBT is a popular approach to restructure erroneous cognitions by using various techniques (Freeman et al. 1990), to alleviate mood and improve functioning and it has been recommended as the first line of treatment in mild to moderate depressive disorders (Rupke et al. 2006). The within and between-group analyses revealed that CBT alone as well as CBT-with-medication had a significant effect on the reduction of symptoms, altering metacognitive beliefs and improving QoL and functioning. CBT is superior to other psychotherapies and might have a synergistic effect on patients receiving antidepressants and CBT further reduces the risk of relapse (Hofmann et al. 2012, Cuijpers et al. 2013). The between-group analysis showed no significant differences in outcome measures, indicating that CBT not only mitigate symptoms, and dysfunctional metacognitive beliefs but also amplify quality of life and functioning whether employed solely or in combination with pharmacological treatment.

The changes are significant in both groups but effect sizes are larger for CBT group than CBTM. This may be due the multiple causes such as CBT sample had more participants with first depressive episode whereas CBTM sample was composed of those with recurrent depressive episodes. Additionally, duration of illness was longer in CBTM sample than in CBT sample. Moreover, those who were not prescribed with medication by the psychiatrist were included in CBT group presuming lesser severity and better functioning. The current study examined the factors reducing QoL, which was found to improve with and functional recovery in QoL (Shumye et al. 2019, Park and Jung 2019) elevated by engaging in behavioural activation. The techniques of behavioural activation and guided imagery (GI) that encompass daily functioning and mood alleviation are beneficial. The larger effect size in CBT group than CBTM for quality of life is assessed by subjective views of the patient (Katschnig 2006) and research has shown that depression severity is correlated with QOL impairment (Jha et al. 2014), however, the changes in QOL are not fully correlated with variations in the severity of depression (Hirschfeld et al. 2002), and variations in QOL are very slow as compared to those in the severity of depressive symptoms (Trivedi et al. 2006). A meta-analysis looking at the efficacy of antidepressant medication in youth with depression showed that despite improvement in clinician-rated depression symptoms patients did not exhibit improvement in overall well-being and QOL (Spielmans and Gerwig 2014). Thus, quality of life is an independent variable and reduction in symptom-severity may not always improve quality of life. This implies that QoL improved to a greater extent in the CBT sample compared to the CBT with--medication group, which showed greater symptom reduction but lesser QoL improvement scores.

Within and between-group analyses within the scope of this study showed that CBT had a significant effect on the positive belief about worry (POS), negative beliefs about uncontrollability and danger of worry (NEG) and the need for control (NC). Metacognitions concerning uncontrollability and danger of worry show a positive relationship in clinically depressed individuals and positive beliefs about rumination are linked with a tendency to ruminate in both clinical and non-clinical samples in a state of low mood. Thus positive and negative beliefs about worry tend to be predictive as well as a by-product of depressive disorders (Huntley and Fisher 2016, Verplanken et al. 2007, Papageorgiou and Wells 2001). The decreases in confidence in cognitive functioning, a depressogenic by-product, might contribute to negative beliefs about interpersonal and social consequences of rumination as well as positive beliefs (Roelofs et al. 2007), concerning the need to ruminate to facilitate effective coping.

However, the within-group analysis showed no apparently significant effect on cognitive confidence (CC) and cognitive self-consciousness (CSC). This is also supported by western literature where CC was more closely linked to OCD (Janeck et al. 2003, Solem et al. 2009). Individuals with high persecutory thinking have low levels of cognitive self-consciousness leading to poor well-being. The moderation analyses showed the interaction between persecutory thinking and cognitive self-consciousness are predictors of psychological well-being while comparing groups of depressed psychotic and healthy controls (Valiente et al. 2012). Hence, cognitive self-consciousness may be attached to depression with psychotic symptoms than without.

The implemented CBT model was similar to Moritz's approach to metacognitive training as it targeted content of cognition, thereby, altering metacognitive beliefs. Whereas Well's approach is similar to metacognitive training emphasizing the meta-level cognition and not content of cognition (Wells and Carter 2001). It might be possible that CBT, which incorporates GI or/and mindfulness-based technique, has a superior effect than CBT using only cognitive and/or behavioural techniques. Therefore, it is reasoned that CBT as well as anti-depressants not only address the content of cognitions but also is an effective intervention for meta-level beliefs.

Limitations

The study did not use any measures to assess rumination and dysfunctional thoughts. The intensity of rumination or the type of cognitive errors and its relation to metacognitive beliefs and outcomes still require exploration. The small sample size hindered the application of statistics to discover whether or not metacognitive beliefs mediate the improvement in terms of functioning and quality of life.

Implications of the study

CBT with or without medicine is an effective treatment for depressive disorders, altering cognitive content and meta-level cognitive beliefs resulting in symptom reduction and enhanced quality of life. The use of techniques targeting such components as cognition, affect and behaviour, result in a more promising outcome. The use of guided imagery (GI) might have played a role similar to mindfulness, as GI is a form of mind-body therapy (MBT).

Future directions

Future studies can have randomised trials comparing effectiveness of CBT with third-wave therapies in depressive disorders replicating these outcome measures or supplementing it by measuring rumination and dysfunctional thoughts. In addition, the association between pharmacological therapy and metacognition needs to be investigated.

CONCLUSION

CBT alone as well as combined with anti-depressants is an effective treatment alleviating symptoms, metacognitive beliefs, improving functionality and QOL in depressive disorders. Therefore, it is inferred that CBT addresses newer mediators such as metacognition and continues to be a gold standard treatment dealing with negative cognition as well as metacognitive beliefs. The monitoring of metacognitive beliefs can be of immense significance while dealing with individuals having depressive disorders, however, role of anti-depressants on metacognitive beliefs still needs to be explored further.

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Investigation of the Relationship between Inflammation and Oxidative Stress Markers and Treatment Response in First-Attack Major Depression Patients: A Follow-Up Study

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ABSTRACT

Objective: There is a need to biomarkers for major depression (MD). The goals of this study are to compare serum levels of oxidative stress markers malondialdehyde (MDA) and F2-isoprostane and inflammation markers tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6) and C-reactive protein (CRP) between patients with first-episode MD and healthy controls, to investigate the change of these markers after treatment and to investigate the relationship between levels of these markers and treatment response.

Method: Our study was performed in 30 first-episode MD patients and 30 healthy volunteers. During the clinical evaluation Hamilton Depression Rating Scale and Clinical Global Impression Scale were applied to the participants. Serum levels of markers were measured at the baseline and after 8 weeks of treatment.

Results: Compared to the control group, first-episode MD patients had significantly higher IL-6, CRP and MDA levels and lower F2-isoprostane levels. There was no difference between the groups in terms of TNF-α levels. TNF-α, IL-6, MDA and F2-isoprostane levels decreased significantly after treatment, whereas there was no significant change in CRP levels with treatment. Baseline F2-isoprostane levels were found to be significantly higher in treatment responders than non-responders ($p<0.05$).

Conclusion: In our study, it was shown that there are irregularities related to inflammatory processes and oxidative stress in MD, even in patients who had their first-episode and did not take medication, and these irregularities can be resolved after treatment. While there was a relationship between treatment response and baseline F2-isoprostane levels, there was no relationship with other biomarkers.

Keywords: Biomarkers, depression, inflammation, oxidative stress, treatment response

INTRODUCTION

Major depression (MD) is an important public health problem and it directly affects 322 million people worldwide (World Health Organization 2017). Its prevalence is higher in females than males. While its prevalence in women is 5.1% worldwide, its prevalence in men has been reported to be 3.6% (World Health Organization 2017). In Turkey, the prevalence of depressive disorders has been reported to be 7.2% (9.8% in women, 3.9% in men) (Erol et al. 1998). Depression can lead to suicide, being more common in moderate and severe depressions and prolonged periods of illness, and it is among the most important causes of disability (World Health Organization 2017, Öztürk and Uluşahin 2015). Early and accurate diagnosis, and the most appropriate treatment and follow-up of patients are very important in determining the course of depression (Öztürk and Uluşahin 2015). Almost 60% of the patients do not respond to the treatment with the first use of antidepressants, and 20% of these patients are also unresponsive to other treatments (Mora et al. 2018). For these reasons, it is important to develop methods that can predict the response to treatment and determine the best medication for each patient, thus providing personalized medication selection (Mora et al. 2018).

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Today, there are no biological markers among the diagnostic criteria of any psychiatric disease, including depression (Gadad et al. 2018, Hacımusalar and Eşel 2018). Detection of biomarkers for depression will help with providing more accurate treatments, ensuring efficacious treatment and complete well-being, as well as determining new targets for the development of new antidepressant medicines (Mora et al. 2018, Gadad et al. 2018, Hacımusalar and Esel 2018).

The immune system is a complex structure with many cells and secretory factors that regulates inflammation in all tissues (Medina-Rodriguez et al. 2018). It has been suggested that inflammation is important in the etiopathogenesis of major depression and that inflammation markers can be used as markers for the diagnosis and treatment response to depression (Hacımusalar and Eşel 2018). Although changes in immune response elements in major depression have been shown by many studies, no consensus has been reached on the change in cytokine levels (Mora et al. 2018, Hacımusalar and Eşel 2018). In many studies, tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6) and interleukin-1β (IL-1β) levels were found to be significantly higher in both blood and cerebrospinal fluid of depression patients compared to healthy controls (Medina-Rodriguez et al. 2018). In addition, it has been reported that peripheral blood levels of many proinflammatory cytokines are higher in depression patients compared to healthy controls, and cytokine levels change with antidepressant treatment (Mora et al. 2018). In a study, it was reported that there was a significant correlation between treatment resistance, as assessed by number of failed antidepressant treatments and increased plasma TNF, tumor necrosis factor receptor-2 (sTNF-R2), IL-6 and C-reactive protein (CRP) concentrations (Haroon et al. 2018). According to the results of a meta-analysis, IL-6, TNF-α, interleukin-10 (IL-10) and CC chemokine ligand 2 (CCL-2) levels were found to be significantly higher in major depression patients compared to healthy controls, and it has been shown that there is a significant decrease in IL- 6, TNF-α, IL-10 and CCL-2 levels after antidepressant treatment (Kohler et al. 2018).

Oxidative stress is a condition associated with the deterioration of the balance between antioxidants and pro-oxidants in favor of pro-oxidants, and it has been suggested that oxidative stress plays a role in the pathophysiology of depression (Lopresti et al. 2014, Liu et al. 2015). There are studies reporting that the levels of lipid peroxidation products such as malondialdehyde (MDA) increase in depression patients, and that MDA levels decrease and return to normal with antidepressant treatment (Hacımusalar and Eşel 2018). Köhler et al. (2018) found that the first-episode depression patients had increased MDA and decreased superoxide dismutase (SOD) levels compared to healthy controls. According to the results of a meta-analysis, it was found that lipid peroxidation markers are elevated in depression patients, there is a relationship between the levels of these products and the severity of depression, and the levels of these markers decrease with antidepressant treatment (Mazereeuw et al. 2015).

In the literature, there are only few studies that investigates the relationship between treatment response and markers of inflammation and oxidative stress in depression patients together. In one of these studies, the relationship between oxidative stress and inflammation and treatment response was investigated in depression patients, and the initial F2-isoprostane (F2-iso) levels were found to be significantly lower in those who responded to treatment (Lindqvist et al. 2017).

There are some inconsistencies in the results of studies which investigate inflammation markers and oxidative stress markers together. It is believed that the reasons for this situation are the differences in the methods and patient group characteristics of the studies (Gadad et al. 2018). Detection of biomarkers is important in the diagnosis of depression, in determining which treatment method is more convenient in which patient and predicting the possible response to treatment. Therefore, there is a need for studies in this field especially in patient clusters with similar clinical characteristics (Gadad et al. 2018, Hacımusalar and Eşel 2018).

The goals of this study are as the following: (a) to determine the serum levels of oxidative stress markers (MDA and F2-isoprostane) and inflammation markers (TNF-α, IL-6 and CRP) in first-episode major depression patients and to compare them with those in the healthy control group, (b) to investigate whether the levels of these markers in the patient group changed after 8 weeks of treatment compared to pre-treatment, (c) and whether the baseline levels of these markers were associated with treatment response. The first hypothesis of the study is that peripheral blood levels of oxidative stress and inflammation markers will be higher in first-episode major depression patients compared to healthy controls. The second hypothesis is that the levels of these markers will decrease after treatment. The third hypothesis is that there will be a difference between those who respond to treatment and those who do not, in their pre-treatment levels of these markers. We believe that this study will contribute to both the clarification of the pathophysiology of depression and to the identification of biomarker candidates that can be used to diagnose depression and/or predict treatment response.

METHODS

Before starting the research, an application was made to the Çanakkale Onsekiz Mart University Rectorate Clinical Research Ethics Committee and ethics committee approval was obtained with the date of 28.11.2018 and decision number 21-10.1.2018.

For this study, the patient group was formed among the patients who applied to the outpatient clinics of Çanakkale Onsekiz Mart University Faculty of Medicine, Department of Psychiatry between 28 May 2019 and 4 December 2019, was diagnosed with MD according to the DSM-5 diagnostic criteria, were diagnosed with MD according to DSM-5 diagnostic criteria and decided to use a member of the selective serotonin reuptake inhibitors (SSRI) group in treatment. Among the 64 patients who were between the ages of 18-65 and met the inclusion criteria, 42 patients who volunteered to participate were included in the study. After the informed consent of the participants was obtained, a detailed clinical evaluation was made and the sociodemographic data form, Hamilton Depression Rating Scale (HAM-D) and Clinical Global Impression Scale (CGI) were applied for each patient. After the initial interviews were completed and the blood sample was taken, the predetermined treatment was started, and the study was completed with 30 patients as a result of 12 patients leaving the study during the 8-week follow-up period, which included a total of 2 interviews conducted every 4 weeks. After 8 weeks of treatment, blood samples were taken again from the patient group and the response to treatment was evaluated. The control group was formed with 30 healthy volunteers who were matched one-on-one with each patient who completed the study in terms of gender and smoking and after clinical evaluations were made and sociodemographic data form, HAM-D and CGI were applied, blood samples were taken.

Exclusion criteria for both patient and control groups are as the following: Having a history of any psychiatric disease that requires treatment; risky use of alcohol or alcohol use disorder, substance abuse; acute or chronic infectious disease or inflammatory disease, neurological disease, eating disorder, other chronic medical diseases (obesity, cancer, cardiovascular diseases, diabetes mellitus, thyroid diseases, etc.), being pregnant for female participants, using psychotropic medications and/or medicine that will affect the endocrine system or with anti-inflammatory or antioxidant properties in the last 6 months, a situation that prevents them from continuing the clinical interview and filling the scales (mental retardation, dementia, significant comprehension and speech difficulties due to previous cerebrovascular diseases, etc.). In addition, the condition of not having any comorbid psychiatric disease and not having depression with psychotic features was required for the patient group, while the condition of not having any psychiatric disease was sought for the control group. In order to minimize the possible undesirable effects on the results due to the different mechanisms of action of the medications, patients who were started on an antidepressant medication other than SSRI or who were recommended to use an additional medication for any reason were not included in the study.

All blood samples were taken between 09:00 and 11:00 in the morning after 12 hours of fasting and after 30 minutes of rest, and the serum samples obtained were stored at -40 °C until analysis. TNF α, IL-6, CRP, MDA and F2-isoprostane levels were measured in serum samples of all participants using ready-made kits by ELISA method. TNF α, IL-6, CRP and F2-isoprostane levels were calculated in ng/L (nanogram/liter), MDA levels were calculated in nmol/ml (nanomoles/milliliter). All clinical evaluations and blood sampling of the participants were completed on February 28, 2020. Those who showed a 50% or more decrease in their total score after 8 weeks of treatment compared to the initial HAM-D total score were considered as "treatment responders" while those with a HAM-D score of less than 7 and a CGI-Severity score of 1 after 8 weeks of treatment were considered to have shown "improvement".

Data Collection Tools

Sociodemographic Data Form: A questionnaire asking about the age, gender, educational status, occupation, marital status, medical background, alcohol and substance use status and medical family background of the individuals were developed by the researchers.

Hamilton Depression Rating Scale (HAM-D): Validity and reliability studies of this scale, which is applied by the clinicians, have been carried out in our country as well. It is a scale that measures the level of depression and changes in severity in the patient. The scale includes 17 questions, where each question is scored between 0 and 4. The total scale score is formed by adding the scores (Akdemir et al. 1996). According to the total scale score, the cut-off point was determined as 7. The total score is evaluated in favor of mild depression between 8-13, moderate between 14-18, severe depression between 19-22, and very severe depression above 23.

Clinical Global Impression Scale (CGI): In this scale, the severity of the disease is graded by the clinician between 1 (normal, not sick) and 7 (most severely ill) (Busner and Targum 2007). There is no study for the validity and reliability of the scale in our country.

Statistical Analysis

Data collected were analyzed using SPSS 19 statistical package program. Categorical variables were given as numbers and percentages. Whether the variables violated the normal distribution was evaluated with both analytical methods (Kolmogorov-Smirnov and Shapiro-Wilk tests) and visual data (histogram and probability graphs). The mean and standard deviation values were given for the numerical variables that fit the normal distribution. The median, interquartile range and minimum (lowest)- maximum (highest) values were given for the numerical variables that did not fit the normal

distribution. Pearson Chi-Square test, Continuity correction and Fisher Exact test were used when necessary in order to compare categorical variables between the patient and control groups. In cases where at least one of the variables did not fit the normal distribution or to determine the relationships between ordinal variables, correlation coefficients and statistical significance were determined using the Spearman Test. The Mann-Whitney U test was used for pairwise comparison of numerical variables between the control and patient groups, and the Wilcoxon test was used for the comparison of numerical variables before and after treatment in the patient group. BackWard logistic regression analysis was used to determine the factors affecting the treatment response. The level of significance was accepted as $p<0.05$.

RESULTS

The gender distribution was balanced in the patient and control groups of the study, and 80% (n=48) of all participants were female. It was observed that 33.3% (n=20) of all participants were smokers, and the distribution of smokers by gender was the same across the two groups. None of the participants had a history of substance use or suicide attempt. Some sociodemographic and clinical data of the participants are summarized in Table 1.

It was examined whether there was a significant difference in serum inflammation markers (TNF-α, IL-6 and CRP) and oxidative stress markers (MDA and F2-isoprostane) levels between the patient and control groups. The results are summarized in Table 2, Figure 1 and Figure 2.

For the HAM-D total scores of the participants in the patient group at the first examination, the median value was 14, the lowest value was 12, the highest value was 30, and the interquartile range was 6.75. According to the baseline HAM-D total scores of the patients, 40% were mild, 30% moderate, and 30% severe/very severe. The median CGI scale-disease severity scores of the patients in the patient group at the first examination were 4, the lowest value was 4, the highest value was 5, and the difference between quartiles was 0.25. It

Table 1. Comparison of age, Body Mass İndex, Smoking, Alcohol Use, and Some Sociodemographic Characteristics Between Groups

	Patient Group (n:30) Median (min-max) Interquartile range	**Control Group (n:30) Median (min-max) Interquartile range**	**p**
Age*	42.5 (20-59) 20.5	29 (23-64) 13.25	0.005
Total years of education*	12 (5-20) 9	18 (5-20) 8	< 0.001
Body Mass Index*	23.2 (18.6-24.9) 2.7	21.7 (18.7-24.9) 3.8	0.093
Living in urban area**	63.3% (19)	100% (30)	< 0.001
Living in rural area	36.7% (11)	0% (0)	
Employed**	26.7% (8)	73.3% (22)	< 0.001
Unemployed	73.3% (22)	26.7% (8)	
Lives alone**	10% (3)	36.7% (11)	0.015
Lives with relatives	90% (27)	63.3% (19)	
Family history of psychiatric disease**	23.3% (7)	16.7% (5)	0.519
No family history of psychiatric disease	76.7% (23)	83.3% (25)	
Alcohol **	16.7% (5)	33.3% (10)	0.136
No alcohol	83.3% (25)	66.7% (20)	
Smoker	33.3% (10)	33.3% (10)	
Non-smoker	66.6% (20)	66.6% (20)	
Other medical disease	3.3% (1)	3.3% (1)	
No other medical disease	96.7% (29)	96.7% (29)	
On medication	3.3% (1)	3.3% (1)	
Non-medicated	96.7% (29)	96.7% (29)	

*Mann-Whitney U Test was used. Min: lowest value, Max: highest value
** Chi-square test was used.

Table 2. Comparison of the Levels of Markers of Inflammation and Oxidative Stress Between Groups

	Patient Group (n:30) Median (min-max) Interquartile range	Control Group (n:30) Median (min-max) Interquartile range	p *
CRP	13.66 (4.95-15.36) 2.51	13.38 (3.49-14.38) 2.95	0.044
IL-6	70.15 (41.15-1265.27) 404.59	59.52 (5.13-139.12) 95.90	0.015
TNF- α	44.45 (20.14-833.93) 224.62	42.26 (2.89-84.97) 68.29	0.055
MDA	6.49 (0.07-118.55) 42.15	4.75 (0.20-13.34) 6.58	0.03
F2-iso	86.19 (56.46-1288.39) 404.90	642.12 (71.04-1434.27) 1039.12	0.0004

*Mann-Whitney U Test was used. Min: lowest value, Max: highest value

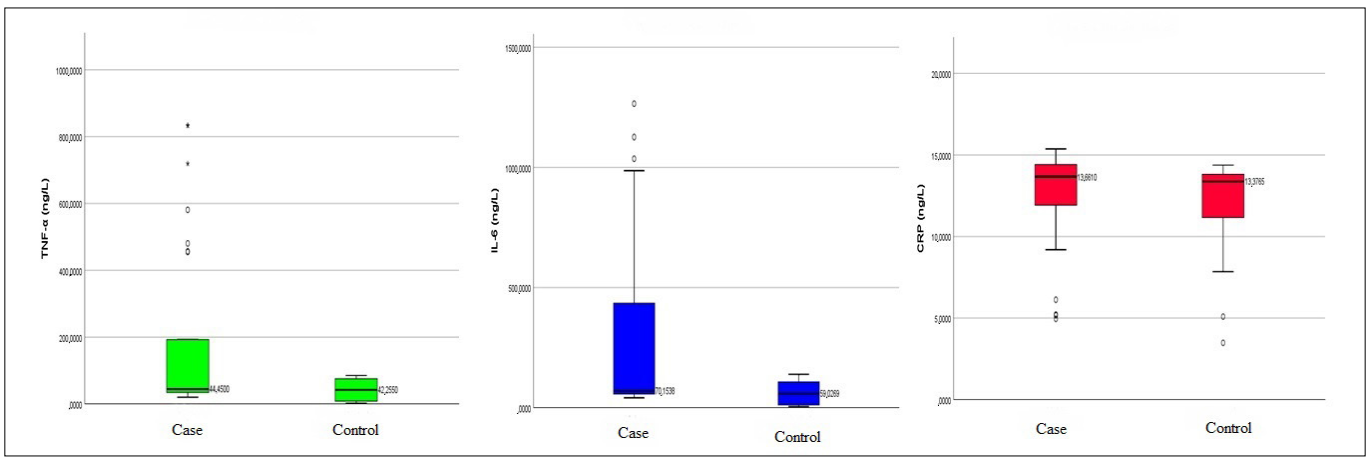

Figure 1. Comparison of TNF-α, IL-6 and CRP levels in the case and control groups.

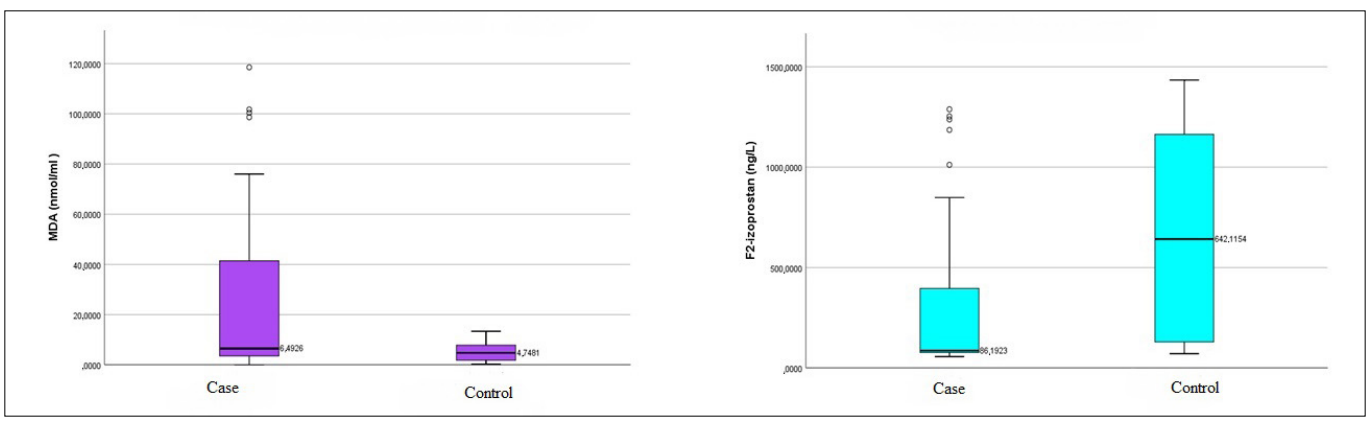

Figure 2. Comparison of MDA and F2-isoprostane levels in case and control groups.

was observed that the participants in the healthy control group did not have any depressive symptoms and all of them scored 0 on the HAM-D scale. The CGI scale-disease severity score for each healthy control was also assessed as 1 (normal, not sick).

The relationship between the variables of the patients was examined and as a result of the correlation analysis. Significant correlations were found between the treatment response and gender (rho=0.582, p<0.01), alcohol use status (rho=-0.447, p<0.05), and initial F2-isoprostane level (rho=-0.391, p<0.05). Accordingly, a positive correlation was found between responding well to treatment and being female, while a negative correlation was found between alcohol use and initial F2-isoprostane levels (see Table 3).

It was investigated whether there was a difference between the levels of inflammatory markers (TNF-α, IL-6 and CRP) and oxidative stress markers (MDA and F2-isoprostane) in the serum obtained from the blood samples taken before the treatment and the blood samples taken 8 weeks after the treatment of the first-episode depression patients (see Table 4, Figure 3, and Figure 4 for the summary of the results).

Table 3. Correlation Analyzes of Patients' Baseline Marker Levels, Gender, Alcohol Use Status, and Treatment Response Variables

	Gender	Alcohol use	CRP	IL-6	TNF- α	MDA	F2-iso	Treatment response
Cinsiyet	1.000	-0.447*	0.010	-0.106	0.000	0.000	-0.125	0.582**
Alcohol use	-0.447*	1.000	0.078	-0.160	-0.243	-0.367*	-0.098	-0.488**
CRP	0.010	0.078	1.000	0.027	0.133	0.060	-0.076	-0.155
IL-6	-0.106	-0.160	0.027	1.000	0.903**	0.622**	0.823**	-0.189
TNF- α	0.000	-0.243	0.133	0.903**	1.000	0.668**	0.834**	-0.214
MDA	0.000	-0.367*	0.060	0.622**	0.668**	1.000	0.605**	-0.147
F2-iso	-0.125	-0.098	-0.076	0.823**	0.834**	0.605**	1.000	-0.391*
Treatment response	0.582**	-0.488**	-0.155	-0.189	-0.214	-0.147	-0.391*	1.000

Spearman correlation analysis was applied. The numbers represent the Spearman correlation coefficient (rho).
* p<0.05 ** p<0.01

Table 4. Comparison of Inflammation and Oxidative Stress Markers Levels Before and After Treatment

	Pre-treatment (n:30) Median (min-max) Interquartile range	Post-treatment (n:30) Median (min-max) Interquartile range	p *
CRP	13.66 (4.95-15.36) 2.51	14.02 (2.23-15.03) 3.20	0.894
IL-6	70.15 (41.15-1265.27) 404.59	66.67 (19.92-1177.12) 354.673	0.032
TNF- α	44.45 (20.14-833.93) 224.62	39.06 (15.88-842.05) 261.13	0.041
MDA	6.49 (0.07-118.55) 42.15	5.72 (0.00-105.83) 24.31	0.001
F2-iso	86.19 (56.46-1288.39) 404.90	77.15 (36.92-1207.89) 373.59	0.00026

*Two-sided p-value determined using the Wilcoxon test. Min: lowest value, Max: highest value

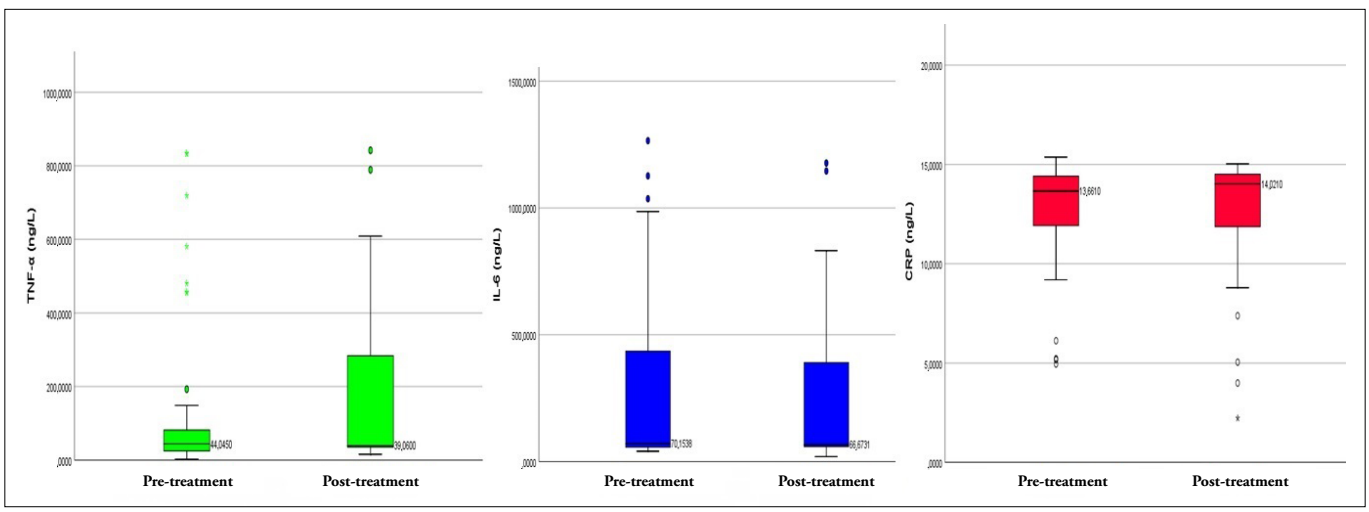

Figure 3. Comparison of TNF-α, IL-6 and CRP levels before and after treatment.

The median value of the HAM-D total scores at the first examination of the patient group was 14, the lowest value was 12, the highest value was 30, and the interquartile range was 6.75. In the control examination performed 4 weeks later, the median value of HAM-D total scores was 6.5, the lowest value was 1, the highest value was 16, and the interquartile range was 6. In the control examination performed after 8 weeks, the median value for HAM-D scores was 3, the lowest value was 0, the highest value was 13, and the interquartile range was 6.25. At the end of eight weeks, it was observed that all 21 patients who responded to the treatment (HAM-D total scores decreased by 50% or more from baseline) also showed 'improvement' (HAM-D total scores of 7 or lower). While the median value of HAM-D total score at the first examination of the responders was 14, the lowest value was 12, the highest value was 30, and the interquartile range was 8.5; the median for those who did not respond to treatment was 14, the lowest value was 12, the highest value was 21, the interquartile range was 5.5. This difference was not statistically significant (p=0.41). It was examined whether the

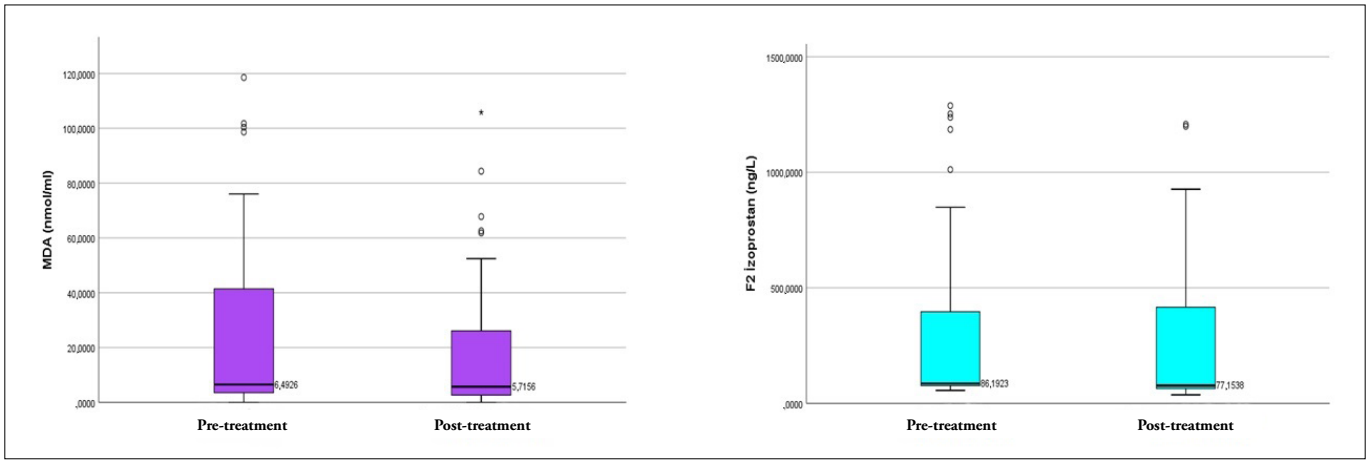

Figure 4. Comparison of MDA and F2-isoprostane levels before and after treatment.

Table 5. Comparison of Pre-treatment Levels of Markers Between Treatment Responders and Non-responders

	CRP	IL-6	TNF- α	MDA	F2-iso
Treatment responders (n= 21)					
Median	14.02	77.23	46.33	7.06	92.58
Minimum	5.22	41.15	23.88	1.100	56.46
Maximum	15.37	1265.27	833.93	118.55	1288.39
Interquartile range	1.83	748.14	431.32	58.29	791.115
Non-responders (n= 9)					
Median	13.33	63.15	42.44	5.93	76.77
Minimum	4.95	48.08	20.14	0.0074	61.35
Maximum	14.83	539.85	456.72	76.05	848.77
Interquartile range	8.88	59.87	64.6	37.52	171.29
p*	0.402	0.309	0.249	0.428	0.035

*Mann-Whitney U Test was used.

Table 6. Logistic Regression (backward) Analysis Model Examining the Effects of Gender, IL-6 and MDA Levels on Treatment Response

	BETA	Standard error	P	Odds Ratio (OR)	95% Confidence Interval for OR
Gender	6.037	3.388	0.70	418.757	0.604-290429.659
IL-6	-0.012	0.006	0.032	0.988	0.977-0.999
MDA	0.097	0.048	0.044	1.102	1.002-1.211

Nagelkerke R^2=0.654

baseline levels of the markers differed between patients who responded to treatment (n:21) and non-responders (n:9) and the results are shown in Table 5.

When the initial serum values are compared; TNF-α, IL-6, CRP and MDA levels did not show a statistically significant difference between those who responded to treatment and those who did not. Baseline F2-isoprostane values were significantly higher in responders compared to nonresponders (p=0.035).

The gender variable, which was found to be significantly correlated (p<0.05), with univariate analyses of the factors that may be associated with the response to treatment of first-episode depression patients, some variables associated with Type I error level p<0.25 (IL- 6, CRP and MDA) were evaluated with the logistic model and the model including gender, IL-6 and MDA was found to be valid. As a result of the logistic regression (backward) analysis, it was determined that the risk of not responding to treatment increased 1.102 times with a 1-unit increase in MDA. It was observed that the probability of responding to treatment increased by an increase in IL-6 value (OR=0.988, 95% CI=0.977-0.999). As a result of logistic regression analysis (Backward), the CRP variable included in the model was not associated with treatment response (Table 6).

DISCUSSION

In our study, IL-6, CRP and MDA levels were found to be significantly higher and F2-isoprostane levels were lower in first-episode MD patients compared to the healthy control group, but there was no significant difference between the groups in terms of TNF-α levels. Thus, it has been shown that there are some changes in the inflammatory system and oxidative stress in first-episode MD patients. While significant decreases were observed in TNF-α, IL-6, MDA, and F2-isoprostane levels after treatment with one of the medications in the SSRI group for 8 weeks in first-episode MD patients, there was no statistically significant change in CRP levels between before and after treatment measurements. With these findings, attention was drawn to the effect of treatment with an antidepressant from the SSRI group on the levels of this biomarker in first-episode MD patients. When the initial serum values were compared between those who responded to 8 weeks of treatment and those who did not; TNF-α, IL-6, CRP and MDA levels were not statistically significantly different, whereas baseline F2-isoprostane levels were significantly higher in responders compared to non-responders. No statistically significant correlation was found between baseline TNF-α, IL-6, MDA, and CRP levels and treatment response.

It was found that IL-6, CRP and MDA levels were statistically significantly higher in first-episode MD patients compared to the control group. These results are consistent with the knowledge that the levels of inflammation markers (Osimo et al. 2020, Hashimoto 2015) and oxidative stress markers (Lopresti et al. 2014, Liu et al. 2015, Mazereeuw et al. 2015, Lindqvist et al. 2017, Palta et al. 2014) increase in depression patients, which has been found in many existing studies and meta-analyses. In the study reported, there were no statistically significant differences between the patient and control groups in terms of TNF-α levels. Although most studies and meta-analyses in the literature have shown that TNF-α levels significantly increase in depressed patients, this is not true for all studies, and there are studies reporting that there is no increase in TNF-α levels in depressed patients compared to healthy controls (Himmerich et al. 2019, Köhler et al. 2017). It can be suggested that among the possible reasons for the conflicting findings related to TNF-α in depression is the presence of confounding factors such as chronic diseases, the different biochemical measurement methods, and the lack of clinical homogeneity of the patients (first-episode or recurrent episode, presence of other medical problems, taking medication, type of depression, etc.) participated in the studies. It is possible that the younger age group of the healthy control group compared to the patients in our study affected the results. It is reported in the literature that as age increases, CRP (Cattaneo et al. 2015), TNF-α and IL-6 (Himmerich et al. 2019) levels also increase. Although there is information that MDA levels do not change with age (Tsikas 2017), and that F2-isoprostane levels are not associated with age (Czerska et al. 2015), it can be thought that age may have affected the levels of these markers. Due to this age difference between the patient and control groups in our study, it is thought that the results, especially the findings related to inflammatory markers, may have been affected.

In this study, it was observed that F2-isoprostane levels were significantly lower in the patient group compared to the healthy control group. Contrary to this result, previous studies that evaluated F2-isoprostane levels in patients with depression reported higher levels in the patient group compared to the control group (Lopresti et al. 2014, Liu et al. 2015, Mazereeuw et al. 2015, Lindqvist et al. 2017, Palta et al. 2014). In a study, it has been reported that oxidative stress markers, especially F2-isoprostane levels, change in parallel with estradiol concentrations during the menstrual cycle (Schisterman et al. 2010). It was thought that the reasons such as 80% of the participants in our study were women and the healthy control group was younger than the patient group, lack of data on the stage of the menstrual cycle and estrogen levels of female participants at the time of sampling, may be among the possible reasons for the higher F2-isoprostane levels in the healthy control group. It is thought that the inconsistent findings from time to time in studies evaluating oxidative stress markers may also play a role in the failure to evaluate the levels of menstrual cycle and reproductive hormones (Schisterman et al. 2010) Future studies designed by taking this into account are much needed.

As a finding similar to the decrease in TNF-α and IL-6 levels after treatment in our study, in a meta-analysis, it was reported that TNF-α and IL-6 levels were decreased with antidepressant treatment (Köhler et al. 2018). It has been reported that TNF-α, IL-6 and CRP levels, which were elevated in depression patients, returned to normal with antidepressant treatment (Hacımusalar and Esel 2018, Park et al. 2019). As a result of a meta-analytical evaluation, it was reported that there was no change in the levels of many markers, including IL-6 and CRP, after treatment, while TNF-α levels decreased only in those who responded to treatment (Liu et al. 2020). In the light of all this information, although it has been reported that inflammatory markers, especially TNF-α, IL-6 and CRP, decrease after antidepressant treatment in a significant part of other studies, there are also studies reporting a decrease in some markers, while no significant change was observed in some. In the previous studies, it is seen that there are results that show a significant change between antidepressant treatment and CRP levels, but there are also study results that did not show any difference (Hashimoto 2015). In our study, while TNF-α and IL-6 levels were found to decrease with antidepressant treatment, no significant change was observed in CRP levels.

In a significant number of studies, it was reported that MDA levels decreased and returned to normal following antidepressant drug treatment (Lopresti et al. 2014, Liu et al. 2015), and F2-isoprostane levels decreased with antidepressant treatment (Lindqvist et al. 2017). Although findings similar to our study, such as a decrease in MDA and F2-isoprostane levels after treatment, were obtained in previous studies, there are also studies that did not detect a decrease in oxidative stress markers with treatment. It can be thought that the heterogeneity in the design of the studies, such as the sample sizes of the studies, the clinical characteristics of the participants, the status of the confounding factors, the biochemical measurement methods used, the duration of the treatment or the medications used, may have caused this situation (Palta et al. 2014). Although the results of studies investigating the effects of antidepressant treatment on the levels of inflammation and oxidative stress markers are not consistent, there is strong evidence that the levels of these markers decrease with treatment (Hacımusalar and Eşel 2018, Haroon et al. 2018, Liu et al. 2015). In our study, there was a significant decrease in TNF-α, IL-6, MDA and F2-isoprostane levels after treatment, but no significant difference was found in CRP levels. Based on this information, it can bethought that inflammatory processes and oxidative stress are associated with depression and antidepressant treatment, but it is seen that there may still be other mechanisms and interactions that need to be explained about the direction and nature of this relationship.

In our study, after 8 weeks of treatment, 'improvement' was observed in all of the patients who responded to the treatment at the same time. There was no significant difference between those who responded to treatment and those who did not in terms of initial levels of TNF-α, IL-6, CRP and MDA. It was found that F2-isoprostane levels before treatment were significantly higher in treatment responders than in non-responders. This finding is not consistent with a previous similar study reporting that F2-isoprostane levels were found to be lower in responders (Lindqvist et al. 2017). On the other hand, Lindqvist et al., in their study, stated that it is remarkable that they found a relationship between high F2-isoprostane levels and poor response to treatment, but also they stated that it should be considered as a preliminary finding and stated that since the treatment response was evaluated with a small number of patients, it is necessary to confirm the results with larger-scale repeated studies (Lindqvist et al. 2017). Again, in the same study, it was reported that no significant relationship was found between the treatment response and the initial levels of CRP, IL-6, and TNF-α, and this may be due to the small sample size (Lindqvist et al. 2017). In our study, it is possible that reasons such as the fact that most of the patients were female and that menstrual cycle periods or reproductive hormone values were not evaluated, may create an important limitation especially by affecting F2-isoprostane levels. Therefore, new studies designed by considering all confounding factors are needed.

There are many studies, meta-analyses and reviews reporting that the high level of markers such as IL-1, IL-6, TNF-α and CRP seen in depression patients is associated with treatment unresponsiveness to antidepressants (Hacımusalar and Eşel 2018, Syed et al. 2018, Eller et al. 2008). On the other hand, there are also studies reporting results that are inconsistent with these findings. For example, in a study, it was reported that basal plasma IL-6 levels were found to be significantly higher in those who responded to treatment with SSRI than in those who did not (Yoshimura et al. 2013). In another study, it was reported that there is a relationship between good response to amitriptyline in long-term treatment and high pre-treatment CRP levels (Harley et al. 2010). These findings suggest that the use of inflammatory biomarkers in the clinic requires further validation in larger samples (Mora et al. 2018). In our study, in the logistic regression (backward) analysis performed to examine the variables that may be related to the response to treatment of first-episode depression patients: included gender, IL-6 and MDA. The model was found valid. It was seen that the risk of not responding to treatment increased by 1.102 times with a 1-unit increase in MDA, and the probability of responding increased 1.012 times in case of an increase in IL-6 value. These findings suggest that even if the markers alone are not sufficient to predict treatment response, models that evaluate multiple markers together can predict treatment response.

It is known that both inflammation markers and oxidative stress markers can be affected by many conditions such as Acute (such as infectious diseases) and chronic diseases (especially obesity, cancer, cardiovascular diseases, diabetes mellitus, thyroid diseases, etc.), medicine use, smoking, substance use, heavy alcohol use, and previous psychiatric illness (Liu et al. 2015, Himmerich et al. 2019, Ambrosio et al. 2018, Czerska et al. 2015). For this reason, these characteristics were taken into account in the determination of both first-episode depression patients and healthy volunteers to participate in the study. Although it was aimed to match one-to-one regarding age, this goal could not be achieved because the study had to be completed quickly in order not to affect the results of the study due to the Covid-19 pandemic during the conduct of the study. The volunteers in the healthy control group were younger than the patients, and this is the most important limitation of our study. Although it is known that depression is more common in women than men, the fact that the majority of the participants were women can be considered as another limitation of the study. The fact that female participants are in the majority leads to a significant limitation as the stage of the menstrual cycle and reproductive hormone levels of the participants are not evaluated when

blood samples are taken, and it can be thought that this situation may have affected especially F2-isoprostane levels. In order to clarify this issue, studies with large samples are needed, in which the ratio between male and female patients is similar to that in the population, and the menstrual cycle and reproductive hormone levels in female participants are taken into account. Despite these limitations, the strength of our study is recruting the evaluation of first-episode MD patients (patients who have not had any psychiatric disease and have not been treated before), which constitutes the patient group, and thus, enabling the examination of the relationship between MD and inflammatory and oxidative processes without the effect of recurrent depression episodes.

Another strength of our study is that the markers of inflammation and oxidative stress were evaluated together. The findings obtained as a result of examining the inflammation and oxidative stress status both before and after treatment, as well as evaluating the relationship between treatment response and inflammation and oxidative stress, especially in first-episode depression patients, contribute to the elucidation of the pathophysiology of depression and the detection of possible biomarkers that could be used in the diagnosis and determination of treatment.

In conclusion, in the light of the findings of our study, it was determined that there are irregularities in terms of inflammatory processes and oxidative stress in major depression patients, even during the first-episode and without any medicine. These irregularities can be improved by treating the disease with antidepressant medicine, and it seems promising in terms of finding markers that can be associated with treatment response. However, there are still many issues to be clarified in this area. In order to reveal how and to what extent inflammatory and oxidative stress markers can be used as biomarkers in the diagnosis and treatment process, future studies with large sample sizes, evaluating all possible confounding factors, investigating many markers together, and including diagnosis and treatment processes with long follow-up periods are needed.

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Effects of Problem Solving Therapy in Substance Use Disorder in Adolescents

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ABSTRACT

Objective: In this study, it was aimed to examine the effects of problem solving therapy, which is a cognitive behavioral method, on adolescents diagnosed with alcohol and substance use disorder.

Method: A semi-structured interview and intelligence test were administered to adolescents with diagnosis of substance use disorder to identify comorbidities. 46 adolescents who met the inclusion criteria were divided into two groups. Problem solving therapy was applied to the first group for 5 weeks, once a week, while the other group continued their routine controls in the center. Beck Depression Inventory, Screen for Child Anxiety Disorders, Revised Social Problem Solving Inventory, Addiction Profile Index and Treatment Motivation Questionnaire were administered to the groups at the beginning of the study and at the end of the 5th week and the results were analyzed.

Results: Sociodemographic and substance use characteristics, comorbid psychopathologies and scale mean scores of the groups in the first evaluation were found to be similar to each other. Although the depression and anxiety scores decreased significantly in both groups, no significant difference was found between the groups. Problem-solving skills and treatment motivation increased in the therapy group and decreased in the control group. The difference between groups was found to be significant (p=0.045, 0.037 for problem solving and treatment motivation respectively). While the severity of addiction decreased in therapy group, it increased in control group, but the difference was not significant.

Conclusion: This study is important in that it shows that psychosocial interventions strengthen the treatment of substance use disorder in adolescents. In our country, no other study was evaluating the effects of the intervention methods in addicted adolescents was found. Future studies with larger sample sizes and where the long-term results of substance use disorder are evaluated are needed.

Keywords: Adolescent psychiatry, substance-related disorders, cognitive therapy, psychotherapy, group psychotherapy

INTRODUCTION

Problem Solving Therapy (PST) is a therapy method that uses Cognitive Behavioral Therapy (CBT) techniques to solve psychological problems caused by daily life's challenges. The objective of PST is to teach individuals how to tackle encountered problems and also to teach about problem solving paths and strategies. The goal of PST is to cure the psychological distress caused by such problems and also prevent distress before it happens. In other words, PST is used both in therapy and in prevention; it is also utilized in gaining resilience or enhancing inherent capacity (Eskin 2011).

PST can be used in mental healthcare to treat different psychopathologies. A recently published meta-analysis encompassing 30 studies (with a total of 3530 patients) has concluded that PST is effective in the treatment of depression, with its impact dimension being found low yet comparable to other psychosocial treatment options (Cujipers et al. 2011). A meta-analysis that assesses PST use in primary healthcare found that PST is effective in anxiety disorders and depression (Zhang et al. 2018). A randomized controlled study comparing the use of PST with motivational interview (MI) in the treatment of substance use disorders has shown that, against MI only, the use of PST+MI together significantly decreased

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screening test scores (Sorsdahl et al. 2015). In another study investigating the use of PST in adolescents and young adults, results showed that there was a significant decrease in depression and suicide risk scores of the PST group compared to the wait list group (Eskin et al. 2007).

The treatment of addiction in adolescence is a long-term process as in all age groups. Adolescent addiction treatment should include multidimensional biopsychosocial interventions. Psychosocial interventions should be among the top priority approaches in adolescent addiction treatment. Such approaches include 12-step therapy, therapeutic communities, family-based therapies, behavioral approaches, individual and/or group Cognitive Behavioral Therapy (CBT) approaches. The purpose of CBT is to identify circumstances that trigger substance use in adolescents, develop coping mechanisms appropriate to these situations, and enhance communication and problem solving skills.

A study conducted with adolescents and young adults with substance use problems has shown that such individuals took up maladaptive problem solving methods to a greater extent. A 2009 study investigated the relationship between problem solving, personality characteristics and substance use among 307 high-school students. The study in question has revealed that hopelessness had a significant negative impact on rational problem solving skills (Winters et al. 2011). For such reasons, it is considered that applying problem solving therapy to adolescents who struggle with substance use disorders would increase their problem solving skills, decrease the intensity of comorbid conditions and contribute positively to addiction treatment.

There is a lack of studies which discuss non-pharmacologic treatment options and specialized intervention methods in adolescent addiction. Therefore, the purpose of the present study is to investigate the effects of "problem solving therapy" as an intervention method on adolescents who suffer from substance use disorders.

METHOD

Study Design and Sample

This study was designed to be prospective and experimental. The blinding procedure was not applied during the assignment of cases included in the study to groups. At the beginning, it was planned to include 30 persons per group, totaling up to 60 people. Because of time limitations and the need to see the effectiveness of this application, cases included in the study were primarily assigned to the PST group. The control group was formed after the PST group. We were able to reach 16 cases for the control group. Following this, a power analysis was conducted as the study ran. Sample size of the study was calculated by using the G*Power software package (Faul et al. 2009). Duplicate measurement results showed that in order to achieve an 80% statistical power with an alpha error rate of 0.05 and Cohen's effect size of 0.30, the required sample size was at least 12 participants per group. Due to time limitations and the fact that the required number of cases as calculated under the power analysis was reached, no further cases were added to the control group.

The study sample consists of 46 adolescents between the ages of 14-18 who are first application or follow-up patients diagnosed with alcohol/substance use disorder (ASUD) at Child and Adolescent Alcohol-Substance Addiction Research and Application Center. All subjects participated in the study on a voluntary basis. At the beginning 40 cases were included in PST group; however, 10 of them were subsequently excluded from the study. Of these 10 cases, 4 were excluded due to absenteeism, 2 due to displaying mental retardation (IQ<70) as a result of the intelligence tests performed, 1 due to attending the sessions under the influence and the remaining 3 cases due to missing data in the scales. The control group consisted of 20 cases, with 4 of them being excluded from the study later on. The reasons for exclusion for these 4 cases are as follows: according to the structured interview conducted, 1 of them had a psychotic disorder; 2 were excluded because of missing data in the second scale, and 1 case was excluded due to missing data in all scales. The study was completed with 46 participants with 30 cases in the PST group and 16 cases in the control group. Before participating in the study, a written statement of informed consent was taken from patients and their first degree relatives or their legal guardians (as per the Helsinki Declaration). An approval was received from Ege Faculty of Medicine Ethics Committee with the decision dated 29.06.2015 and numbered 15-5.1/5.

Inclusion and Exclusion Criteria

Volunteer cases between 14-18 years of age diagnosed with alcohol/substance use disorder (ASUD) according to the DSM-5 criteria (Diagnostic and Statistical Manual of Mental Disorders) (American Psychiatric Association 2013) were included in the study. Cases who had a mental retardation diagnosis or psychopathologies which prevent them from attending the sessions were excluded from the study. Cases who did not obey group rules, who were coming to sessions under the influence, absent for more than two sessions and wished to be excluded from study were also excluded from study.

Data Collection Tools

Socio-Demographic Information Form

This form was prepared by researchers to collect information on age, gender, educational status, family type, socioeconomic status, place of residence, status of parents, personal background, and family history.

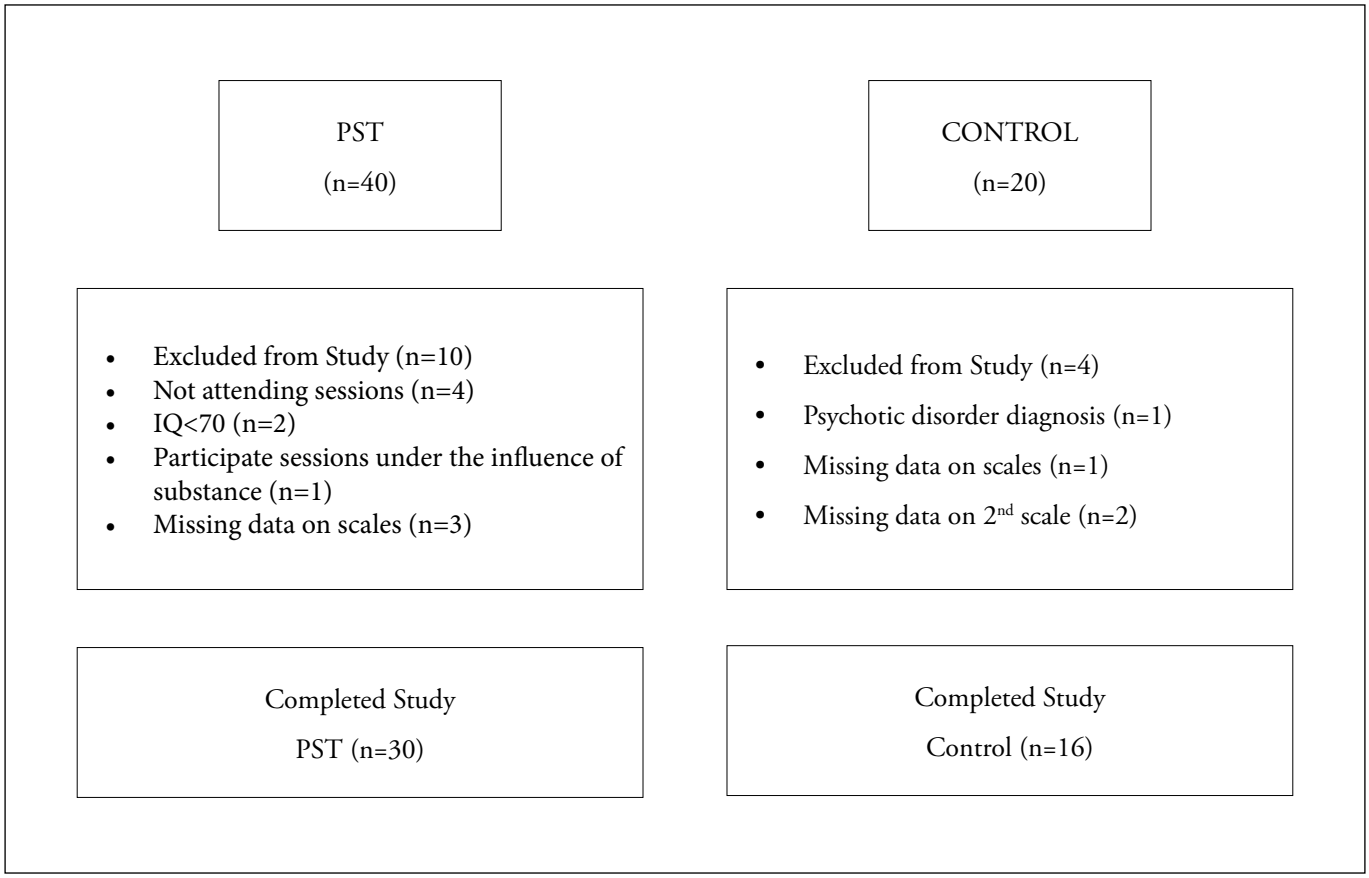

Figure 1. Flow Chart

PST: Problem Solving Therapy, IQ: Intelligence Quotient

Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL)

K-SADS-PL is a semi-structured interview form that aims to identify present and lifetime psychopathologies in children and adolescents. The form consists of three sections. Reliability and validity of the scale for the Turkish sample was ensured (Kaufman et al. 1997, Gökler et al. 2004).

Beck Depression Inventory (BDI)

Beck depression inventory (BDI) is a self-report scale developed by Beck in 1961 for the purpose of evaluating emotional, cognitive, somatic and motivational components of depression. Even though its primary aim is to assess depressive symptoms it also enables the evaluation of cognitive contents. Scale scores range between 0-63. Any score equal to or above 10 is considered as a signifier for depression. Validity and reliability of BDI for the Turkish society was provided (Beck 1969, Hisli 1989).

Treatment Motivation Questionnaire (TMQ)

It is a self-report 5 point Likert scale with 26 items, developed to measure reasons of participating and continuing alcohol/substance use treatment. Scale was developed by Ryan et al. in 1995 and in 2006 reliability and validity study was conducted by Evren et al. (Ryan et al. 1995, Evren 2006).

Social Problem-Solving Inventory-Revised (SPSI-R)

The scale developed by Maydeu-Olivares and D'Zurilla between 1995-96 was revised later on in 2002. The inventory consists of 2 main domains that identify problem orientation and problem solving methods with subdomains for each domain. These are:

"Positive Problem Orientation, Negative Problem Orientation, Reasoning, Handicapping, Failure Avoidance, Problem Solving". Social Problem-Solving Inventory-Revised (SPSI-R) was translated into Turkish and its reliability and validity was ensured by Eskin and Aycan (D'Zurilla et al. 2002, Eskin 2009).

Addiction Profile Index (API) Adolescent form

API was developed by Ögel et al. They also provided the reliability and validity of this scale. The scale consists of 25 items and 5 subdomains (diagnosis, characteristics of substance use, the effect of the substance on person's life,

craving and motivation). It is a self-report, 5-point Likert scale (Ögel et al. 2012).

Screen for Child Anxiety Related Emotional Disorders (SCARED)

Screen for Child Anxiety Related Emotional Disorders (SCARED) scale was developed by Birmaher et al. (1999) for screening childhood anxiety disorders. Its reliability and validity was ensured by Çakmakçı (2004). Child and parent forms of the scale are available. The SCARED scale consists of 41 items, with a total score of 25 and above being considered as a warning sign for anxiety disorder (Birmaher et al. 1999, Çakmakçı 2004).

Wechsler Intelligence Scale for Children-Revised (WISC-R)

Wechsler Intelligence Scale for Children was developed by Wechsler in 1949 to measure the intelligence of children between the ages of 5-15. In 1974, it was revised and the applicable age group was updated to between 6-16 years old. Adaptation of WISC-R for the Turkish culture was performed by Savaşır and Şahin (Wechsler 1974, Savaşır 1995).

Wechsler Adult Intelligence Scale (WAIS)

WAIS is a scale that evaluates intelligence on a multidimensional level and is applied individually. In 1945 when Wechsler developed WAIS, it could be administered to individuals at the age of 16 and above, with 11 sub-tests evaluating verbal and performance skills. Reliability and validity of the Turkish version of the scale was provided by Epir and İskit. Even though the reliability and validity of the scale was ensured, Turkish norms are not yet available (Wechsler 1974, Epir 1972).

Procedure

This study started after introducing the aim of the research, answering the questions of volunteers and signing of the informed consent forms. All cases included in the study were administered with the K-SADS-PL, which is a test assessing sociodemographic characteristics and comorbid psychiatric disorders, during a clinical interview in the first application. After that, in order to determine intelligence level of cases, WISC-R was administered to cases under 16 years old and WAIS was administered to cases who were aged 16 years and above. The PST group consisted of 30 cases, and the study was completed by dividing them to sub groups with each group including a minimum of 5 and maximum 10 cases.

Two specialists ran the PST sessions together the first is a lecturer and Mental Health Specialist as well as a cognitive behavioral therapist; the second one is a Research Assistant in Child and Adolescent Psychiatry. Before starting the procedure, a meeting was held with Prof. Dr. Mehmet Eskin who pioneered the use of PST in Türkiye and conducted studies in this area. The researchers received training on problem solving therapy. The training materials were obtained and studies in the field of PST were examined. The contents of structured sessions were prepared together.

All cases included in the study group were administered with problem solving therapy. PST involves 8 stages. In this study, for the regular attendance of adolescents, therapy sessions were planned to be completed in 5 weeks and each session lasted 45 minutes. During this time, outpatient follow-up controls of cases continued without interruption. In sessions participants played warm-up games; then the agenda was set with theoretical explanations always being supported with practice, and at the end homework was given. During the sessions, the story of an addicted adolescent was told; examples from this story were given to facilitate the active participation of the cases in detecting problems and finding solution options. Cases included in the control group continued their regular follow-ups in the center. Social Problem-Solving Inventory-Revised (SPSI-R), Beck depression inventory (BDI), Screen for Child Anxiety Related Emotional Disorders (SCARED), Addiction profile index (API) (adolescent form) and Treatment motivation questionnaire (TMQ) were administered to all cases at the beginning of study and on the 5th week of the study.

Stages of Problem Solving Therapy

Evaluation and debriefing interview: This constitutes the first interview with participants. The aim of this stage is to create a collaborative trust environment by evaluating the individual's existing complaints and their problem solving skill levels and informing them about the content of therapy.

Problem orientation training: The purpose of this second session is to assist individuals in recognizing their existing problems and exhibiting positive attitude while tackling these problems. In this stage, our aim was to develop a mindset of positive problem orientation in our cases. This mindset involves believing that problems can be solved, seeing problems as a part of life, and not evading the issues.

Describing problems: In this stage, reasons or problems that contribute to existing distress or complaints of individuals are identified and formulated. The aim is to evaluate and describe problems that can cause distress by answering the questions of where, when, how often and with whom these problems occur.

Setting goals: After overcoming existing problems, the individual tries to evaluate his/her current situation and set goals with a realistic attitude. This session is centered around the question of whether the goals set by the individual have to do with changing the problem or decreasing the emotional impact thereof.

Coming up with possible solution options: The aim of this stage is to create as many solutions as possible to the existing problem. All possible solutions are noted down without discussing whether it is suitable or effective.

Choosing a suitable solution option: All solution options are evaluated according to their problem solving and goal achieving power and acceptability and applicability with the highest rated option being selected at the end.

Implementing the solution: This is the stage where the individual is prepared for the implementation. For this, all advantages and disadvantages of such implementation are discussed with the person in advance.

Evaluation of the Procedure: At this stage, results of the implementation are evaluated by asking whether the problem is solved or not, and whether the goal is achieved or not. In the case of an unsuccessful implementation, all stages are reviewed. If there is an error in the implementation of a particular stage, the procedure is backtracked and started again from there.

In our study, the 8-stage PST sessions were administered as follows:

1. Week: Evaluation, debriefing, and problem orientation training (1. and 2. stages)

2. Week: Describing problems (3. stage)

3. Week: Setting goals and coming up with possible solution options (4. and 5. stages)

4. Week: Choosing the suitable solution option and implementing the chosen solution (6. and 7. stages)

5. Week: Evaluating the whole procedure (8. stage)

Statistical Method

The data was evaluated with the SPSS (The Statistical Package for Social Sciences) 22.0 software package. Normality assumption was evaluated by using the Shapiro-Wilk and Kolmogorov-Smirnov tests for normality. Chi-Square test, independent samples T-test and McNemar test were used for the comparison of the groups. In repeated application of scales for evaluating the potential differences between groups, "repeated measures analysis of variance" was used, with $p<0.05$ being accepted as statistically significant. In order to show the significance level of findings, the p value was input directly.

RESULTS

The PST group consisted of 16 (53.3%) girls and 14 (46.7%) boys. The control group consisted of 5 (31.2%) girls and 11 (68.8%) boys. The mean age of participants was 16.3 (PST: 16.2, control: 16.5). Groups were similar to each other in terms of the mean age of participants and gender distribution (p=0.124, 0.152). Nearly half of participants were not attending school (52.2%). Looking at the rates of psychiatric comorbidities, attention deficit and hyperactivity was found to be (ADHD) 82.6% (n=38), conduct disorder (CD) 30.4% (n=14), oppositional defiant disorder (ODD) 63% (n=29), major depressive disorder (MDD) 41% (n=19), and anxiety disorder (AD) 28.4% (n=13). It was found that sociodemographic and clinical characteristics of groups were similar to each other. The relevant data are shown in detail under Table 1.

Tobacco and substance use rates of groups are as follows: tobacco 91.3%, alcohol 93.5%, cannabis 93.5%, ecstasy 69.6%, synthetic cannabinoids 69.6%, inhalants 45.7%, heroin 8.7%. Starting ages are; for tobacco use 12.3, for alcohol 13.4, for cannabis 13.8, for ecstasy 14.5, for synthetic cannabinoids 15.1, for inhalants 14.6, and for benzodiazepines 14.8 years old. Tobacco, alcohol, ecstasy, synthetic cannabinoids, inhalants, benzodiazepines, and heroin rate of use (p=0.759, 1.000, 0.274, 0.316, 0.512, 0.095, 1.000, 0.602), starting ages (p=0.532, 0.818, 0.527, 0.609, 0.667, 0.440, 0.724) and amounts of tobacco use (p=0.286) of groups were found to be similar.

The groups' initial BDI, SCARED, TMQ, API, SPSI-R average scores were found to be similar (p=0.702, 0.523, 0.318, 0.344, 0.091). After 5 weeks a significant decrease was observed in BDI and SCARED scores of both groups (p=0.001); but in terms of such decrease there was no significant difference between the groups (p=0.645, 0.654). It was seen that TMQ and SPSI-R scores increased in the PST group and decreased in the control group; however, the rate of change was not significant (p=0.998, 0.961). In the course of time, SPSI-R and TMQ scores increased in the PST group and decreased in the control group. As a consequence, a significant difference was found between groups (p=0.045, 0.037). Changes in scale scores are presented in detail in Table 2.

When the groups were evaluated in terms of BDI cutoff scores, it was seen that in the first measurement, 80% of the PST group was in the "depressed" category (n=24). In the second measurement this rate decreased with only 30% of group falling in the "depressed" category (n=6). This change was statistically significant (p=0.001). In the control group, it was observed that in the first measurement 81.2% of the group was in the "depressed" category (n=13) and in the second measurement that the same rate decreased down to 56.2% (n=9). This change was found not to be statistically significant (p=0.125). Table 3 presents the changes in BDI cutoff scores.

Table 1. Comparison of Sociodemographic and Clinical Characteristics of PST and Control Groups

		PST		Control		Total		X^2/t	P
Gender (n-%)	Girl	16	53.3	5	31.2	21	45.7	2.051[a]	0.152
	Boy	14	46.7	11	68.8	25	54.3		
Age (mean-SD)		16.2	0.92	16.5	0.62	16.3	0.84	-1.571[b]	0.124
SES (n-%)	Low	11	36.7	6	37.5	17	37	0.138[a]	0.933
	Medium	12	40	7	43.8	19	41.3		
	High	7	23.3	3	18.8	10	21.7		
School (n-%)	Vocational high school	23	85.2	9	60	32	76.2	4.243[a]	0.236
	Other	7	14.8	7	40	14	23.8		
School attendance (n-%)	Yes	16	53.3	6	37.5	22	47.8	1.416[a]	0.493
	No	14	46.7	10	72.5	24	52.2		
Mother's age (mean-SD)		42.5	6.2	41.5	5.7	42.2	6.02	0.534[b]	0.596
Father's age (mean-SD)		48.3	7.6	47.7	4.7	48.1	6.63	0.313[b]	0.756
Psychiatric application (n-%)	Mother	9	30	3	18.8	12	26.1	0.685[a]	0.498
	Father	7	28	2	12.5	9	22	1.368[a]	0.441
Family characteristics (n-%)	Nuclear	20	66.7	14	87.5	34	73.9	2.643[a]	0.267
	Extended	2	6.7	0	0	2	4.3		
	Fragmented	8	26.7	2	12.5	10	21.7		
Smoking (n-%)	Mother	16	53.3	6	37.5	22	47.8	1.048[a]	0.306
	Father	20	80	11	68.8	31	75.6	0.670[a]	0.472
Regular alcohol use (n-%)	Mother	0	0	0	0	0	0	0.006[a]	1.000
	Father	8	32	1	6.2	9	22	3.907[a]	0.142
Intelligence Level (n-%)	Borderline (70-79)	0	0	1	6.3	1	2.2	2.798[a]	0.424
	Low Average (80-89)	4	13.3	1	6.3	5	10.9		
	Average (90-110)	24	80	12	75	36	78.6		
	High Average (111-120)	2	6.7	2	12.5	4	8.7		
Psychiatric Comorbidity (n-%)	ADHD	23	76.7	15	93.8	38	82.6	2.12[a]	0.230
	CD	12	40	2	12.5	14	30.4	3.72[a]	0.092
	ODD	21	70	8	50	29	63	1.79[a]	0.181
	MDD	12	40	7	43.8	19	41.3	0.061[a]	0.806
	AD	8	26.7	5	31.2	13	28.3	0.108[a]	0.744
	No Diagnosis	2	6.7	1	6.2	3	6.5	0.003[a]	1.000

PST: Problem Solving Therapy, SD: Standard Deviation, SES: Socioeconomic Status, ADHD: Attention Deficit Hyperactivity Disorder, CD: Conduct Disorder, ODD: Oppositional Defiant Disorder, MDD: Major Depressive Disorder, AD: Anxiety Disorder.
a: Chi Square Test, b: Independent Sample T-Test, p<0.05

Table 2. Comparison of Baseline Values and Changes in Scale Scores

	1.evaluation				2.evaluation			Change		Between-group difference
	PST	Control	t	P*	PST	Control	F	P**	F	P**
BDI	20.5	19.1	0.385	0.702	9	12.8	33.326	**0.001**	0.215	0.645
SCARED	27.4	30.1	0.645	0.523	22.7	23.9	13.384	**0.001**	0.204	0.654
TMQ	81.2	87.6	1.011	0.318	89.1	79.8	0.001	0.998	4.272	**0.045**
API	8.5	9.6	0.957	0.344	8.2	9.9	0.001	0.977	1.647	0.206
SPSI-R	12.5	11.2	1.728	0.091	13	10.7	0.002	0.961	4.657	**0.037**

PST: Problem Solving Therapy, BDI: Beck Depression Inventory, SCARED: Screen for Child Anxiety Related Emotional Disorders, TMQ: Treatment Motivation Questionnaire, API: Addiction Profile Index, SPSI-R: Social Problem Solving Inventory-Revised
*Unpaired T-test.p<0.05
**Repeated measures analysis of variance p<0.05

Table 3. Comparison of the Change of BDI According to the Cut-off Score

	BDI >9				
	evaluation		evaluation		
	f	%	*f*	%	P
PST	24	80	6	30	0.001*
Control	13	81	9	56.2	0.125

PST: Problem Solving Therapy, BDI: Beck Depression Inventory
*McNemar test, p<0.05

DISCUSSION

This study intends to examine the effects of PST, a cognitive behavioral therapy method, on adolescents who have substance use disorder. At the end of study, BDI and SCARED scores decreased significantly in both groups but a statistically significant difference was not found between the two groups. While mean SPSI-R and mean TMQ scores increased in the PST group, these scores decreased in the control group and a significant difference was found between the groups. As mean API scores decreased in the PST group, the same increased in the control group. However, there was no significant difference between the groups. When the groups were compared according to their BDI score categories, in the PST group the number of cases in the "depressed" category significantly decreased; yet there was no significant decrease in the control group.

Cognitive Behavioral Therapy (CBT) methods are used effectively in depression treatment by themselves or in combination with pharmacotherapy. In the treatment of children and adolescents who are diagnosed with mild to moderate major depressive disorder (MDD), CBT is recommended as the first option (Melvin et al. 2006). In studies falling within the scope of Treatment of Adolescent with Depression (TADS) wherein 4 different treatment methods (medication, medication+CBT, CBT, and placebo) are compared, it was reported that medication+CBT treated depression faster than fluoxetine treatment or CBT treatment alone (AACAP 2007, TADS Team 2009). Similarly, in the study titled "Treatment of SSRI-Resistant Depression in Adolescents (TORDIA)" it was found that on the 12th week, medication+CBT was more effective than only medication (AACAP 2007). The present study confirms the findings in the literature in that PST administered in addition to routine treatment gives way to a more positive change according to evaluations made over the BDI cutoff scores.

In a study including 6050 adults who use alcohol, it was reported that the group that was diagnosed with alcohol addiction diagnosis according to DSM-IV had 4 times higher MDD comorbidity when compared to the group that was not diagnosed with alcohol addiction (Hasin & Grant 2002). ASUD may give way to other disorders or, more frequently, it follows other disorders. It is known that adolescents diagnosed with ASUD have a psychological disorder which possibly had its outset in childhood, that affects etiology and treatment (Kaplan & Sadock 2012). Considering the fact that MDD is a disorder that disrupts the psychosocial adaptation of an individual, similarly to our study, it could be said that treating this disorder will positively contribute to ASUD treatment.

Looking at the efficacy of PST in the treatment of MDD in adolescents, a study conducted in Türkiye included 27 adolescents and young adults in the problem solving group and 19 adolescents and young adults in the wait list, all between the ages of 15-18. Said cases were administered with 6 sessions of PST. BDI scores showed that in the PST group 77.8% of participants were considered to be treated; however, in the control group only 15.8% of participants were treated. In addition to this, researchers conducted a follow-up interview one year after the study, with results showing that treatment gains were maintained (Eskin et al. 2008). In another study, 22 cases were included in the problem solving group and 23 in the waitlist group, with the ages of the participants ranging between 12-21 years old. This study revealed that depression scores of the PST group decreased significantly (Hoek et al. 2012). Our study was found to confirm these two studies evaluating depression scores. On the other hand, our study differs from other studies in that it only involves adolescents.

In a meta-analysis examining the effects of CBT on adolescents who are diagnosed with anxiety disorder (AD) a comparison of 3 treatment types as CBT+medication, CBT treatment alone and medication alone was performed. In turn, response to treatment rates were reported to be 68%, 46% and 46% respectively. 36 weeks later, response treatment rates were reported to be 73%, 52% and 52% in the same order (Kendall & Peterman 2015). In a controlled study where a CBT method titled "Coping Cat Program" was applied to 488 children and adolescents between 7-17 years old, it was found that all CBT, medication and CBT+medication methods were effective, as well as CBT+medication being found superior to other methods (Kendall et al. 2016). In another meta-analysis encompassing 44 different studies comparing different CBT methods in treatment of anxiety disorders as counselling, CBT and PST, all methods were found effective but differences between the methods were not statistically significant (Cape et al. 2010).

Our study found that the decrease in mean SCARED scores was statistically significant in the PST group, which corresponds to other studies in the literature that state combined treatment approaches are effective in the treatment of anxiety disorders. However, no studies were found in the literature wherein the implementation of problem solving therapy in the treatment of anxiety disorder in children and adolescents was practiced.

Patients who present with ASUD-comorbid anxiety disorder display the following characteristics: higher levels of incapacity, heavier drinking/smoking, worse social adaptation, higher hospitalization numbers and more severe psychiatric distress (Grant et al. 2005, Burns et al. 2005). A longitudinal follow-up study on generalized anxiety disorder patients reported that ASUD comorbidity decreases the possibility of treatment for generalized anxiety disorder and also increases its recurrence probability (Bruce et al. 2005). It is observed that there is a frequent comorbidity between ASUD and anxiety disorder (as well as other mental disorders) and that this comorbidity affects response to treatment rates. It could be deduced that the treatment of anxiety disorder is an effective option in treating ASUD.

Motivation is an internal state affected by external factors and is therefore changeable. Motivation is necessary in the treatment of addiction. In a study assessing 170 adolescents between 13-18 years old who are diagnosed with ASUD, the cases received CBT for 10 weeks and it was reported that their treatment motivation increased. The same study emphasizes that with the increase of treatment motivation, the amount of substance use decreased (Kaminer et al. 2016). A longitudinal follow-up study conducted in 2011 evaluated addiction severity and treatment motivation of 167 adults diagnosed with ASUD through psychometric scales. As a result it was stated that high treatment motivation was a predictor of low addiction severity (Korcha et al. 2011). During a study wherein 142 patients who were receiving smoking cessation treatment were evaluated, all cases were examined 3 times; before treatment, after CBT+medication treatment and 6 months after treatment, and it was emphasized that the success of treatment was significantly related to low levels of anxiety and depression and to high levels of treatment motivation (Pawlina et al. 2015). In our study, it was found that receiving PST in addition to regular treatment increased treatment motivation and this result is compatible with literature.

Cognitive behavioral group therapy (CBGT) seem to be more practical in terms of its low cost and power of reaching more people. In a review study assessing CBGT involving the adult age group, it was found that CBGT is generally more efficient than standard treatments. In the same study, CBGT was compared with pharmacotherapy and it was found that the efficiency of CBGT alone is similar to medication treatments (Yıldırım & Sütçü 2016). In a study published in 2014, 279 cannabis addicts between 16-63 years old were examined, with 149 of them receiving combined treatment (CBT, motivational therapy and problem solving training together) and the remaining 130 being kept the in waitlist group. At the end of treatment, it was reported that cannabis use decreased in a statistically significant manner in the therapy group compared to the waitlist group. Also, the amount of cannabis use and problems associated with cannabis use decreased significantly in the therapy group (Hoch et al. 2014). Another study was conducted with 240 young adults who had cannabis dependence according to DSM-IV with all participants being randomly assigned to 4 groups. Each group received different modes of treatment as follows: the 1st group had a standard psychiatric interview, the 2nd group motivational interview and CBT, the 3rd group contingency management and avoidance reinforcement approach, and the 4th group motivational therapy, CBT and additionally, contingency management. At the end of treatment these four groups were compared and it was seen that the decrease in substance use frequency and intensity was lowest in the standard therapy group and such frequency and intensity was significantly decreased in the contingency management group. 1 year later cases were evaluated again and it was determined that individuals in the combined therapy group used significantly less amounts substance and that the severity of their addiction decreased (Kadden et al. 2007). In 2009, a controlled study was conducted with adolescents who were between 14-18 years of age and had cannabis addiction; one group received motivational therapy+CBT+contingency management and psychoeducation was delivered to their families, and the other group was included in the waitlist. 69 adolescents were included in this study and 3 months, 6 months and 9 months after treatment, the cases were evaluated in terms of their restarting cannabis use. In all measurements, restarting rates were significantly less in the group receiving therapy when compared to the control group (Stranger et al. 2009).

In the literature, we found a study wherein PST was administered in substance use disorder treatment in the adolescent age group. In this study, 29 cases received family supported behavioral therapy, and 27 cases were included in the individual PST group. Results of satisfaction scale for young people, satisfaction scale for family and urine tests showed that there was a statistically significant decrease in substance use for both groups; besides this, it was emphasized that none of the methods applied was superior to the others (Azrin et al. 2000).

In the literature there were 7 studies practicing CBGT including problem solving therapy in the treatment of alcohol use disorder in adults. In a study involving 78 convicted adult males diagnosed with alcohol addiction according to DSM-IV, it was found that CBGT including problem solving training is superior to 12-step programs (Easton et al. 2007). In another study comparing naltrexone, CBGT and placebo, it was emphasized that CBGT including naltrexone+problem solving training reduced cravings for alcohol more (O'Malley

et al. 2007). In a study comparing CBGT including problem solving training to motivational group intervention (MGI), it was reported that CBGT including problem solving training is superior to motivational group intervention (Rosenblum et al. 2005). In a study conducted in our country which examined 90 alcohol dependent patients, CBGT including problem solving training was administered alongside standard therapy procedures; yet a control group was not established for the study. In the follow-up it was found that 72.3% of cases were in remission (Türkcan et al. 2001). Our study shows that adding PST to regular interviews decreases addiction severity and also that CBT approaches decrease addiction severity; thus, the findings of our study are in accord with the literature. However, the difference between groups was not statistically significant. This could be explained with the inadequate size of the sample, methodological differences and the application of a different intervention method.

The literature includes a study wherein SPSI-R is administered to adolescents diagnosed with ASUD. In said study it was reported that with PST, the subscale mean scores for PPO (positive problem orientation) and RPS (rational problem solving) increased whereas NPO (negative problem orientation), ICPSS (impulsive-careless problem solving style), APSS (avoidant problem solving style) subscale mean scores decreased (Azrin et al. 2001). In our study, mean SPSI-R scores increased in the PST group and decreased in the control group. It was seen that such changes were statistically significant (p=0.037). When evaluated in terms of subscale scores, there was no statistically significant difference between the groups.

CONCLUSION AND LIMITATIONS

In ASUD treatment for adolescents, in addition to pharmacotherapy, psychosocial interventions are needed. Nowadays CBT techniques are practiced in centers that administer such treatment, but this procedure is not prevalent and has not become the standard. As a cognitive behavioral intervention method, PST could be considered as an effective option. Our study is the first one in Türkiye examining an intervention method applied to adolescents with addiction. The limitations of our study were as follows: low number of cases, case numbers in the groups not being equalized, gender distribution not being homogenous, blind procedure not being used while forming and evaluating the groups, interventions administered to groups not starting at the same time, case numbers included in groups not being equal, and power analysis not being performed at the beginning of the study. Different studies which do away with these limitations and evaluate the long term results are needed.

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Validity and Reliability Study of Mental Health Recovery Measure's Turkish Version

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ABSTRACT

Objective: The present study aims to translate into Turkish and investigate the validity and reliability of the Mental Health Recovery Measure (MHRM).

Method: The sample consisted of 343 outpatients - and in-patients under treatment for a variety of psychiatric diagnoses at a state hospital and a university research hospital. The MHRM along with the Subjective Recovery Assessment Scale (SRAS), Psychological Well Being Scale (PWBS), Emotional Eating Scale (EES), and The Internalized Stigma of Mental Illness Scale (ISMI).

Results: The mean MHRM total score was estimated at 31.66 (sd=10.02). Exploratory factor analysis revealed one single robust factor explaining 64% of the variance of the total scores. Alpha internal consistency coefficient was calculated as 0.94 and corrected item-total correlation coefficients were entirely above 0.60. The MHRM scores showed positive and strong correlations with the PWBS (r=0.695; p<0.001) and SRAS (r=0.732; p<0.001), negative and strong correlation with the ISMI (r=-0.696; p<0.001) and no correlation with the EES scores (r=-0.021; p=0.703).

Conclusion: Our data provides initial evidence supporting the validity and reliability of the Turkish MHRM in evaluating the tendency for recovery of mental health consumers for clinical and research purposes. Further studies addressing psychometric properties of the scale are warranted.

Keywords: Mental Health Recovery Measure, validity, reliability.

INTRODUCTION

Mental health is defined as a state of well-being in which each individual is aware of their own potential, can cope with the usual challenges of life, work productively and efficiently, and contribute to their environment (RSKT 2017). Healing, on the other hand, is defined as a highly personal and unique process of change in one's attitudes, values, feelings, goals, skills, and/or roles, in its broadest definition, and includes developing new meaning and purpose that grows beyond the destructive effects of mental illness (Anthony 1993, Şenocak et al. 2019, Yüksel and Arslantaş 2021). Leamy et al. (2011) discussed the recovery process under five categories, namely, connectedness, hope and optimism about the future, identity, meaning in life, and empowerment. 'Recovery' is the process of learning how to live with a persistent psychotic disorder rather than an outcome in which symptom relief and improvement in functionality are defined by clinical criteria (Davidson 2010). The concept of mental health brings with it the distinction between clinical recovery and personal recovery. While clinical improvement is defined by mental health professionals as the reduction or cessation of symptoms and the recovery of social functioning, personal recovery refers to an ongoing holistic process that is determined by the individual receiving treatment and includes personal development, recovery, and self-determination (Stuart 2013, Güler 2017, Şenocak et al. 2019, Yüksel and Arslantaş 2021).

It is argued that the recovery movement first emerged in the United States of America (Meehan et al. 2008). It is difficult to say exactly when the movement emerged, but it is reported to have originated from self-help groups that were part of the wider sphere of addictions and that it was, as a concept, guided by approaches such as the 12-step approach of Alcoholics Anonymous founded in the 1930s.

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Today, recovery is related to the concept of personal recovery (Sowers 2005). Social movements that emerged in the 1960s and 1970s contributed to the development of the concept of recovery. The human rights movement and the consumer rights movement, which oppose the beliefs and values that oppress and limit social groups, the anti-discrimination and anti-stigmatization movements, and the anti-psychiatry movement, which questions the tendency of psychiatrists to detain and treat individuals with mental disorders by force and to solve all kinds of health problems by using drugs, are shown as examples of these movements. Advances in psychopharmacology also offer opportunities for people with psychiatric illnesses to keep their symptoms under control. Thanks to these movements and developments, people who benefit from mental health services have been able to participate more in the planning, delivery, and evaluation processes of mental health services, in addition to the protection of their individual rights. Thus, the necessary groundwork has been prepared for the transition from hospital-based services to community-based services and the development of psychiatric rehabilitation (Noordsy et al. 2000, Van Tosh et al. 2000, Berlim et al. 2003, Dixon and Goldman 2003, Sowers 2005, Ramon et al. 2007, Field and Reed 2016). With a better understanding of the recovery process, its importance and value for people struggling to overcome their problems and the mental health systems that serve them have increased. Thus, the need for the transformation of service systems has become more apparent. Recovery attracted considerable attention with the publication of the President's New Freedom Commission Report on Mental Health (2003), which was the first national report emphasizing recovery. The report recognizes that there are widespread barriers to recovery in the existing mental health system for individuals with mental illnesses and aims to transform the mental health system into a recovery-oriented system. According to the report, mental health care in the transformation to recovery process should be shaped according to people who receive mental health services and their families. The focus should be on tackling life challenges for clients, building resilience, and collaborating with clients in decision-making at all stages of care. Care that focuses only on symptom-management will be inadequate (President's New Freedom Commission on Mental Health 2003, Sowers 2005, Caldwell et al. 2010). Some guidelines based on the recovery-oriented approach (Sowers 2005, Mental Health Commission of Canada 2015) and various models related to recovery have been developed. These models include the Strengths Model (Tse et al. 2016), Recovery Alliance Theory (RAT) (Shanley and Jubb-Shanley 2007), Conceptual Recovery Model (Jacobson and Greenley 2001), Collaborative Recovery Model (Oades et al. 2005), and Tidal Model (Barker 2001, Barker 2004, Buchanan-Barker and Barker 2008, Barker and Buchanan-Barker 2010). Although a large number of tools have been developed to measure mental health recovery and to evaluate recovery-oriented services and professionals, there are a limited number of scales in Turkish, whose validity and reliability have been examined (Telef 2013, Yıldız et al. 2017, Yalçıner et al. 2019, Guler and Gurkan 2019). Indeed, it is extremely important to develop and use practical, reliable, useful, and multifunctional screening tools to provide an effective health service. This study was conducted to analyze the validity and reliability of the Mental Health Recovery Measure (MHRM), which facilitates such an assessment, by translating it into Turkish.

It is important to consider subjective recovery in planning health education interventions for mental illness recovery. For this reason, it is highly important to introduce a scale in our language, which has little number of items (questions), is easy to understand, and which can be easily applicable in routine-care environments. In this study, the aim was to translate the MHRM into Turkish and to examine its validity and reliability in a sample of individuals with chronic mental illnesses. More precisely, the aim, again, was to collect different types of evidence regarding the validity of MHRM scores. In line with these objectives, the following research questions were determined.

1. Is the internal consistency of the Mental Health Recovery Measure acceptable (Cronbach's alpha=0.70–0.79) or adequate (alpha≥0.80 for studies; alpha≥0.90 for individual clinical assessment) (Nunnally et al. 1994) (construct validity)?
2. Is the factor structure of the Mental Health Recovery Measure similar to the factor structure of the original scale (Young and Bullock 2003) (factorial validity)?
3. Is there a correlation between the scores of individuals who have recovered from the Mental Health Recovery Measure and the scores obtained from the Psychological Well-Being Scale (PWBS), the Subjective Recovery Assessment Scale (SRAS), the Internalized Stigma of Mental Illness Scale (ISMI), and the Emotional Eating Scale (EAS)?

METHOD

The Translation Process

First, necessary permissions were obtained from the first author of the original development study of the MHRM (Young and Bullock 2003). Then, the back-translation method was used to minimize the conceptualization and expression differences in the language adaptation of the scale. The scale was translated into Turkish by three psychiatric nurses, who were blinded to each other's translations. These translations were checked by the research team and translated into English by a psychiatrist and a clinical psychologist who

did not participate in the initial translation process. This text, which was translated back into English, was compared with the original Mental Health Recovery Measure, and it was sent to the first author who developed the scale and their approval was obtained. It was decided that the latest version of the Turkish translation was appropriate. During the adaptation process of the scale to our language, no changes were made in the scale items during the translation and retranslation, and the items that were the same with those in the original scale were accepted.

The Sample

The study was carried out with 343 patients who were treated in Aydın Adnan Menderes University Research and Application Hospital Psychiatry Service and Psychiatry Outpatient Clinic, Torbalı State Hospital Psychiatry Service, and Community Mental Health Center and were diagnosed with a psychiatric disorder according to DSM 5. It is stated that a sample size of 100 to 200 individuals or 10 times the number of total items on the scale would be enough for factor analysis to be used in scale development (DeVellis 2003). For this reason, the calculation of the sample size was based on the number of questions on the scale (30 items) in the beginning, which required 300 (10x30) participants for the validity and reliability study of the scale. Considering possible data losses, 20% extra sample size was added and the sample size was calculated as 360. However, the sample consisted of 343 people because some patients did not want to continue filling out the questionnaires. The inclusion criteria of the study for the patients included with a previous diagnosis of a psychiatric disorder according to DSM 5 and volunteering to participate in the study, while the exclusion criteria were determined as the presence of a secondary mental disorder and/or alcohol and substance addiction. Data for the study was collected by the researchers (RY, MK, and SI) in one year through face-to-face interviews. No adverse events were experienced during data collection.

The participants were evaluated cross-sectionally by using some scales. Of the participants, 61.2% (n=210) were female, 55.7% (n=190) were single, mean age was 37.41±19.70 years, 40.1% (n=137) of the participants had a secondary school education, 55.4% (n=190) were unemployed, and 48.7% (n=164) considered their income level as less than their income. Also, 47.5% (n=162) of the participants lived in the city (province). The mean age when participants were diagnosed with a mental illness was 27.31±11.61 years, and the mean number of hospitalizations was 2.63±3.02. Considering the psychiatric diagnoses of the participants according to DSM 5, 19.5% (n=67) had schizophrenia spectrum and other disorders accompanying psychosis, 19.0% (n=65) had bipolar and related disorders, 13.7% (n= 47) had obsessive-compulsive disorder and related disorders, 13.1% (n=45) had anxiety disorder, 30.9% (n=106) had depression disorder, and 3.8% (n=13) had other psychiatric diagnoses.

Ethics Committee Approval

The study was approved by the Aydın Adnan Menderes University Faculty of Nursing Non-Invasive Clinical Research Ethics Committee (12/11/2019-E.70083). Participants were informed about the research, and their verbal and written consent was obtained before starting the study.

Data Collection Tools

Data for the study was collected by using the Mental Health Recovery Measure (MHRM), whose validity and reliability studies were conducted in this study, the Psychological Well-Being Scale (PWBS), the Subjective Recovery Assessment Scale (SRAS), the Emotional Eating Scale (EAS), and the Internalized Stigma of Mental Illness Scale (ISMI).

The Mental Health Recovery Measure (MHRM): This scale was developed by Young et al. in 1999 to evaluate recovery from mental illnesses and was revised in 2003 by Young and Bullock (2003). The item content of the MHRM and its conceptual domains is based on a specific model of mental health recovery based on the experiences of people with psychiatric disabilities (Young and Ensing 1999). The MHRM consists of 30 items and the questions are answered on a 5-point Likert-type scale with options ('0' Strongly Disagree, '1' Disagree, '2' Undecided, '3' Agree, '4' Strongly Agree). The validity and reliability study was conducted on the 30-item form. However, Cronbach's alpha of the scale was found as 0.98, which suggested that the item contents might be close to one another. Thus, exploratory factor analysis was performed to examine the factor structure of the MHRM and to select the ten most appropriate items for a short measurement. Factor analysis revealed an interpretable single-factor structure. The MHRM-10 was formed by choosing the ten items with the highest factor loadings. The researchers found that these ten items were the same as the items which Armstrong et al (2014) obtained as a result of their validity and reliability study in which total items were reduced to 10 (Armstrong et al. 2014). There were no reverse-scored items on the scale. The scores that can be obtained on the scale range between 0 and 40. High scores indicate increased mental illness recovery.

The Psychological Well-Being Scale (PWBS): This scale was developed by Diener et al. (2010) to measure socio-psychological well-being as an 8-item, 7-point Likert-type (1-Strongly disagree; 7-Strongly agree) tool. The scores on the scale range between 8 and 56. Telef (2013), who examined the validity and reliability of the Turkish version of the scale, reported Cronbach's alpha internal consistency coefficient as 0.80. Higher scores indicate that the person has many

psychological resources and resilience. The alpha coefficient of the scale was calculated as 0.93 in our study sample.

The Subjective Recovery Assessment Scale (SRAS): This is a self-report scale that was developed by Yıldız et al. (2017) to evaluate subjective recovery in patients with schizophrenia. It has 17 items and is responded to on a 5-point Likert-type scale (1- Doesn't define me at all, 5- Defines me fully). The scores on the scale range between 17 and 85 points. Yıldız et al. (2017) reported Cronbach's alpha coefficient as 0.98. High scores obtained from the scale indicate the perception of a better recovery. The alpha coefficient of the scale was calculated as 0.95 in our study sample.

The Emotional Eating Scale (EES): This scale was developed to evaluate the emotional eating behaviors of obese and overweight people (Garaulet et al. 2012). It consists of 10 items and three sub-dimensions (disinhibition, type of food, and guilt). The items are evaluated on a 4-point Likert-type scale with options ('0' Never, '1' Sometimes, '2' Usually, and '3' Always). The scores on the scale range between 0 and 30. There are no reverse items on the scale. High scores indicate a high level of emotional eating behavior. The validity and reliability study in our country was conducted by Arslantaş et al. (2020). It was found that the Turkish version, similar to the original scale, also had a three-factor structure, namely, disinhibition, type of food, and guilt. The corrected item-total score correlation coefficients of the scale items were greater than 0.34, and the internal consistency coefficient of the total score was 0.84. In line with the recommendations of the authors, the total score of the scale was used in this study (Arslantaş et al. 2020) and Cronbach's Alpha coefficient was calculated as 0.85.

The Internalized Stigma of Mental Illness Scale (ISMI): This self-report scale was developed by Ritsher et al. (2003) to evaluate internal stigma, and its Turkish validity and reliability study was conducted by Ersoy and Varan (2007). It has 29 items and a 4-point Likert type scale (1-I strongly disagree, 4-I strongly agree). The scale has five sub-dimensions, namely, alienation (6 items), stereotype endorsement (7 items), discrimination experience (5 items), social withdrawal (6 items), and stigma resistance (5 items). Items of the 'stigma resistance' subscale are reverse-scored. The total ISMI score obtained by summing up the scores of the five subscales varies between 4 and 91 points. High scores on the ISMI mean that the person's internalized stigma is more severe negatively. Cronbach's alpha internal consistency coefficient of the scale was calculated as 0.91 in our study sample.

Statistical Analysis

As a result of the preliminary analysis, it was understood that all scale scores conformed to the normal distribution. To examine the reliability of the Mental Health Recovery Measure, Cronbach's alpha internal consistency coefficient of the scale and corrected item-total score correlations were calculated. The Mental Health Recovery Measure was factor-analyzed to determine the content of the items. In the validity examination, the level of agreement between the MHRM total score and the score of the other scales used in the research were examined. In the evaluation of the correlation coefficients, the values were accepted as low between 0.10 and 0.29, moderate between 0.30 and 0.49, and a high degree of correlation above 0.50 (Cohen 1988). All statistical analyses were conducted on the IBM SPSS version 22.0 software package.

RESULTS

Factor Structure of the Mental Health Recovery Measure

The suitability of the data for factor analysis was tested by using the Kaiser-Meyer-Olkin (KMO) and Barlett's tests. In the preliminary analysis, KMO was 0.94, and Barlett's test was found to be significant ($p<0.001$). Accordingly, these values indicated that our data were suitable for factor analysis. As a result of the principal components factor analysis, it was seen that the eigenvalue of the first component was 6.85 and that the eigenvalues of all the other components were less than 1. Upon examination of both these values and the scree plot (Figure 1), it was concluded that the scale had a single factor structure. The ten items of the scale explained 64.35% of the variance in the total score. Since the scale items were collected under a single factor, no rotation was applied. The factor loads of the scale items are explained in Table 1. The factor loadings of the items between 0.66 and 0.87 suggested that all items were highly correlated with this factor.

The Internal Consistency of the Mental Health Recovery Measure

Cronbach's Alpha internal consistency coefficient of the scale was calculated as 0.94 [0.93–0.95]. When Table 1, which contains the corrected item-total correlations calculated for the evaluation of the psychometric properties of individual scale items, was examined, it was seen that all items showed correlations over 0.60 with the total score. These data suggest that each item contributed adequately to the total score. Studies interpret alpha coefficients of 0.70 for group-level measurements indicate an acceptable reliability of the scale, and alpha coefficients of 0.80 are considered to indicate adequate reliability (Nunnally and Bernstein 1994, Erdoğan et al. 2015).

The Distribution of the Total Score of the Mental Health Recovery Measure

The mean score of the patients on the Mental Health Recovery Measure was found to be 31.66±10.02 (25^{th} p=22; 50^{th} p=33, 75^{th} p=39).

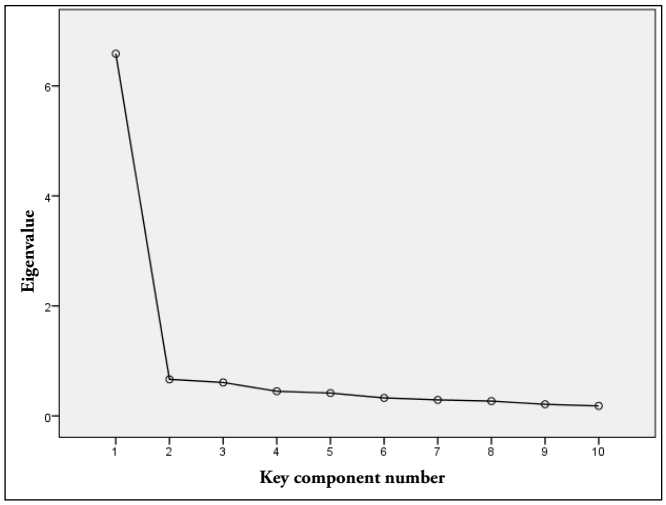

Figure 1. Scree Plot

Concordance between the Total Scores of the Mental Health Recovery Measure and the Scores of the Other Scales

The distribution properties of the total score of the Mental Health Recovery Measure are given in Table 2. The calculations indicated that the 95% confidence interval of the mean score was between 30.6 and 32.7 and that the 99% confidence interval of the mean score was between 30.2 and 33.0. Correlations between the MHRM and other scale scores were calculated to obtain evidence of validity for the MHRM total score. Accordingly, the MHRM showed a highly positive correlation with the PWBS (r=0.695; p=0.001), a highly positive correlation with the SRAS (r=0.732; p=0.001), and a highly negative correlation with the ISMI (r=-0.696; p=0.001). It did not show any correlation with the EAS (r=-0.021; p=0.703) (Table 2).

DISCUSSION

Recovery is a process where an individual learns to lead a meaningful and satisfying life despite a permanent mental disorder as well as to live with this disorder. It is highly important to be able to subjectively evaluate and monitor the improvement of individuals throughout the psychiatric treatment process. In this way, it can be ensured that the individual gains skills requied for the self-management of the disease by being included in the treatment. In this study, data supporting the reliability and validity of the Turkish form of the MHRM, which will help to evaluate mental recovery in a short and precise way, were obtained.

Table 1. Reliability Data of Mental Health Recovery Measure, Factor Structure, and Factor Loads of the Items (N=343)

	Items of the Mental Health Recovery Measure	Item-total Correlation Coefficients	Factor Loads
1.	I believe in myself.	0.71	0.77
2.	Despite having mental problems, I keep changing and making progress in the right direction.	0.67	0.73
3.	Even if I still have problems, I value myself as I deserve to be valued.	0.81	0.85
4.	I feel good about myself.	0.79	0.83
5.	My way of handling events in my mind helps me reach my goals.	0.81	0.85
6.	I feel at peace with myself.	0.83	0.87
7.	I am in a positive attitude over the last weeks.	0.78	0.82
8.	I do something productive each morning.	0.69	0.75
9.	I make progress toward my goals.	0.82	0.86
10.	I get involved in tasks or activities that are enriching for me and my world.	0.60	0.66
	Explained Variance	**64.35%**	

Table 2. Distribution Parameters of the Scale Scores of Participants and the Correlation of Mental Health Improvement Measure Scores with Other Scales

Scale	n	Minimum	Maximum	Mean	SD	r	p
The Mental Health Recovery Measure	343	11.00	50.00	31.65	10.02	-	-
The Psychological Well-Being Scale	343	8.00	56.00	34.42	12.34	0.695	0.001
The Subjective Recovery Assessment Scale	343	17.00	85.00	51.35	17.09	0.732	0.001
The Emotional Eating Scale	343	10.00	40.00	20.14	6.16	-0.021	0.703
The Internalized Stigma of Mental Illness Scale	343	33.00	113.00	71.62	16.76	-0.696**	0.001

The Factor Structure of the Mental Health Recovery Measure

The exploratory factor analysis method was used to examine the factor structures of the Mental Health Recovery Measure (MHRM). Gorsuch (1997) stated that exploratory factor analysis could be used instead of confirmatory factor analysis in cases where the same factors could be obtained from previous analyses (Gorsuch 1997). In the light of literature, it was concluded that there was no need for confirmatory factor analysis since exploratory factor analysis showed that the factor structures of both measurement tools were the same as the factor structures of their original forms. Analysis results showed that the items on the scale were collected under a single factor and that this factor explained 64.35% of the total variance of the scale score. This result was consistent with the single-factor structure (with an explained variance rate of 56%) reported by Armstrong et al. (2014).

Reliability of the Mental Health Recovery Measure

The alpha internal consistency coefficient of the scale was calculated as 0.94 (95% CI:0.94 [0.93-0.95]). A calculated reliability coefficient of 0.70 or higher indicates that the reliability of the measurement tool is sufficient for use in research (Tavşancıl 2002, Büyüköztürk 2007). The results showed that the reliability level of the MHRM was quite high. Both the internal consistency coefficient and the item-total score correlation coefficients observed in our study were quite high. In our study, all items showed a strong positive (r>0.60) correlation with the total score. Considering all the results, it can be said that the MHRM reliably measures the recovery status of individuals diagnosed with mental illnesses. Studies conducted in other countries regarding the scale also showed that the alpha coefficient of the scale varied between 0.91 and 0.95 (Bullock 2009, Chang et al. 2013, Nieuwenhuizen et al. 2014, Armstrong et al. 2014, Abraham et al. 2016). The fact that the internal consistency coefficient of the scale is so high indicates that the scale can be applied safely in routine care settings.

The Distribution of the Total Score of the Mental Health Recovery Measure

The mean score of the patients on the Mental Health Recovery Measure was determined as 31.66±10.02 (25^{th} p=22; 50^{th} p=33; 75^{th} p=39). Similarly, Armstrong et al. (2014) reported that a mean MHRM score of 26.60±7.30. Considering that the maximum score that can be obtained from the scale is 40, it can be said that the recovery score of individuals in the sample was above the average. This result can be explained by cultural factors. This finding may have stemmed from the fact that our country has a collectivist rather than individualistic social structure (Kağıtçıbaşı 2007).

Concordance between the Total Scores of the Mental Health Recovery Measure and the Scores of the Other Scales

In the correlation analyses applied to examine the agreement validity, high correlations were observed between the MHRM score and those of other scales measuring the same and different domains. Accordingly, the MHRM was highly positively correlated with the PWBS (r=0.695; p<0.001), highly positively correlated with the SRAS (r=0.732; p<0.001), and highly negatively correlated with the ISMI (r=-0.696; p<0.001). It did not show any correlation with the EAS (r=-0.021; p=0.703). These results can be interpreted as follows: As psychological well-being and subjective well-being increase in individuals with a psychiatric diagnosis, recovery tends to increase. A high level of negative correlation was found between recovery and stigma. In other words, as internalized stigma increases, recovery decreases. In the study of Bilge and Çam (2010), it was reported that stigma reduced recovery. The finding that recovery increases as psychological and subjective well-being increases and that it decreases as stigma increases, may contribute to the planning of mental health and rehabilitation services. No correlation was found between recovery and emotional eating. This is a finding that was already expected by the authors. No results that supported our findings were found in literature. Studies reported that emotional eating was mostly related to negative emotions, such as anxiety, depression, fury, anger, and worry (Laitinen et al. 2002, Macht 2008, İnalkaç and Arslantaş 2018, Arslantaş et al. 2021).

Strengths and Limitations of the Research

The strongest aspect of this study is that it was conducted with a large sample of patients who had a psychiatric diagnosis from two different hospitals. The large sample size enables the narrowing of the confidence interval of the alpha values, that is, it ensures that the true alpha value in the population can be estimated very precisely and accurately. In addition, the research was carried out in about a year, and the researchers themselves filled out the questionnaires one-to-one with the participants, which is a good indicator for the results and reliability of the research. In addition, the MHRM had a high positive correlation with the PWBS, the SRAS, and the ISMI, which showed the MHRM had a high capacity to predict recovery status. The scale was applied to individuals who had a psychiatric diagnosis according to DSM 5, which shows that the scale can be used in all mental illnesses. The recovery scale was not conducted on a specific mental disorder (schizophrenia, depression, etc.), which can be considered as a limitation of the study. In addition, limited resources were used in the discussion due to the inadequate number of studies using the same/similar scales in the world and our country, which was another limitation of the study.

Conclusion and Recommendations

The high internal consistency of the Turkish version of the Mental Health Recovery Measure in this study was a finding that supported both the reliability and the validity of the construct of the scale. Our data provided evidence supporting the validity of the Turkish version of the MHRM for assessing the mental health improvement tendencies of the patients. All of the items on the scale contributed appropriately to the total score, Cronbach's alpha value calculated for the total score (0.94) indicated adequate internal consistency despite the relatively low number of items on the scale, and factors similar to the original factor structure of the scale were obtained in the factor analysis, which suggested that the Turkish translation of the Mental Health Recovery Measure was a valid and reliable measurement tool. With these features, the MHRM is appropriate for use in research.

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Mental Health Recovery Scale (MHRS)
(Young & Bullock, 2003)*

Name-Surname: **Date:**

This questionnaire aims to collect information regarding your assessment of your own recovery process. Mental recovery is a complicated process which is unique for each individual. Hence, no right or wrong answers. Please read carefully and rate each item to indicate the extent to which it applies to your recovery process.

		Absolutely disagree	**Disagree**	**Neither agree nor disagree**	**Agree**	**Absolutely agree**
1.	I believe in myself.	O	O	O	O	O
2.	Despite having mental problems, I keep changing and making progress in the right direction.	O	O	O	O	O
3.	Even if I still have problems, I value myself as I deserve to be valued.	O	O	O	O	O
4.	I feel good about myself.	O	O	O	O	O
5.	My way of handling events in my mind helps me reach my goals.	O	O	O	O	O
6.	I feel at peace with myself.	O	O	O	O	O
7.	I am in a positive attitude over the last weeks.	O	O	O	O	O
8.	I do something productive each morning.	O	O	O	O	O
9.	I make progress toward my goals.	O	O	O	O	O
10.	I get involved in tasks or activities that are enriching for me and my world.	O	O	O	O	O

Thank you for rating all the items.

*The MHRM© was developed with the help of mental health consumers by researchers at the University of Toledo, Department of Psychology. This research was supported through a grant from the Ohio Department of Mental Health, Office of Program Evaluation and Research. For further information, please contact Wesley A. Bullock, Ph.D. at (419) 530-2721 or email: wesley.bullock@utoledo.edu.
*Young SL, Bullock WA (2003) The mental health recovery measure. University of Toledo, Department of Psychology.

RESEARCH ARTICLE

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Validity and Reliability of the Turkish Version of the Mentalization Scale (MentS)

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ABSTRACT

Objective: This study, aims to translate the Mentalization Scale (MentS) into Turkish and investigate the reliability and validity of the Turkish version.

Method: The participants, consisting of 615 (310 female and 305 male) Turkish speaking adults, were asked to complete the MentS and the Emotional Intelligence Feature Scale-Short Form (EIFS) and the Borderline Personality Inventory (BPI).

Results: The factor structure of the scale was investigated by exploratory and confirmatory factor analysis. Similar with the original scale, findings demonstrated a three-factor structure, namely, 'the self,' 'others' and 'motivation'. Corrected total score correlations for each item were between 0.28 and 0.52. The MentS score showed positive correlations with the EIFS score ($r=0.49$; $p<0.001$); and negative correlations with the BPI score ($r= -0.37$; $p<0.001$). Cronbach's alpha internal consistency coefficient was calculated as 0.84 for the total score, 0.78, 0.80, and 0.79 for MentS-S, MentS-O, and MentS-M, respectively.

Conclusion: The findings show that the 25-item MentS Turkish form has sufficient psychometric properties. Our data supports the use of the Turkish version of MentS in future studies for assessment of mentalization capacity.

Keywords: Mentalization, validity, reliability

INTRODUCTION

Mentalization was introduced in 1960's as a psychoanalytic concept to describe mental processes related to symbolization (Freeman 2016). Mentalization is also associated with the Theory of Mind (ToM), which was defined by Premack and Woodruff after an experiment on chimpanzees in 1978. Bateman and Fonagy (2013) defined mentalization as the capacity "to attend to mental states in ourselves and in others as we attempt to understand our own actions and those of others on the basis of intentional mental states." Mentalization develops based on early experiences of secure bonding with primary caregivers, and both clinical experience and research have shown that children who have not developed secure attachment may experience attachment problems extending to their adulthood (Bateman and Fonagy 2013). Studies have also shown that problems in mentalization may be related to various psychopathologies.

The relationship between mentalization and psychopathology was first studied by Baron-Cohen et al. (1985). In this study, Baron-Cohen et al. (1985) proposed that autism was associated with the Theory of Mind. The problem of mentalization in autism spectrum disorder has been supported by many other studies later (Baron-Cohen 2001). Current literature indicates that problems in mentalization may also account for the increasing incidence of several other disorders. For example, Frith (1992) revealed the limitations of individuals diagnosed with schizophrenia in making sense of mental processes. Studies flag diagnosis-specific anomalies of mentalization in schizophrenia and autism (Chung et al. 2008, Stichter et al. 2010), in eating disorders (Redondo and Luyten 2018), conduct disorder, antisocial personality

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disorder (McGauley et al. 2011), borderline personality disorder (Fonagy and Bateman 2008) and depression (Belvederi et al. 2017). Deficiencies in mentalization capacity are considered as an important indicator, especially for personality disorders (Fonagy and Bateman 2008). Particularly for Borderline Personality Disorder (BPD), deficient mentalization is recognized as a core feature (Fonagy et al. 2015). It has been emphasized that in BPD, symptoms such as emotion regulation difficulties, impulsivity, intense interpersonal difficulties, and problems in reflective capacity and sense of self are related to lack of effective mentalization (Fonagy et al. 2015).

Clinical studies on mentalization in Turkey especially focus on people diagnosed with schizophrenia and bipolar disorders. For example, Bora et al. (2005, 2008) showed that deficiency in ToM may persist in the remission period of bipolar disorder and schizophrenia. Balıkçı et al. (2017) showed that mothers of schizophrenia patients performed significantly worse in the Reading the Mind in the Eyes Test and had lower mentalization capacity. Using the Coding System for Mental State Talk in Narratives, Duman and Oral (2018) have demonstrated that tales contribute to the mentalization ability more than animated films and consequently that they are helpful for improved mentalization.

When mentalization assessment instruments are examined, three paths appear in literature. First, in a wide range of research, constructs like empathic capacity and emotional intelligence are used interchangeably with mentalization. In parallel, it was noteworthy that measurements that were originally developed to assess the level of emotional intelligence (Mayer–Salovey–Caruso Emotional Intelligence Test; Mayer et al. 2002) and empathy (Empathy Quotient, EQ; Baron-Cohen and Wheelwright 2004) were used to assess mentalization but also failed to cover all aspects of mentalization during assessments despite some common aspects (Dimitrijević et al. 2018). The second way of measuring mentalization is by using interview-based techniques. Following a detailed coding system, it is possible to score mentalization capacities of individuals (Rudden et al. 2005). However, such interviews are not ideal for quantitative research with large sample-size (Dimitrijević et al. 2018). As the third way of mentalization assessment, self-report measures seem to provide advantageous alternatives, since they are easy to administer and can be used with larger samples. Ha et al. (2013) developed a measurement for people between the ages of 12-17. Following this measurement for adolescents, some other measurements are developed for adults as well (e.g. Badoud et al. 2015; Fonagy et al. 2016). These measurements indicate that mentalization is positively associated with concepts such as empathy and awareness and have negative associations with various psychopathological symptoms.

The relationship between mentalization and psychopathology has led to an increase in research on the subject. In this context, Dimitrijević et al. (2018) developed an easy-to-administer, reliable, self-report measure of mentalization, namely, the 'Mentalization Scale' (MentS), which they validated on both community and clinical samples. During the validation of the scale, which was developed based on the theoretical definition of the concept of mentalization, Experiences in Close Relationships Inventory-II (Fraley et al. 2000), Empathy Scale (Baron-Cohen and Wheelwright, 2004), Emotional Intelligence Scale (Petrides 2009) and the Five-Factor Inventory (McCrae and Costa 2004) were used. According to results, mentalization is positively related to emotional intelligence, empathy, openness, extraversion, and conscientiousness; and negatively related to anxious and avoidant attachment and neuroticism. That it contributed to the determination of borderline personality disorder was also emphasized.

In the literature, there are also some mentalization-related measurement tools that were adapted to Turkish. One of these is the 'Encoding System of Mind Situations in Narratives' that was adapted by Çorapçı and Bekar (2016) on mother-child pairs. This tool aims to evaluate mentalization skills in narratives (Bekar et al. 2014). 'Reading the Mind from Eyes Test' (Baron-Cohen et al. 2001) is another tool that was adapted to Turkish, revised by Yıldırım et al. (2011). This tool evaluates mind reading-abilities, which is a key component of ToM. In this respect, people are asked to predict the mental states of others from 36 pictures in which only the eyes and their contours are visible.

When related literature in Turkish is examined, one can see that a tool is missing to evaluate mentalization that could be used in large-scale quantitative studies conducted in both population-based and clinical samples. In order to bridge this gap between scientific research and clinical investigation, the present study seeks to adapt the Turkish version of the Mentalization Scale (MentS; Dimitrijević et al. 2018) and to determine its psychometric characteristics as part of the Turkish-speaking community sample.

METHOD

Participants

Data was collected from 615 participants aged between 18 and 65 (M=35.22, SD=10.05) from various cities of Turkey (e.g. Ankara, Istanbul and Mersin). The sample distribution by gender was 50.4% female (n=310) and 58.6% male (n=305). Among the participants 321 (52.2%) were single and 294 (47.8%) were married. Of the participants, 8 (1.3%) were primary school graduates, 6 (1.0%) secondary school, and 89 (14.5%) high school graduates with 303 (49.3%) undergraduate and some 209 (34.0%) holding postgraduate degrees.

Data-collection Tools

Socio-demographic Information Form

This form was prepared by authors to collect the demographic information including age, gender and level of education.

The Mentalization Scale (MentS)

The MentS consists of 28 items with a 5-point Likert scale (1- Completely incorrect, 5- Completely correct). The MentS has three sub-dimensions: self-based mentalization (MentS-Self, MentS-S), others-based mentalization (MentS-Others, MentS-O), and motivation to mentalization (MentS-Motivation, MentS-M). In the original study, Dimitrijević et al. (2018) reported Cronbach's alpha internal consistency coefficients of the scale as 0.84 for the total score, 0.76 for self (MentS-S), and 0.77 for others (MentS-O) and motivation dimensions (MentS-M) (Dimitrijević et al. 2018).

Trait Emotional Intelligence Questionnaire - Short Form (TEIQue-SF)

The TEIQue-SF was developed by Petrides and Furnham (2001) to assess the level of self-perception about the individual's emotional competency. The scale was adapted to Turkish by Deniz et al. (2013). The Turkish form of the scale consists of 20 items with 7-point Likert type rating (1-Strongly disagree, 7-Strongly agree). In TEIQue-SF studies (Petrides 2009; Petrides et al. 2010), Cronbach's alpha internal consistency coefficients were reported within the range of 0.87 and 0.90. In the Turkish version Deniz et al. (2013) reported Cronbach's alpha internal consistency coefficient as 0.81. In the present study, the Cronbach's alpha internal consistency coefficient of the scale was found as 0.85.

Borderline Personality Inventory (BPI)

The BPI was developed by Leichsenring (1999) and aims to determine borderline personality traits. The scale is a self-information tool that consists of 53 true or false items. The scale was adapted to Turkish by Aydemir et al. (2006). In the original study, the Cronbach's alpha internal consistency coefficient was reported as 0.91 (Leichsenring 1999). Aydemir et al. (2006) reported Cronbach's alpha internal consistency coefficient as 0.92 in the Turkish adaptation of the scale. In the present study, the Cronbach alpha internal consistency coefficient of the scale was calculated as 0.90.

Procedure

Prior to the adaptation of the Mentalization Scale into Turkish, the author of the scale was contacted via e-mail for permission to carry out such a study. Following receipt of permission to continue, items in the scale were translated from English to Turkish. This process was handled by two experts who are proficient in English and have Ph.D. degrees clinical psychology. Then, the two individual translations were reviewed and merged into a final form, which then was back-translated to English by another expert. After the completion of the back-translation, the scale was sent to its developer for review. Language validation was completed upon developer's approval of the back-translation.

In order to examine the test-retest reliability, Turkish translation of the scale was applied twice with an interval of three weeks to a total of 65 participants (30 male, 35 female) studying in sociology and philosophy departments (first and second grades) of the Faculty of Arts and Sciences at Mersin University. The average age of the participants was 20.58 (SD=1.24). Main data was collected after the test-retest stage. With the onset of COVID-19 measures in Turkey from March 2020 and on, study forms were delivered to the participants via the online survey program (i.e. Google Forms). Survey links were also shared on social media platforms (e.g. Facebook, Twitter).

This study was approved by Baskent University Institutional Review Board and Ethics Committee (Project No: KA20 / 17) and supported by Baskent University Research Fund.

Statistical Analysis

To validate the construct of the Turkish Form of the MentS, exploratory and confirmatory factor analyzes were applied. Related studies about factor analysis (e.g. Henson and Roberts 2006; Worthington and Whittaker 2006) recommend conducting the exploratory and confirmatory factor analyses with two different data-sets. Moreover, Suhr (2006) stated that using the same data for exploratory and confirmatory factor analysis reconfirms an already found result. In line with the recommendations mentioned above, the sample was randomly split into two data-sets with 307 and 308 participants. There was no significant difference between the two data-sets in terms of age ($t(613)=-1.436$, $p=0.152$) and gender ($\chi^2(1)=0.079$, $p=0.778$). In order to determine the criterion-related validity, Pearson Moments Correlation analysis was used to examine the relationship between the MentS, the BPI, and the TEIQue-SF. For reliability, Cronbach's alpha internal consistency coefficients and test-retest methods were used. Finally, an independent sample t-test analysis was conducted to compare the scores obtained from the scale in terms of gender.

RESULTS

Construct Validity

Exploratory Factor Analysis (EFA)

As a result of the first EFA, an 8-factor structure with an eigenvalue above 1 explained 56% of the variance. Similar to the original structure of the MentS, the scree plot graph

showed that items were distributed into 3 factors. The results of the second EFA, showed that the factor loading of item numbers 15, 17, and 28 were lower than 0.30. After these items were excluded, 3-factor and 25-item final form of scale explained 40.32% of the variance (KMO=0.775, $\chi^2(200)=2257.592$, $p<.001$).

Confirmatory Factor Analysis (CFA)

To verify the three-factor structure obtained from the exploratory factor analysis, a confirmatory factor analysis was performed with 'Lavaan' version 0.5-22 (Rosseel 2012) in the R 3.3.1. Results of the CFA revealed that the three-dimensional structure with 25 items was demonstrated acceptable fit indices (χ^2[296, N=307]=519.017, $\chi^{2/df}$=1.75, RMSEA=0.05, GFI=0.98, CFI=0.90, AGFI=0.98, SRMR=0.06). According to these findings, it can be said that the three-dimensional structure of the Turkish version of MentS has acceptable fit indices, similar to the three-dimensional structure of the original scale. The factor loading of the items are shown in Table 1 based on the results of the EFA and the CFA.

Criterion-Related Validity

To determine the criterion-related validity, the relationship between the dimensions of the MentS and other variables was examined. As presented in Table 2, the total score and dimensions of the MentS were statistically associated with the TEIQue-SF and the BPI. Moreover, borderline personality traits were negatively correlated with emotional intelligence traits.

Reliability

To determine the reliability of the MentS, first, test-retest reliability analysis was conducted twice to 65 participants at a three-week interval. The Pearson Moments correlation coefficients between these two applications were 0.73 for the MentS total score, 0.68 for self-dimension (MentS-S), 0.70 for the others dimension (MentS-O), and 0.64 for

Table 1. The factor loadings of the items from the results of exploratory and confirmatory factor analysis

Factor	MentS Items	EFA	CFA
1	4. I often think about other people and their behaviors.	.723	.610
1	24. I have always been interested in the reasons why people behave in certain ways.	.707	.649
1	13. I find it important to understand what happens in my relationship with people close to me.	.670	.716
1	1. I find it important to understand the reasons for my behaviors.	.638	.739
1	7. When someone annoys me, I try to understand why I react in that way.	.621	.695
1	16. I often talk about emotions with people that I am close to.	.567	.573
1	27. Since we all depend on life circumstances it is meaningless to think of other people's intentions or wishes.*	.457	.546
1	9. I do not like to waste time trying to understand other people's behavior in detail.*	.432	.472
2	12. Sometimes I can understand someone's feeling before s/he tells me anything.	.767	.614
2	10. I can make good predictions of other people's behavior when I know their beliefs and feelings.	.719	.553
2	5. Usually I can recognize what makes people feel uneasy.	.693	.679
2	3. I can recognize other people's feelings.	.669	.694
2	20. I can describe significant traits people who are close to me with precision and in detail.	.558	.724
2	2. When I make conclusion about other people's personality traits, I carefully observe what they say and do.	.756	.523
2	6. I can sympathize with other people's feelings.	.487	.430
2	23. People tell me that I understand them and give them sound advice.	.483	.472
2	25. I can easily describe what I feel.	.430	.492
3	21. I am often confused about my exact feelings.*	.741	.610
3	11. I often cannot explain, even to myself, why I did something.*	.729	.459
3	18. I find it difficult to admit that I am sad, hurt, or afraid.*	.679	.625
3	22. It is difficult for me to find the right words to express my feelings.*	.635	.615
3	8. When I get upset, I am not sure whether I am sad, afraid, or angry.*	.615	.524
3	26.While people talk about their feelings and needs my thoughts often drift away.*	.472	.547
3	19. I do not like to think about my problems.*	.467	.567
3	14. I do not want to find out something about myself that I will not like.*	.421	.662
Eigenvalue	Factor 1: 2.237, Factor 2: 4.693, Factor 3: 3.149		
Explained variance	Factor 1: 8.957, Factor 2:18.772, Factor 3:12.596		

Note. Factor 1: MentS-M, Factor 2: MentS-O, Factor 3: MentS-S, EFA: Exploratory Factor Analysis, CFA: Confirmatory Factor Analysis; * Reverse items

Table 2. The correlations between the MentS, TEIQue-SF, and BPI scales.

	1	2	3	4	5	6
1. MentS-Self	-	.317**	.362**	.697**	.628**	-463**
2. MentS-Others	-	-	.547**	.701**	.388**	-.124*
3. MentS-Motivation	-	-	-	.796**	.241**	-.125*
4. MentS-Total	-	-	-	-	.528**	-.293**
5. TEIQue-SF	-	-	-	-		-.468**
6. BPI	-	-	-	-	-	-

Note 1. **p<.001, *p<.05,
Note 2. TEIQue-SF: Trait Emotional Intelligence Questionnaire-Short Form; BPI: Borderline Personality Inventory.

the motivation dimension (MentS-M). Internal consistency reliability of the MentS was calculated with 615 participants. Cronbach's alpha internal consistency coefficient was 0.84 for the total score of the scale, 0.78 for MentS-S, 0.80 for MentS-O, and 0.79 for MentS-M. Item-total correlations of the scale range from 0.28 to 0.52 for the total score, from 0.43 to 0.57 for MentS-S, from 0.38 to 0.57 for MentS-O, and from 0.38 to 0.58 for MentS-M.

Gender-Based Comparison for the Sub-Scales and Total Score of the MentS

This study examined whether or not the scores of the participants from the sub-scales and total score of the MentS differ in terms of gender. Independent sample t test analysis revealed that female participants (M=101.28, SD=11.81) obtained significantly higher scores compared to males (M=99.29, SD=11.98) in the total scale score (t(613)=2.07, p<0.05). Similarly, MentS-M scores showed statistically significant difference (t(613)=2.89, p<0.01), and females (M=35.52, SD=5.80) got higher scores compared to males (M=34.15, SD=5.92). There was no significant gender-based difference in the MentS-O (t(613)=0.85, p=0.40) and MentS-S scores (t(613)=0.66, p=0.51).

DISCUSSION

Empirical studies carried out in recent years show an increased interest in mentalization studies. The MentS, developed by Dimitrijević et al. (2018), is a comprehensive measurement tool that is frequently used in studies for the evaluation of mentalization capacity (e.g. Seydi et al. 2019). The present study aimed to adapt the MentS into Turkish and determine its psychometric properties on a community-based sample.

Field-literature often recommends the use of both the EFA and the CFA as because structural changes could occur in the Turkish form of the scale due to language and cultural differences for determining the validity in adaptation studies (Orçan 2018). In line with this recommendation, the data set was divided into two, and EFA and CFA were performed. EFA results revealed, first, a scree plot that was distributed over three factors similar to the original structure of the scale. As a result of the analysis, it was observed that the factor loadings of the three items in the original form of the scale were lower than 0.30. After these items were removed from the analysis, the explained variance of the 3-factor and 25-item structure was 40.32%, and this value was close to the variance (37.51%) reported for the three-factor structure of the original scale (Dimitrijević et al. 2018). Secondly, CFA was performed to confirm the resulting structure from the EFA. The results revealed that the three-dimensional structure of 25 items had an acceptable level of fit indices. Consequently, the EFA and CFA exhibited that the Turkish form could be considered as a three-dimensional structure in line with the three-dimensional structure of the scale in its original language.

Another method for the assessment of construct validity is to examine the relationship between the dimensions of the scale and the total score. Accordingly, in our study we found that the correlations of each dimension of the scale with the total score were high and their correlations with each other were moderate. In order to determine criterion-related validity, the relationship between emotional intelligence and borderline personality traits was examined. Consistent with the literature, the self (MentS-S), others (MentS-O), and motivation (MentS-M) sub-dimensions and total scores were positively related to emotional intelligence and negatively related to borderline personality traits. These findings are consistent with clinical observations (Allen et al. 2008) and empirical studies (Dimitrijević et al. 2018), and point out that mentalization is related to emotional intelligence. Hence, Fonagy and Bateman (2008) stated that mentalization is a developmental success related to understanding one's own and others' mental states and developmental failure in this regard is a crucial element in the formation of borderline personality patterns. In other words, the lack of mentalization ability may amplify borderline personality traits, which our findings also confirm.

The reliability of the scale was examined by test-retest analysis and calculation of Cronbach's alpha internal consistency coefficients. As a result of the two applications performed three weeks from one another, the test-retest reliability analysis revealed that the stability of the scale over time was at the desired

level in terms of both the total score and its sub-dimensions. The Cronbach's alpha internal consistency coefficients of the total score and sub-dimensions of the MentS were higher than 0.70 and the sub-dimensions of the scale had acceptable internal consistency coefficients ($\alpha_{MentS-S}$=0,76, $\alpha_{MentS-O}$=0,77 and $\alpha_{MentS-M}$=0,77). The results indicate that the internal consistency of the scale is good and similar to the original scale's (Dimitrijević et al. 2018). In addition, the item-total correlation coefficients were found to be higher than 0.25. The item-total correlations calculated for the total score of the scale ranged from 0.28 to 0.52 and are similar to the item-total correlations reported in the original study (0.26-0.51). To sum up, the Turkish version of the MentS consisting of 25 items was found reliable measurement tool.

Finally, the total score of the scale and the scores of the sub-scales were compared in terms of gender. The scores obtained from the self (MentS-S) and others (MentS-O)-based mentalization dimensions did not differ in terms of gender. However, in terms of the motivation (MentS-M) sub-dimension and the total score, the scores of the female participants were significantly higher than those of male participants. The finding that total mentalization skills are higher in female compared to male participants is consistent with previous studies (e.g. Dimitrijević et al. 2018, Krach et al. 2009). According to Rutherford et al. (2012), higher scores on mentalization in female participants are associated with their higher intrinsic motivation (social interaction motivation) to understand the mental states of others from the early developmental periods. In addition, studies indicate that women score significantly higher in terms of emotional intelligence (Joseph and Newman 2010) and empathy (Ibanez et al. 2013), which are both related to mentalization. These results may also be linked to women's motivation to empathize rather than their ability to empathize (Ickes 1997). In the current study, higher scores of female participants in the motivation dimension of mentalization can be explained within the framework of such findings in the literature.

The current study also has limitations. First, all data was obtained from self-reported measures. Since the participants may have answered the items with a tendency to behave in the direction of social desirability, it is recommended to control such bias in future studies. Second, the data was collected through online surveys due to COVID-19 pandemic regulations. Although this method is advantageous in terms of providing data from participants living in different cities and from a larger sample, it may also hold adverse effects in terms of not being able to reach a homogeneous sample, standardizing the level of education of participants and lack of information on the kind of environment people participated in the study. Third, since the majority of the participants were university and postgraduates, cognitive status was not considered as an exclusion criterion, assuming no impairment in cognitive functions. In further studies, taking the cognitive functions of the participants as an inclusion/exclusion criterion and/or examining the relationship between the level of intelligence and mentalization capacity are recommended. Another limitation of the study is that, due to the difficulty of reaching the same sample twice, the test-retest reliability analysis, which was conducted to determine the consistency of the answers over time, was carried out with 65 university students, while other validity and reliability analyses were carried out with 615 participants forming the entire sample of the study. Finally, only data collected from the community sample were used in this study. The inclusion of the clinical sample in future studies and the examination of disorders related to mentalization capacity, especially in individuals with borderline personality disorder, is recommended for future studies in Turkey.

In conclusion, the MentS (Dimitrijević et al. 2018) was adapted into Turkish and our findings confirm it is a valid and reliable measure. This study indicates that the Turkish form of the MentS is suitable for evaluating the level of mentalization in future studies based on population samples.

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REVIEW ARTICLE

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Association Between Loneliness and Suicidal Behaviour: A Scoping Review

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ABSTRACT

Objective: Suicide is a public health issue, and there are several factors leading to suicide, like mental illness and psychosocial stressors. Actual loneliness (living alone) and subjective loneliness (feeling of being alone) and different suicidal behaviors have been reported to have some link. This scoping review aimed to assess the association between loneliness and suicidal behaviour by exploring the existing literature.

Methods: A scoping review was conducted implementing the appropriate framework and in accord with the PRISMA-ScR extension. A PubMed database search was made using a combination of terms to find publications in English from 2011 to 2021. Studies were included if they reported quantitative outcomes of the association between loneliness and suicidal experiences, including suicidal thoughts, plans, and/or attempts. Screening and data charting of the published literature was conducted by a panel of authors. The accuracy and clarity of extracted data was checked by three reviewers.

Results: Among 421 articles found, 31 full texts were evaluated based on exclusion and inclusion criteria, out of which, 18 papers that reported quantitative outcomes of the association between loneliness and suicidal experiences were included. We found that association between loneliness and suicidal behaviour is determined by individual, social and cultural factors. Co-existing mental illness, substance use disorder and economic hardship play an important role for the completion of suicide.

Conclusion: Loneliness is correlated with suicide, and the knowledge about this association could assist in the identification of suicidal individuals or those at elevated risk of suicidal behaviour. Future studies should focus on loneliness and its relation to suicidal ideation in individuals with different mental health disorders and personalities.

Keywords: Suicide, loneliness, mental disorders, stress, psychological

INTRODUCTION

Suicide is the deliberate act of ending one's life. It makes up 1.4% of deaths worldwide (Bachmann 2018). Suicide attempts are more common among females, while deaths due to suicide are more prevalent among men (Freeman et al. 2017). Common methods of suicide include exsanguination, poisoning, asphyxiation, falls from height, firearms, and electrocution. The prevalence of methods used varies according to situational factors such as the availability of firearms, access to tall buildings, and unique geographical features. Firearm suicides are considered to be the most prevalent method in the United States and Europe, as it is common for people to own firearms at home, which, in turn, influences the number of suicides (Vladeta et al. 2008). Poisoning was found to be common in South Asian countries, with ingestion of pesticides frequent in India (Rane and Nadkarni 2014, Arafat et al. 2021).

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Several mental health disorders are known to be associated with suicides. The suicide risk has been estimated to be 5–8% for depression, alcoholism, and schizophrenia (Inskip et al. 1998, Nordentoft et al. 2011). A study by Shoib and colleagues reported that the majority of the cases of completed suicide are primarily associated with mental illness (Shoib and Kim 2019). In a US-based study, Brown and colleagues found that individuals diagnosed with mood disorders such as major depressive disorder and bipolar disorder had a three to ten times higher risk of suicide-related deaths (Brown et al. 2000). In another US-based study involving veterans (Ilgen et al. 2010), it was revealed that anxiety disorder, bipolar disorder, depression, and schizophrenia spectrum disorders were related to a two to three times higher risk of suicidal death. However, the evidence underlying these claims states that the correlation to mental disorders differs from the socio-cultural context. Certain countries such as India may not see a strong correlation between mental disorders and suicide. However, poverty and suicide are more closely related (Rane and Nadkarni 2014, Shoib et al. 2021). Other factors leading to suicide or possibly triggering suicide attempts include life stressors, adverse life events, psychological trauma, and poor social support (Kumar and George, 2013, Shoib et al., 2020).

Loneliness is one of the known stressors experienced by people at risk of suicide (Stravynski and Boyer 2001). The feeling of loneliness is determined by how individuals perceive their social support and not by the number of social connections or emotional ties. Feelings of hopelessness, meaninglessness, and anhedonia often accompany loneliness. Research shows that loneliness peaks in late adolescence, gradually reduces during middle adulthood, and rises in late adulthood (Luhmannand and Hawkley 2016). Wang et al. (2018) found an association between patients' perception of loneliness and worsened outcomes of mental disorders, which could explain the positive correlation between loneliness and suicide. Further, beyond diagnostic categories, loneliness was associated with low life satisfaction and low resilience (Zebhauser et al. 2014). A 9-year cohort study found loneliness to be a predictor of suicide and self-harm, with a positive correlation between increased loneliness and lethality of suicide in men (Shaw et al. 2021).

Social isolation is defined as the absence of social interactions, contacts, and relationships on an individual level and society on a broader level (Berg and Cassells 1992). On the other hand, loneliness is not necessarily about being alone; it is a state of mind with the perception of being isolated (Tiwari 2013). Living alone per se was not associated with loneliness; however, limited social relationships and a smaller social network indicated loneliness in all genders (Zebhauser et al. 2014). Trout (1980) proposed that social isolation strongly correlates with suicide. This notion is supported by findings from multiple researchers that loneliness, one's social standing, and level of social organisation correlate to suicidal ideation and the individual being progressively isolated (Jacobs and Teicher 1967).

Although there have been multiple studies that show a positive association between loneliness and suicide, these studies are mostly conducted in a Western socio-cultural context and may not represent other settings in the world. Personal traits also influence the relationship between loneliness and suicide (Abdellaoui et al. 2019). There is a need to study the connection between loneliness and suicide further, and it should be established and distinguished from the quantity and quality of one's social support networks, especially concerning modern times (Killgore et al. 2020). This review aims to compile an updated picture of how loneliness correlates to suicide in males and females across diverse cultures and contexts. Our review may help identify individuals at considerable risk of suicide.

METHODS

In this scoping review, the literature was searched with PubMed, using the search terms 'loneliness' OR 'lonely' AND 'suicide' OR 'suicidal'. Suicidal behaviour includes suicidal ideation, suicide attempts, and completed suicide (Esposito-Smythers et al. 2011). The search was limited from July 2011 to July 2021, and publications written in English. The PRISMA chart in Figure 1 shows the shortlisting process. Studies were included if they reported quantitative outcomes of the association between loneliness and suicidal experiences, including suicide thoughts, plans, and/or attempts. Qualitative studies, case series, case studies, position papers, reviews, dissertations, theses, and those that did not provide necessary data for the review were omitted. The relevant studies were identified by scanning the titles and articles' abstracts by a panel of consultant psychiatrists. All studies were scrutinised, and data were then entered into a spreadsheet designed in line with the aims of our study. Country of study, study design, methods of assessment, focused domains of the study, mean age of the respondents with the standard deviation, and prevalence were included. Three consultant psychiatrists' authors checked all information for clarity and accuracy in the spreadsheets and publications.

RESULTS

The search found 421 papers, and after deleting 154 duplicates and excluding 227 studies based on the title and abstract, 31 full-text articles were evaluated for inclusion. Of these, 12 papers failed to meet the eligibility criteria and were subsequently excluded, and 18 articles were included in this scoping review (Figure 1). Table 1 summarises findings from these studies in terms of type of study, country, population, gender and

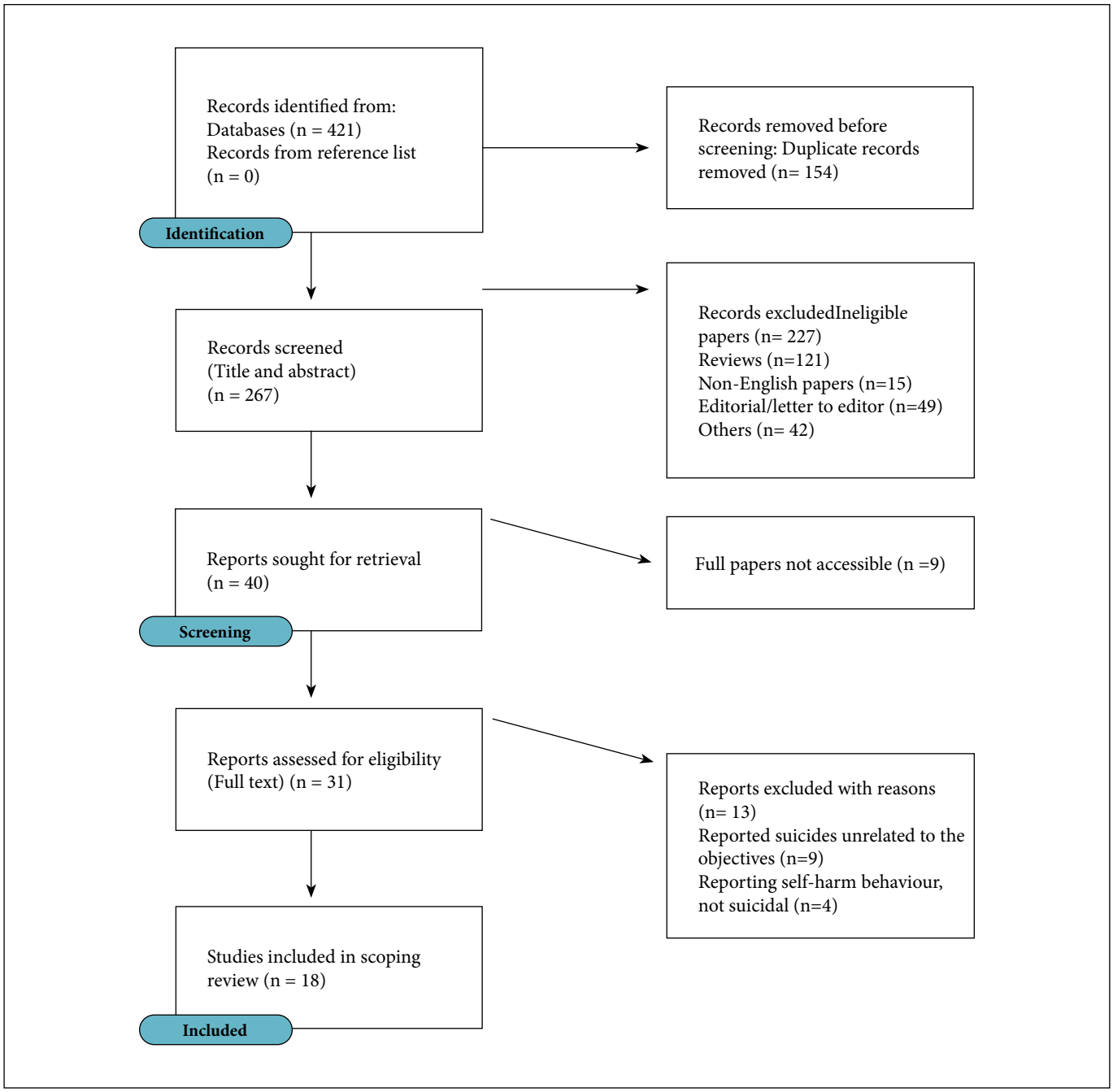

Figure 1. PRISMA flow diagram

findings. Of the included studies, six (33.3%) were from the USA, and seven (38.8%) were from Europe. Other studies were from Asia and the Pacific islands. Three longitudinal studies were analysed, and others were cross-sectional.

DISCUSSION

We assessed the association between loneliness and suicidal behaviour by analysing quantitative studies from the past decade. Several psychiatric and psychosocial factors were important for this association. In relevance to psychiatric disorders, Stickley and Koyanagi (2016) found that loneliness is correlated with suicidal behaviour both in people with and without common mental disorders. However, lonely people diagnosed with a mental disorder have a heightened risk of suicidal ideation. Mushtaq and others (2014) mentioned specific mental disorders resulting from loneliness including depression, alcohol abuse, and personality disorders as risk factors for suicidal behaviour. Chang and others (2017) support this with the proposition that loneliness is a noteworthy predictor of suicide risk. It strongly correlates with suicidal behaviour, and the risk could be changeable if loneliness is addressed. Although hopelessness is not directly correlated to loneliness, it may be a mediator that

Table 1. Summarize of Studies

Author, Year	Country	Study characteristics	Sample	Male	Female	Mean Age (Years)	Findings
North America							
Chang EC et al., (2019).	United States of America	Observational study using regression analysis	156 Latino college students	35	121	19.78	Regression analyses results, after controlling for age and sex, showed that depression and loneliness were noteworthy predictors for suicide risk. Depression was a twofold stronger predictor of loneliness. A significant depression-loneliness interaction was found to be predictive of suicide risk. Dysphoric and socially isolated Latino students had the highest level of suicide risk.
Teo et al., (2018).	United States of America	Cross-sectional	301 primary care patients	251	50	55.4	Loneliness was linked with high levels of depression and suicidal ideation. Loneliness and lower help-seeking behaviours were also interlinked.
Chang EC et al., (2017).	United States of America	Cross-sectional	228 College Students	54	174	19.69	Loneliness was a significant predictor of suicidal risk. Presence of future orientation significantly heightened depressive symptoms and suicidal ideation, even after controlling for loneliness. Students who had higher future orientation reported significantly lower depression and suicidal ideation.
Lamis DA et al., (2014).	United States of America	Cross-sectional	207 undergraduate drug-using students	69	138	19.84	Drug use was found to be a potential mediator (indirect effect) in the loneliness-suicidal ideation link, after controlling for several covariates.
Hirsch JK et al., (2012).	United States of America	Cross-sectional	385 ethnically diverse college students	118	267	19.61	Loneliness was found to be a moderator between societal problem-solving aptitude and suicidal behaviours, particularly for African Americans, European Americans, and Asian Americans. For Hispanic Americans, life stress was a moderator.
Lutzman M et al., (2021)	United States of America	Cross-sectional	198 elderly men	198	0	76.14	Loneliness and social integration moderated the association between physical pain and suicidal ideation. This effect was significantly higher among single men.
South America							
Salvo GL et al., (2013).	Chile	Cross-sectional	763 high school students	374	389	14-19	Loneliness, female gender, impulsivity, and alcohol use were directly associated with suicidal behaviour and predicted 31% of the suicidal behaviour.
Europe							
Stickley A et al., (2016)	England	Cross-sectional	7403 household residents aged ≥16 years	3142	4061	44.78	Loneliness was associated with suicidal behaviour. Odds ratios for suicidal behaviour were similar for lonely individuals without common mental disorders (CMDs), and for individuals with CMDs who did not experience loneliness. Individuals with loneliness and CMDs had higher odds for suicidal ideation.
Ernst M et al., (2021).	Germany	Cross-sectional	633 adult long-term CCS	352	281	-	Loneliness predicted severe anxiety symptoms and suicidal ideation in childhood cancer survivors (CCS). Loneliness did not predict somatic and depressive complaints at follow-up (which increased with age).
Pitman AL et al., (2020).	Europe	Cross-sectional	3193 adults	607	2586	25.1	Among bereaved adults, loneliness was significantly related with suicidal ideation and suicide attempts. The link between loneliness and suicide attempt risk was alike whether respondents were bereaved by suicide or not.
Bennardi M et al., (2019).	Spain	Cross-sectional	2392 from general population	1103	1289	58.68	In 18-59-year-old individuals, lower positive affect was related to suicidal ideation. In 60 years and older individuals, loneliness was related to suicidal ideation.

continuation of Table 1

Gunzelmann et al., (2016).	Germany	Cross-sectional	795 elderly living without a partner	371	424	70	Elderly individuals, 80 years or older, who were living without a partner and experiencing a high degree of loneliness and hopelessness reported more suicidal ideation.
Creemers D et al., (2012).	The Netherlands	Cross-sectional	95 female undergraduate students at the College for Higher Education Arnhem/ Nijmegen (HAN)	0	95	21.2	Explicit (not implicit) self-esteem was inversely related to depression symptoms, suicidal ideation, and loneliness. Hurt self-esteem (high implicit self-esteem combined with low explicit self-esteem) was steadily related to amplified levels of depression symptoms, suicidal ideation, and loneliness. Defensive or fragile self-esteem (high explicit and low implicit self-esteem), however, was not.
Middle East							
Stein JY et al., (2017).	Israel	Case-control	106 ex-POWs	-	-	53.4	Captivity, versus war, was associated with more post-traumatic stress syndrome (PTSS), worse loneliness, resulting in higher suicidal ideation (SI). Loneliness was not directly impacted by trauma type. Also, its relation to SI was not associated with subsequent PTSS.
China							
Niu L et al., (2020).	China	Case-control autopsy study	242 elderly suicide cases	136	106	74.4	Loneliness, hopelessness, and depression symptoms were connected to completed suicide. They also found a link between loneliness and hopelessness. Elderly, unemployed individuals, living alone, lesser subjective social support, experienced depression symptoms, showed advanced levels of hopelessness, significantly associated with raised suicide risk.
Zhang D et al., (2020).	China	Cross-sectional	538 residents from 37 nursing homes, aged > 60 years.	21	321	With suicidal ideation: 79.10 Without suicidal ideation: 77.96	Resilience partially mediated the relation between loneliness and suicidal ideation. Social support moderated the resilience on suicidal ideation, and indirectly affected loneliness on suicidal ideation.
Southeast Asia							
Yadegarfard M et al., (2013).	Thailand	Cross-sectional	190	-	-	Respondents 47.7% (n = 90): 15–19 yrs; 52.6% (n = 100): aged 20–25 years	The level of education significantly influenced depression, loneliness. Several sex partners significantly influenced sexual-risk behaviour and suicidal ideation, and age significantly influenced sexual-risk behaviour and suicidal ideation.
West Pacific							
Sharma B et al., (2017).	Western Pacific Islands	Case-control	4122 students	1876	2158	≤14 years (52%), ≥15 years (45.9%)	Individuals with higher exposure to bullying, fighting, and injury (highest odds for physical injury) had higher odds of loneliness, insomnia, suicidal ideation, and suicide attempt compared to the non-exposed group.

Key: CMDs: common mental disorders; CCS: childhood cancer survivors; PTSS: post-traumatic stress symptoms; SI: suicidal ideation; CHAID: chi-square automatic interaction detection.

modifies the suicide risk in lonely individuals. McClelland and others (2020) also support loneliness as a predictor of suicide risk while proposing that depression is a mediator. They also found females to report a stronger relationship between loneliness and suicidal ideation. However, these findings are only applicable to selected populations. On the other hand, a longitudinal study in 2010 reported that loneliness correlated with depressive symptoms independent of gender; however, it did not predict suicide ideation when controlled for depressive symptoms (Lasgaard et al. 2011). Therefore, whether loneliness predicts suicide independently is doubtful and would require further longitudinal studies for confirmation in non-depressed populations.

There seems to be a three-way association between loneliness and suicidal behaviour concerning anxiety. While acknowledging the research gap in loneliness in association with suicide due to its subjectivity, Zalsman (2020) concluded that living alone increases the risk of suicidal behaviour. He links loneliness to depression and anxiety, which results in a higher risk of suicide (Zalsman 2020). According to a study by Teo and others (2018), loneliness was associated with lower patient activation and help-seeking intentions

that limited mental health access. Social isolation is seen in depression and, coupled with loneliness, may be a risk factor for suicide rather than anxiety, perceived burdensomeness and hopelessness, as reported in a study by Hom and others (2017). In childhood cancer survivors, loneliness was predictive of more severe anxiety symptoms and suicidal ideation (Ernst et al. 2021). Further, captivity associated post-traumatic stress symptoms, loneliness, and suicidal ideations were seen in participants of a study from Israel (Stein et al. 2017). Moreover, Gallagher and others (2014) found that loneliness mediates the relationship between social anxiety and suicidality in adolescents, highlighting the triangular association between anxiety, loneliness, and suicidality.

There have been several studies on loneliness and suicidality in specific demographic populations. In relevance to older adults, Lutzman and others (2021) studied older men and found a relationship between physical pain and suicidal ideation, mediated by loneliness and social integration. In addition, Niu and others (2020) found that loneliness, hopelessness, and depressive symptoms were related to completed suicide in older adults. Nursing home residents had suicidal ideation linked to loneliness and poor social support (Zhang et al. 2020). Also, Gunzelmann and others found that loneliness with hopelessness predicted suicidal ideation in people over 80 (Gunzelmann et al. 2016). In younger populations, students who experienced dysphoria and social isolation had the highest risks of suicide. For adolescents in school, Sharma, Lee and Nam (2017) found bullying to cause loneliness and suicidal ideation, especially for students who were physically injured when they were bullied. Chang and others (2017) studied Latino students and found that although loneliness is correlated with suicide, depression was twice as highly correlated to suicide compared to loneliness. An earlier meta-analysis did not find any significant effect of age on the relationship between loneliness and suicide behaviour (McClelland et al. 2020). A recent online Slovenian study found that emotional loneliness is a significant factor in relation to suicidal ideation in all age groups they studied (Gomboc et al. 2022).

In relevance to grief, although bereavement may be intuitively linked to loneliness and suicide, Pitman and others (2020) found that the correlation between loneliness and suicide is independent of whether or not the subject is grieving. Interestingly, according to Shaw and others (2021), post-traumatic stress is not linked to loneliness and suicidal ideation. According to a follow-up study, social support does not necessarily help alleviate loneliness and suicidality, as loneliness depends on the individual's perception of their social circles and can manifest even though an individual has vibrant or supportive social circles (Bennardi et al. 2019). In addition, socio-cultural aspects such as living in extended families, the role of grandparents, elderly participation in the workforce, and respect for older adults in society would also affect the relationship between loneliness and suicidality in diverse ethnoreligious settings (Barreto et al. 2021).

Concerning coping strategies, Zhang and others (2020) proposed that resilience is mediated by the correlation between loneliness and suicidality. Teaching resilience and coping strategies through therapeutic interventions could help lonely individuals cope with their loneliness and reduce their risk of suicidal ideation. Furthermore, Hirsch and others (2012) found that loneliness was a moderator between social problem-solving ability and suicidal behaviours. In addition, Creemers and others (2012) stated that damaged self-esteem was consistently associated with increased suicidal ideation and loneliness. Lamis and others (2014) found that substance use could be another potential mediator. Although drug use tends to complicate matters and may even lead to substance use disorders, it was found to help alleviate loneliness potentially.

All studies reviewed agreed that there was a positive association between loneliness and suicide, but with differing views on the possible contexts in which they could be correlated, as highlighted by some studies. As humans are social animals, socialisation is vital to our welfare and psychological wellness. Intuitively, loneliness and isolation would cause psychological instability, ranging from irritability to severe psychological damage such as trauma. The mechanism by which loneliness is linked to suicide is complicated, just as suicide itself. There have been insufficient studies on how they are interconnected in varying socio-cultural tabulations (Van Staden and Coetzee 2010). Our review will help understand the factors associated with loneliness across different age groups, cultures, and genders and how they are related to suicidal ideation and suicide attempts.

One viable way loneliness could result in suicide is by developing and worsening depression in the lonely individual. When one's social circles are inadequate to sustain them socially, they may develop depressive symptoms, which worsen over time, driving them towards suicidal behaviour. However, the loneliness could also have stemmed from depression, meaning the relationship between loneliness and depression is probably bidirectional. Likewise, other common mental disorders such as post-traumatic stress disorder and borderline personality disorder could cause loneliness, worsening the disorder and contributing to suicidal ideation (Nenov-Matt et al. 2020). The dynamics of loneliness and suicidal ideation in the presence of one or more mental disorders are not widely studied, mainly because most studies correlated depression with suicide or poor social networks with suicide instead of the feeling of loneliness that suicidal persons may feel.

Loneliness may also be more strongly correlated to suicide in more conservative countries, as expressing one's emotions may be taboo (Van Staden and Coetzee 2010). Countries with a strong stigma against mental disorders also worsen this issue as suffering individuals are dissuaded even further from expressing their emotions (Nawal 2021). This culture of containing one's emotions instead of confiding in another may lead to suppression of emotions, which predisposes one to emotional distress that could lead to suicidal ideation. Though loneliness in conservative countries has not been explored explicitly, this could be a critical step in improving measures to counter suicide and loneliness in such cultures. In such settings, religion and family relationships also play a major role in mediating loneliness with their psychological well-being (Wijesiri et al. 2019).

CONCLUSION

The scoping review revealed an association between loneliness and suicide, with a different manifestation of suicidal behaviours found in different sociodemographic populations (age, gender, race) and subgroups of individuals (patients with mental illness, elderly, students); with mitigating and mediating factors. As we understand, loneliness is correlated with suicide, and the knowledge about this association could assist in the identification of suicidal individuals or those at substantial risk of suicidal behaviour. We recommend that in dealing with at-risk individuals, perhaps addressing loneliness with greater emphasis could impact their suicidal ideation. Research gaps that should be filled could include studies focusing on loneliness and its relation to suicidal ideation in individuals with different mental disorders and different personalities. We also propose to form models to explain the correlation between loneliness and suicidal ideation in people with different personality styles, socio-cultural learnings, and life experiences.

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Safety Profile of Aripiprazole During Pregnancy and Lactation: Report of 2 Cases

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ABSTRACT

Aripiprazole, a second-generation antipsychotic (SGA) medication, is an efficacious treatment for schizophrenia and bipolar disorder. However, its effects on pregnancy and lactation are not yet fully documented. Despite aripiprazole being available since 2002, there is only limited information on the risks and benefits of this treatment during pregnancy. Most of the information is limited to population-based studies examining malformation risk or case studies or small case series. The knowledge in this topic is still insufficient and there is a need to expand the literature. In this report, we present 2 cases exposed to aripiprazole during pregnancy and lactational period. In both our cases of aripiprazole exposure, no teratogenic effects were reported, and it was reassuring that the mothers did not develop gestational diabetes. However, both patients reported lactation failure.

Keyword: Mental illness, antipsychotics, aripiprazole, pregnancy

INTRODUCTION

Aripiprazole, a second-generation antipsychotic (SGA) medication, is an efficacious treatment for schizophrenia and bipolar disorder. However, its effects on pregnancy and lactation are not yet fully documented (Gentile 2004). Generally, antipsychotic treatment during pregnancy is associated with potential obstetric, teratogenic, neurobehavioral, and neonatal risks of toxicity. Weighing up these risks against the risks associated with untreated psychosis is a concern for clinicians and the patients (Klier and Lanczik 2005). A recent study aimed at documenting patterns of antipsychotic medication use among pregnant women in the period from 2001 to 2010 found that the use of SGAs during pregnancy increased threefold, from 0.4% to 1.3%, while the prescription of first-generation antipsychotics (FGAs) remained constant at around 0.1%. Quetiapine and aripiprazole were the most frequently dispensed drugs (Park et al. 2017).

Moreover, it is known that women treated with antipsychotic drugs are less fertile than controls, partly because of hyperprolactinemia secondary to antipsychotic drugs. However, aripiprazole is unlikely to increase prolactin levels and may therefore be linked to the likelihood of getting pregnant that is higher than for other antipsychotics (Paulus 2013, Jones et al. 2014).

Despite aripiprazole being available since 2002, there is limited information on the risks and benefits of this treatment in pregnancy (Gentile 2014a). Most of the information is limited to population-based studies examining malformation risk or case studies or small case series (Gentile 2014b, Huybrechts et al. 2016, Gentile et al. 2011). Frequently missing from these studies is confirmation of timing and dose of exposure, mental health indications, information on confounding factors in pregnancy such as body mass index, smoking, and alcohol use, and other concomitant exposures (Huybrechts et al. 2016, Bellet et al. 2015).

The knowledge in this topic is still insufficient and there is a need to expand the literature. In this report, we present 2 cases, exposed to aripiprazole during pregnancy and lactational period.

CASE

Case 1: Mrs RK, 29-year-old, a primigravida came to antenatal facility of our hospital at 10 weeks of pregnancy. She

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was diagnosed with schizophrenia [based on the International Classification of Diseases, tenth revision (ICD-10)], and was being followed up in the psychiatry outpatient department for the last 7 years with symptoms of auditory hallucinations, persecutory delusions, and social withdrawal. At the time of determination of pregnancy, she was in clinical remission and on stable doses of Tablet aripiprazole 20mg/day and Tablet escitalopram 10 mg/day for 1 year. She was referred to psychiatry outpatient services for evaluation. As the patient was exposed to both drugs for 10 weeks of pregnancy, the risk of fetal exposure to both drugs was explained to the patient and family members. After understanding the risk and pros and cons of continuing the pregnancy, the patient and her family members decided to continue the pregnancy. Both drugs were continued to prevent relapse of psychotic symptoms and recent depressive symptoms. She was continued on Tablet aripiprazole 20mg/d and Tablet escitalopram 10mg/d throughout pregnancy without exacerbation of any psychiatric symptoms.

Her routine ultrasonography at 12 weeks, anomaly scan at 18 weeks and triple markers tests for chromosomal abnormalities did not reveal any abnormality. Her blood sugar and other routine blood tests also did not reveal any abnormality. She was admitted to our hospital at 33 weeks with complaints of reduced fetal movements. She was managed conservatively and monitored. Her ultrasonogram was normal and all cardiotocography (CTG) during the hospital stay were reactive and fetal movement was good at discharge after 1 week. She was admitted at 38 weeks of gestation and had a spontaneous normal vaginal delivery. The baby cried immediately after birth and weighed 2.69 kg and the APGAR score of the baby at birth was 6. The mother could not breastfeed the baby as there was the scanty secretion of milk despite the best effort by the mother. The child is now 16-month-old and as per the history and physical examination, the child has no developmental issue.

Case 2: Mrs LP, 24 years, female had a history of catatonic symptoms, social withdrawal, apathy, auditory hallucination, and hallucinatory behavior during the initial presentation. She was diagnosed with schizophrenia based on thorough clinical history and examination. She was receiving treatment from the psychiatry outpatient department for the last 5 years. She was maintaining well on Tablet Aripiprazole 10 mg/day for the last 2 years. Although she was counselled to take precautions to avoid pregnancy while taking aripiprazole, she became pregnant after 6 months of marriage. Once the pregnancy came to light, the pros and cons were discussed. The patient and her husband decided to continue the pregnancy and the medication. The risk of continuation of the drug was explained to the family members. She continued her antenatal check-up throughout pregnancy. Her routine ultrasound at 12 weeks, anomaly scan at 18 weeks and triple markers tests for chromosomal abnormalities did not reveal any abnormalities. Her blood sugar and other routine blood tests were within the normal range during the antenatal period. There were no other complications noticed during the antenatal period. The patient was admitted to our hospital with spontaneous progress of labor at 38 weeks of pregnancy. The patient became uncooperative during labor and became agitated and hostile. Outlet forceps were used, under general anesthesia. On delivery, the baby was intubated and shifted to the nursery. The birth weight of the baby was 2.7 kilograms and the baby recovered well in the nursery over the next 3 days. During the postpartum period, the mother continued to be followed up in the psychiatry outpatient department and maintained well on Tab aripiprazole 10 mg/day. The mother could not breastfeed the child due to lactation failure. As per history and physical examination, the baby is healthy with normal developmental milestones. Now he is 1 years old with no developmental issues.

DISCUSSION

Although the course of schizophrenia during pregnancy is not well defined, these pregnancies should be considered high risk (Howard 2005). The offspring of women with schizophrenia appear to face an increased risk of lower APGAR scores, low birth weight, intrauterine growth retardation, preterm delivery, stillbirth, malformation, and infant death (Howard, 2005).

The second-generation antipsychotics (SGA), like clozapine, olanzapine, risperidone, ziprasidone, and quetiapine have been reported to be associated with increased risk of weight gain during pregnancy (Nasrallah 2003). Aripiprazole has become one of the most commonly prescribed psychotropics.

Gestational diabetes mellitus has been reported with the SGAs such as olanzapine and clozapine (Goldstein et al. 2000); it is reassuring that gestational diabetes mellitus did not develop with aripiprazole exposure in our patients. Similar findings have been reported in previous case reports (Mendhekar et al. 2004, Bellet et al. 2015).

Selective Serotonin Reuptake Inhibitors (SSRIs) are first-line pharmaceuticals for treating depression as well as the favoured antidepressants during pregnancy; with escitalopram displaying a good safety profile during pregnancy and breastfeeding. In our first patient, Tablet escitalopram, was continued keeping in mind the safety profile, as mentioned in the literature (Trifun et al. 2020).

In both our patients the outcome of pregnancy remained safe as described in the literature (Mervak et al. 2008, Paulus 2013, Bellet et al. 2015) but the first patient was admitted with reduced fetal movement at 33 weeks of pregnancy. The reason for reduced fetal movement in index patient cannot

be attributed to aripiprazole as there is no specific evidence in the literature to substantiate this (Cuomoet et al. 2018). In a recent study by Freeman et al. (2021), in which they compared 158 women who were exposed to aripiprazole in their first trimester to 690 controls, they concluded that the risk of major malformations after first trimester exposure to aripiprazole was not significant compared to controls. While these results are reassuring, they are limited by relatively small numbers of participants and require more research. However, increased incidence of miscarriages due to aripiprazole has been described in the literature, where it is elucidated that the probable mechanism could be attributed to the decrease in prolactin levels (Sakai et al. 2017).

In both our patients, there was lactation failure. This occurrence has also been seen in a recent study by Komaroff (2021), where the patient was treated with 10 mg aripiprazole which lead to lactation failure, while few other cases in the past have also reported similar findings (Mendhekar et al. 2004, Lutz 2010, Nordeng 2014). Lactation failure has important clinical implications. A possible explanation is the partial agonistic effect of aripiprazole in the tuberoinfundibular dopaminergic system. This interferes with prolactin release, resulting in the failure of lactation. In this context, clinical trials have confirmed that prolactin levels may drop during aripiprazole therapy (Kane et al. 2002, Potkin et al. 2003). Hence, a decision as to whether to discontinue nursing, discontinue the drug, or continue both, can be made only after several variables have been considered, including the clinical need and benefits of the drug for the mother, the potential for serious adverse reactions in the infants, and the benefits of breastfeeding (American Academy of Paediatrics Committee on Drugs 2001). Clinicians should provide anticipatory guidance for women who desire pregnancy or who are early in pregnancy and taking aripiprazole, including a discussion regarding medication alternatives (Komaroff 2021).

Further, the risk of relapse in the mother during the immediate postpartum period must be considered. In both our patients, aripiprazole was not switched, in view of the risk of relapse in mother and non-acceptability of other antipsychotics in view of the side effect profile of other antipsychotics.

CONCLUSION

Literature suggests that the risk of adverse events in infants exposed to aripiprazole is low, and therefore the risks of withdrawing this medication during pregnancy should always be weighed against the risks of continuing it. Further studies with larger sample sizes are needed and the drug should be used with caution during pregnancy and lactation, with decisions made on a case-by-case basis, until a larger database on safety is available.

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Emergence Agitation with Earthquake-Related Traumatic Stress Symptoms After Intravenous Sedation

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ABSTRACT

Sedation with intravenous anesthetics is a sedation method that is often preferred during minor surgical procedures for anxious patients. Among the anesthetic agents used are drugs such as midazolam and ketamine, which can cause psychiatric symptoms such as loss of control over the behavior of the person (disinhibition) or dissociation. In people with high anxiety levels, a paradoxical rise of anxiety may rarely occur with midazolam, and emergence agitation or delirium may occur after anesthesia with ketamine. Post-traumatic stress disorder is a known risk factor for emergence agitation. Accompanying traumatic stress symptoms are reported to have persisted for a long time in the case reports of emergence agitation with a past history of trauma. It is aimed to discuss the importance of traumatic stress symptoms in sedation management in the post-earthquake period by presenting a case with increased anxiety and emergence agitation with acute stress symptoms such as re-experiencing the earthquake after sedation with intravenous anesthetics for a local surgical procedure immediately after experiencing the Kahramanmaraş earthquake on February 6 in Turkey.

Keywords: Earthquakes, intravenous anesthetics, emergence, psychomotor agitation, acute stress disorder, post traumatic stress disorder, post-traumatic stress disorder

INTRODUCTION

In terms of the rapid onset of effect and easy regulation of sedative depth, intravenous anesthetic sedation is the most utilized procedure among the sedation techniques. Fentanyl and midazolam are two agents with different mechanisms of action that are frequently combined for intravenous (IV) administration to induce sedation. Midazolam is a short-acting benzodiazepine that causes powerful amnesia and has sedative and hypnotic properties, while fentanyl is an opioid analgesic (Saiso et al. 2017). Ketamine is a safe and effective sedative agent for painful procedures. Ketamine is preferred for its rapid onset of action, quick recovery time, analgesic and amnesia-inducing properties, however delirium, unpleasant dreams, excitation, and hallucinations during recovery can be major drawbacks. Emergence agitation can be seen in up to 30% of ketamine administrations (Azizkhani et al. 2021).

In this article, we present the case of a patient who was given IV midazolam and ketamine one week after the earthquake without realizing his exposure to the disaster and exhibited re-experiencing symptoms, intense fear of losing his family, and psychomotor agitation. The choice of appropriate anesthetic medications in the early post-traumatic period will be discussed.

CASE

A 45-year-old man experienced the 7.7-magnitude earthquake in Kahramanmaraş with his wife and two children in their home in one of the adjacent provinces. During the severe earthquake, they all managed to leave their home, which was later discovered to be moderately damaged. None of their family members were hurt. The following day, they left the epicenter and reached Ankara, where their friends and relatives were living. Due to the damage on the road, the drive took much longer than anticipated.

After this trip, the tenderness and intermittent discomfort he had been experiencing around the anus became constant and

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worsened over the following days. A week after the earthquake, he was subsequently checked out in the Department of General Surgery. Pilonidal sinus and abscess were identified to be the causes, and abscess drainage was recommended. Although the procedure was scheduled to be performed under the conditions of the outpatient clinic, the patient requested that it be performed under general anesthesia because he was having difficulty tolerating the pain and was too nervous. Then the Anesthesiology and Reanimation Department was consulted for the application of sedation.

The risk of sedation-related complications was determined to be low by the Anesthesiology and Reanimation Department, based on the patient's overall health status assessment and physical examination. The patient had no prior surgery or anesthetic history. Since it was not part of the standard evaluation, neither the information regarding the patient's residence nor whether he was impacted by the earthquake was collected. The treatment was intended to be carried out under sedation with the patient's consent. The staff noticed that he was anxious when he entered the operating room and was distressed by severe pain in the perianal region. After calming him down verbally, surgery preparations began. Midazolam 2 mg was administered intravenously. The patient then reported feeling lightheaded and described it as feeling "as if he had drunk". When the surgical team began administering the local anesthetic, the patient said he could not tolerate the pain. Fentanyl 50 μg was consequently administered intravenously. However, the patient's agony prevented him from allowing the local anesthetic to be administered. To intensify the sedation, midazolam 1 mg, fentanyl 25 μg, and ketamine 50 mg IV were administered. After calming down for about five minutes, the patient started to speak incoherently and kept repeating that he was in pain. Noticing he was uncomfortable, he was given 50 mg of propofol IV. The procedure was performed with spontaneous respiration and vital signs at normal ranges.

Following the surgery, the patient was positioned on a stretcher in the supine position. When he awoke, he shouted "There is an earthquake; my wife is under the rubble", and it was noted that his psychomotor activity had increased. For an additional 8 to 10 minutes, the patient was agitated and made claims about an earthquake, being buried by rubble, and that his wife and children were under the rubble. He was then given 50 mg of propofol IV and allowed to sleep once again in the recovery unit. Then, the patient was transferred to an inpatient treatment room with his wife, and his wife was informed of his status. He was allowed to wake up with his wife by his bedside. The patient who saw his wife stated that his children were under the rubble and he did not believe that they were healthy and that they were not under the rubble. He shouted and cried, asking, "We are trembling, where are my children?" The treatment team learned for the first time that the patient had suffered the recent Kahramanmaraş earthquake as a result of the agitation, which led to an interview with his wife. It was believed that the use of midazolam might have been responsible for the ongoing agitation. Approximately 40 minutes after taking midazolam, the patient kept displaying incoherent speech and increased psychomotor activity. Flumazenil was administered intravenously in the amount of 0.2 mg, and after five minutes, despite being calmer, the patient kept asking where his children were. An additional 0.1 mg of flumazenil was administered. He relaxed and stopped asking questions ten minutes after receiving flumazenil. After an hour, when the patient was prepared to be discharged, he said that he couldn't recall what happened during this process.

The Department of Anesthesiology and Reanimation referred the patient to the Department of Psychiatry after learning that he had traveled from the earthquake center. In the evaluation of the Department of Psychiatry, it was learned that the patient was staying at his mother's house with his wife and children. He was intending to reconsider whether they would return to the city where they currently reside and continue their work there or migrate to Ankara after his medical condition improved. No close relatives had died in the earthquake, but numerous friends and colleagues of theirs had. He stated that they have access to social and familial support.

He has been consuming two glasses of wine or beer every two days while smoking a pack of cigarettes every day for 25 years. There was no prior history of psychiatric disorders, no history of psychiatric treatment, and no family history of psychiatric disorders. The patient was only taking antibiotics at the time, and he was able to adjust to receiving antibiotics. He mentioned witnessing a fire, being in a car accident once, and being physically assaulted once when asked about past traumatic life events that may have increased his tendency to develop traumatic stress symptoms. The patient denied having signs of acute stress disorder, post-traumatic stress disorder, or a dissociative experience as a result of these experiences, and he also denied having any ongoing psychiatric complaints connected to them.

When the potential psychiatric symptoms that may be experienced after the earthquake were examined, it was discovered that the patient had been having intrusive memories and flashbacks of the event, had been experiencing intense emotional swings regarding what had occurred, and had been experiencing mild physical reactions like heart palpitations in response to things that reminded him of the event. He received a score of 23/88 on the Impact of Events Scale, which consists of 22 questions scored from 0 to 4 and was developed to assess the intensity of traumatic stress symptoms in individuals who have had any kind of psychological trauma (Çorapçıoğlu et al. 2006). He stated that he had not been

experiencing any avoidance symptoms. Except for a slight desire to cry, indecisiveness, sleeplessness, and a low appetite, he had no other depression symptoms. He received a 5/63 on the Beck Depression Inventory (Hisli 1988). There was no prior history of predisposition to dissociation. The intensity of somatic dissociation symptoms was assessed using the 20-item, five-point Likert-type Somatoform Dissociation Scale (Nijenhuis et al. 1996, Şar et al. 1998). It was discovered that the patient, who had a Somatoform Dissociation Scale score of 21/100, had not currently been exhibiting somatization or dissociation symptoms. In the previous week, he had had no obvious signs of anxiety [Beck Anxiety Inventory score: 3/84 (Ulusoy et al. 1998)].

The symptoms he experienced were evaluated as an acute stress response. The patient was informed that he had been experiencing some expected symptoms after the earthquake and that he and other family members could apply to the psychiatry clinic whenever needed. The patient's consent was obtained for the case report. Possible psychiatric risk factors in the preoperative evaluation and the role of acute stress responses in anesthesia management were discussed with the Anesthesiology and Reanimation Department.

DISCUSSION

The case of a patient with IV anesthetics administered one week after the earthquake exhibiting symptoms such as re-experiencing the earthquake, anxiety and fear about what may be experienced in the post-earthquake period, and psychomotor agitation during recovery after sedation is presented. No study has been found in the literature on psychiatric complications due to the anesthesia performed shortly after mass traumas or disasters such as earthquakes. Sedation should be avoided whenever possible during times when acute stress reactions may occur. It's also important to avoid using midazolam and ketamine in intravenous sedation procedures as much as possible in these conditions and to be ready for the potential of emergence agitation or paradoxical increase in anxiety should it be necessary.

Despite the lack of research, cases have been described in which post-traumatic stress disorder may be a significant risk factor for emergence agitation or delirium. (Huang et al. 2023). There are previous case reports in the literature with long-lasting post-traumatic stress disorder symptoms when retrospective risk factors are asked, or cases where measures were taken in terms of emergence agitation after learning that they had been diagnosed with post-traumatic stress disorder (Lovestrand et al. 2013, Shoum 2014, Huang et al. 2023). These cases highlight the significance of investigating previous anesthetic procedures as well as previous psychological trauma and associated psychiatric symptoms in the pre-anesthesia examination. In these case reports of emergence agitation, it is detected that traumatic life events occurred a long time ago and that the symptoms of ongoing traumatic stress persisted. The presented case differs from other reported cases in terms of both the occurrence of emergence agitation despite the absence of externally apparent psychiatric symptoms before anesthesia and the clinical appearance of emergence agitation with acute stress symptoms as a result of anesthesia given immediately after a very recent trauma.

Emergence agitation is a state that appears early in the recovery phase from anesthesia and is characterized by symptoms of restlessness, confusion, excitation, inability to calm down, an affinity for aggression, and incoherent speech (Lee and Sung 2020). In this case, acute stress symptoms such as re-experiencing the earthquake, fear of being buried under rubble, and worrying about the loss of loved ones also manifested in addition to the emergence agitation symptoms. A case where emergence agitation was accompanied by acute stress symptoms has never been documented before.

It has been shown that IV midazolam sedation frequently reduces anxiety in people with high anxiety levels prior to operations like dental procedures where increased anxiety is prevalent, but it can also, albeit less frequently, lead to disinhibition or paradoxical anxiety (Wilson et al. 2011). In addition, it has been demonstrated that midazolam increases traumatic stress symptoms in pediatric patients following intensive care unit admission, despite the fact that there is insufficient data for adults addressing the long-term safety of midazolam regarding the development or maintenance of traumatic stress symptoms (Long et al. 2022). In addition, due to the possibility of disinhibition and the long-term persistence of traumatic stress symptoms, other benzodiazepines used in psychiatry practice are not recommended for use in the early post-traumatic period (Morgan et al. 2003 , Yildiz et al. 2023). These findings indicate that the use of midazolam in trauma experiences should be approached with caution. Also, there is no evidence to support the use of ketamine in the early post-traumatic period, and it is known as an agent that promotes dissociative amnesia. Although it has been claimed that midazolam administration lessens the intensity of emergence agitation following ketamine administration (Somashekara et al. 2010), it has also been reported that both medications may have adverse effects on behavioral control in high-risk patients (Wilson et al. 2011, Azizkhani et al. 2021). In terms of behavioral control and agitation, it can be assumed that using propofol for sedation in this population would be relatively safe (Garcia et al. 2021). Contradictory results have been reported regarding the impact of propofol on the emergence and maintenance of long-term post-traumatic stress disorder symptoms (Vogt and Pryor 2022). On the other hand, due to their potential to decrease fear conditioning, opioids like

fentanyl appear to be appropriate for use, despite insufficient evidence (Vogt and Pryor 2022).

When the literature is reviewed, there is no standard protocol for preventing or treating emergence agitation. However, healthcare professionals generally agree that the patient should recover in a calm setting, be with a trusted relative, and be reminded periodically to maintain orientation. Additionally, despite the fact that the expert opinion highlights the risks associated with utilizing benzodiazepine group medications, including midazolam, it is known that midazolam is frequently used to reduce preoperative anxiety (Lovestrand et al. 2013, Shoum 2014, Huang et al. 2023). Although not used in the presented case, case reports are available suggesting that the administration of dexmedetomidine, an alpha-2 receptor agonist, before general anesthesia may be beneficial in patients whose post-traumatic stress disorder symptoms persist while planning the anesthesia and are at risk for emergence agitation and delirium. However, the effectiveness of dexmedetomidine may be impaired due to alpha-2 receptor antagonism if mirtazapine is used (Huang et al. 2023).

Given that acute stress symptoms may be present and increase the susceptibility to dissociative reactions in the post-earthquake period, learning whether there are stressful life events in the recent history of the individuals, whether they have traumatic stress symptoms, and determining their anxiety levels in the pre-procedure evaluation may guide the selection of agents to be used for sedation. This case indicates that even in cases where traumatic stress symptoms are not reported by the patient and are not externally detectable, being prepared for the possibility of emergence agitation in the presence of recent stressful life events is necessary to prevent possible negative consequences during and after the procedure. After large-scale disasters like earthquakes, it seems crucial to carefully consider these issues, avoid using midazolam and ketamine as much as possible, take into account the possibility of psychological trauma exposure if it cannot be thoroughly examined, and take precautions against agitation.

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Letter to the Editor

PSYCHOSOCIAL PERSPECTIVE AND SUGGESTIONS ON THE PENAL EXECUTION SYSTEM IN THE PANDEMIC: THE CASE OF TURKEY

Dear Editor,

The COVID-19 pandemic, which rapidly surrounds our world and has important effects on all aspects of life (especially psychological, social and economic), also affects individuals living in closed prisons (imprisoned, convicted individuals and institution employees), which are physically and socially isolated in different ways. So much so that the World Health Organization (WHO) states that prisons are among the risky groups due to their limited opportunities (difficulty of accessing the diagnostic tests, physical distance as an inherent requirement of the very nature of the service itself, inability to comply with the call to stay at home, etc.) (WHO 2021). With the onset of COVID-19 cases in Turkey, as in many countries, the General Directorate of Prisons and Detention Houses (GDPDH) under the Ministry of Justice of the Republic of Turkey also applied various restrictions to prevent the spread of the virus in prisons. Such liberties as the ability to act autonomously, demonstrating skills and competencies and establishing relationships with others, which Deci and Ryan (2000) define as motivating needs, were/are still significantly restricted by COVID measures. This letter aims to draw the attention of mental health professionals and relevant administrators to the penal system (from the perspective of both service recipients and employees as well as the community) by discussing the COVID-19 restrictions and possible effects, which are thought to have significant effects on the psychosocial status of individuals.

Open and closed visits by the families and relatives of detainees/convicts (D/Cs) were suspended during March-August 2020 and February-June 2021, except for these periods only closed visits with a maximum of 2 people were allowed twice a month (GDPDH 2021a). Like all individuals, being able to establish verbal and physical contact with their relatives is an important requirement for all D/Cs. In Fahmy's (2021) research, it was seen that the general social support from family and friends as perceived by convicts and the consistency in general and emotional social support (empathy, sharing of feelings of joy and sadness, discussing about other problems encountered in life) positively predicted mental health. From this point of view, since the quality and quantity of communication opportunities of individuals in prisons are significantly restricted, they may have negative effects. At this point, GDPDH's doubling the phone call rights and allowing D/C individuals to have 1 open and 2 closed visits a month with their 2 relatives and 1 child as of December 2021 are important initiatives to meet the need for social support (GDPDH 2021b). However, the impoverishment of individuals, especially those with poor socioeconomic status, due to the pandemic may prevent them from adequately benefiting from the right to make phone calls and visits. For this reason, supports (right to free or discounted telephone calls, right to free or discounted transportation for visitors, etc.) for D/C individuals with low income and their relatives are considered helpful.

Family visits, which are an important protective and therapeutic element for delinquent children, who are more sensitive than adults, were also suspended during the pandemic. Studies conducted with delinquent children in institutions have shown that family visits helped reduce repetitive delinquency (Young and Turanovic 2021) and depressive symptoms significantly (Monahan et al. 2011). Considering the longitudinal study findings, the development, implementation and

encouragement of different interview options (weekly video calls with families, open visits conditional with vaccination and negative test results) for children in institutions should be on the agenda to protect the mental health of children and adolescents in insttitutions.

Many practices, especially psychosocial intervention, which is an important part of contemporary penal execution processes, is another aspect of the pandemic requiring further attention. Various studies conducted before the pandemic point out that such activities are very important for protecting the mental health of individuals, ensuring their development, and preventing criminal behavior. The program for convicts in Australia (which includes making job application interviews, avoiding harmful substances, adaptation after release, etc.) was seen to have a significant impact on reducing the rate of recidivism and re-sentencing after 2 years as well as the severity of the crime (injury instead of manslaughter) (Graffam et al. 2014). Woods et al. (2017) draw attention to the positive effects of sports-based interventions in prisons on individuals' self-esteem, confidence, and prosocial behavior. Vocational training and public education courses, which also serve to reduce the possibility of recidivism and meet the need for socialization and adaptation of D/Cs, were suspended during the pandemic, and the study only of individuals staying in the same room by the psychosocial unit specialists (psychologists and social workers) and teachers in the institution were allowed (GDPDH 2020). Carrying out rehabilitation (rehabilitation) studies by taking necessary precautions while protecting the physical health of the individual in prisons would be beneficial in terms of protecting both the mental health of the individuals and the society after release.

The pandemic creates significant difficulties and limitations for children aged 0-6 years who live in the prison with their mothers. Children who go to kindergarten or use the playgrounds within the institution cannot access these facilities during the pandemic. Since this situation may lead to delays in the physical, mental and cognitive development of children, it is recommended that mothers with children are accommodated in the same ward as much as possible, children in the same ward should be taken to playgrounds together, etc. With such interventions, children's need for socialization and exposure to different stimuli can be partially met.

In order to reduce the possibility of virus transmission to the prisons, the employees of the institution (especially the correction officers who are in contact with D/Cs most frequently and closely) started to work with a negative PCR test after 14 days of quarantine before they started to work, and without leaving the prison for 7 days, ensuring uninterrupted service provision (GDPDH 2021a). The practice to prevent prisons from the pandemic causes various stress factors (such as very limited communication with the families, no personal telephone, being in a closed working environment for a long time, and being in contact with COVID-positive individuals who are being treated in the institution) for the employees. For this reason, practices that will reduce the stress level of prison employees (video calls with their families, providing shelter outside the building during rest times, creating indoor recreational/resting opportunities/areas) and activities that will strengthen their stress management skills (distance education/seminars, booklets, counseling services etc.) can be executed. End of 2020, GDPDH's psychological support services to its employees and their first-degree relatives is worthy (T.R. Ministry of Justice 2020).

Another new application that COVID-19 measures entailed in prisons is that individuals who go to the court or hospital could return to their wards with a negative PCR test result after being kept in quarantine wards for 14 days. This practice, which is carried out to prevent transmission inside institution, can create further coping difficulties, especially for individuals with mental/psychiatric problems. In this way, giving the quarantined individuals the right to make phone calls instead of open/closed visits they were not allowed, will both reduce inequality and meet the social support needs of individuals to a certain extent. In addition, telemedicine etc. for individuals who need psychiatric follow-up would be beneficial to provide access to treatment.

Offenders under probation are also considered on leave during the pandemic with Law No. 7242 in Turkey. In studies conducted in different countries (USA and Japan), it has been observed that structured and qualified probation services (close monitoring of the offenders by the officers, consultancy, training, etc.) postponed recidivism for about 1-4 years (Yokotani and Tamura 2017, Zortman et al. 2016). Based on these findings, another issue that should be carefully considered is that the convicts in open prison or on probation were released on leave or exempted from rehabilitation programs, with the legal regulations made to relieve overpopulation in institutions during the pandemic (Republic of Turkey Official Gazette 2020, Issue: 31100). Undoubtedly, physical health is a prerequisite for survival; it is a necessity for D/Cs to continue their improvement and monitoring processes of convicts especially those with a high risk of recidivism.

Many points mentioned above indicate that the pandemic caught the penitentiary system unprepared, which was natural. With a biopsychosocial approach, we believe that the effectiveness and quality of the service provided to D/Cs can be increased by scientific studies and perspectives before, during and after the pandemic. Thus, it can be ensured that both individuals (service recipients and employees) in the penitentiary system and the society experience the pandemic with lesser damage. However, unfortunately, as in many institutions, scientific studies have been suspended in order

to prevent contamination. Examining the psychosocial status of individuals with scientific methods and tools during the pandemic process will guide the employees of the institution in order to prevent negative reactions such as self-harm and suicide and to carry out studies that protect the mental health of individuals. For this reason, it will be beneficial for all parties that GDPDH allows scientific studies and increases cooperation with scientists by applying necessary physical precautions and regulations against contamination.

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