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The relationship between expressed emotion and treatment resistance in patients with major depression

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Abstract
Aim: Expressed emotion (EE) is associated with relapse in major depression. However, past research on its relationship with treatment resistance is limited. In this study, we aimed to investigate whether there is any difference in terms of EE between treatment-resistant depression (TRD) and non-resistant depression (non-TRD) patients, and the relationship between the clinical characteristics of depression and EE.
Material and Methods: The study included 50 patients with TRD, 50 patients with non-TRD and the relatives of these 100 patients. All patients were given the Quick Inventory of Depressive Symptomatology Self-Report Form (QIDS_SR16) and Level of Expressed Emotion (LEE) Scale. Furthermore, the Expressed Emotion (EE) Scale was applied to the relatives of the patients to determine the level of EE.
Results: LEE total score ($p = 0.020$) and EE total score ($p < 0.001$) were found to be significantly higher in the TRD group. There was a positive correlation between the QIDS-SR16 total score and total EE and LEE scores and all subscale scores ($p < 0.05$). Regression analysis revealed that the QIDS total score (0.394) and male gender (0.219) were associated with the total score of EE. The LEE total score was predicted by QIDS total score (0.370), and the higher education level of the close relative (0.219).
Discussion: Besides its limitations, the present study is the first study comparing the expressed emotion between TRD and non-resistant major depression patients. Prospective studies with a large sample size are needed regarding how expressed emotion affects the severity of the disease and its clinical course.

Keywords
Expressed Emotion, Major Depression, Treatment Resistance

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Introduction

Major Depression (MD) is the most common psychiatric disorder and its incidence is increasing day by day. It is an important public health problem due to its high prevalence rates, risk of recurrence or chronicity, and results such as suicidal attempts, loss of functionality and economic burden [1].

The concept of treatment-resistant depression (TRD) is defined as a lack of response to two different groups of antidepressants at adequate doses and duration [2], and clinical studies have shown that 30-40% of patients with MD may be resistant to treatment [3].

The presence of comorbid psychiatric or medical diseases as well as psychosocial stressors should be carefully considered when evaluating patients with TRD [2]. In this context, it has been shown that family-induced stress leads to negative course and low treatment compliance in patients with depression [1].

The concept of expressed emotion (EE) is a multifaceted measure of criticizing, hostile and overprotective attitudes and expressions of relatives towards the individual with the disease. It has been brought to the literature by Brown et al. (1972) to describe the effect of family atmosphere on the course of schizophrenia [4], and EE has been shown to be an important predictor of relapse in schizophrenia, mood disorders, eating disorders and many other psychiatric and medical disorders [5]. Studies on EE in major depression revealed different results. Although there are studies indicating that EE is not related to relapse in major depression, many studies have found that high EE is associated with relapse [6,7]. Although the association of EE with relapse is shown, past research on its relationship with the clinical severity of major depression and treatment resistance is limited. It was also shown that psychosocial intervention studies in families with higher EE may be effective during the treatment process [8,9].

In this study, it was aimed to investigate whether there is any difference in terms of expressed emotion between treatment resistant and non-resistant major depression (non-TRD) patients, and the relationship between the clinical characteristics and severity markers of depression and the expressed emotion.

Material and Methods

Subjects

This cross-sectional study was carried out between January 2017 and December 2017. The study included 50 patients with major depression who did not meet the criteria for treatment-resistant depression, 50 patients with major depression who met the criteria for treatment-resistant depression and the relatives of these 100 patients. Patients who did not show a significant clinical response despite the use of antidepressants from at least two different groups at adequate doses and duration were included in the TRD group.

The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) was performed for diagnosis.

Inclusion criteria for the patient group were as follows: a) age 18-65 years b) having unipolar major depression diagnosis c) in treatment-resistant depression group, the absence of significant clinical response to antidepressant treatment from at least two different groups in sufficient dose and duration. Exclusion criteria for the patient group were as follows: a) the presence of a known decompensated (serious) medical disease b) Illiteracy c) Mental retardation, due to which patient cannot understand the instructions d) history of known head injury e) alcohol-substance use disorder f) having a diagnosis of comorbid psychotic disorder.

Inclusion criteria for relatives were as follows: a) age 18-65 years b) being volunteer to participate in the study c) living with the patient for at least 3 months. Exclusion criteria for relatives were as follows: a) having a psychiatric Axis I diagnosis b) the presence of a known decompensated (serious) medical disease c) Illiteracy d) Mental deficiency precluding to understand the instructions e) History of known head injury.

Ethical approval has been obtained from Ethics Committee of Marmara University (09.2016.559/04.11.2016).

Measures

Level of Expressed Emotion (LEE) Scale

It is a self-assessment tool developed by Cole and Kazarian (1988) to understand the emotional atmosphere between a patient and a person who is important for the patient and to evaluate some of the characteristics of the relationship [10]. Scale is composed of "intrusiveness" (LEE_i), "emotional response" (LEE_e), "attitude toward illness" (LEE_a, "tolerance/expectation" (LEE_t) subscales, each containing 15 items.. The Turkish adaptation and validity-reliability study of the scale was done by Berksun (1993) [11].

Expressed Emotion (EE) Scale

This scale, which is based on the family members' perception of their patients and themselves, is a scale prepared using the concepts and theory of "expressed emotion" to characterize and measure the emotional tone that accompanies the interaction in interpersonal relations. Two subscales ("criticism/hostility" (EE_ch) and "emotional overinvolvement" (EE_eo)) were used for the studies. This scale was developed by Berksun et al. (1993) in our country [11].

Quick Inventory of Depressive Symptomatology Self-Report Form (QIDS-SR16)

The QIDS-SR16 consisting of 16 items was created by A. John Rush [12] and the validity and reliability study in our country was performed by Mergen et al. [13].

Statistical analysis

Data processing was performed using SPSS 20 for Windows. The average of variables was expressed as the mean (M)±standard deviation (SD). Frequency was shown with (n) and relatively was shown with (%). The normality of the distribution of all variables was examined with the Kolmogorov-Smirnov/Shapiro-Wilk's tests. The bivariate analysis was conducted using the chi-square test and the t-test. Relationship between continuous variables was conducted using Pearson's correlation coefficient. Multiple linear regression analysis was applied by using the stepwise method to examine the independent variables affecting on the dependent variable in all participants. Statistical tests were performed at a 2-sided 5% significance level (α= 0.05).

Results

The mean age of the patients included in the study was 38,75 ± 11,32 years. The mean age of the patients in the non-TRD

group was 37.30 ± 10.09, and the mean age of the patients in the TRD group was 40.20 ± 12.36. The age difference between the groups was not statistically significant (p = 0.202). The total number of women in both groups was 72 and the number of men was 28. There was no statistically significant difference between the groups in terms of gender (p = 0.656).

The sociodemographic data of the patients and key relatives are shown in Table 1.

The number of depressive episodes, suicide attempts, duration of the current episode, inpatient treatment and Electroconvulsive therapy (ECT) were statistically significantly higher in the TRD group (p <0.05) compared to the non-TRD group.

The clinical characteristics of the patients are shown in Table 2. LEE total score (p = 0.020), LEE_e subscale score (p = 0.011) and LEE_a subscale score (p = 0.036) were found to be significantly higher in the TRD group.

EE total score (p <0.001) and EE_eo subscale score (p <0.001) were found to be significantly higher in the TRD group.

QIDS-SR16 scale total scores were higher in the TRD group (p <0.001) as expected.

The distribution of scale scores between groups is shown in Table 3.

Correlation Analysis

There was a positive correlation between LEE_i subscale score (r = 0,225; p = 0,025) and history of hospitalization, and between EE_eo subscale scare and the duration of current depressive episode (r = 0,003; p = 0,014). A significant negative correlation was found between the number of past depressive episodes and the EE_eo subscale (r = -0,151; p = 0,046) and the family history of psychiatric disease and EE_ch scale (r = -0,158; p = 0,038).

There was a positive correlation between QIDS-SR16 total

Table 1. The sociodemographic data of the patients and key relatives.

		Total		TRD		Non-TRD		c2/t	p
Age (M ± SD)		38,75±11,32		40,20±12,36		37,30±10,09		1,29	0,202**
		n	%	n	%	n	%		
Sex	Female	72	72	37	74	35	70	0,198	0,656
	Male	28	28	13	26	15	30		
Marital status	Married	72	72	33	66	39	78	2,49	0,288
	Single	15	15	8	16	7	14		
	Widow and divorced	13	13	9	18	4	8		
Employment status	Unemployed	61	61	33	66	28	56	7,923	0,094*
	Full-time	26	26	8	16	18	36		
	Part-time	6	6	5	10	1	2		
	Student	1	1	1	2	0	0		
	Disabled, other	6	6	3	6	3	6		
Key relative	Spouse	62	62	29	58	33	66	4,837	0,304
	Mather	12	12	6	12	6	12		
	Father	6	6	2	4	4	8		
	Sibling	7	7	3	6	4	8		
	Child	13	13	10	20	3	6		
Sex of key relative	Female	39	39	20	40	19	38	0,042	0,838
	Male	61	61	30	60	31	62		

*Fisher's Exact ** Student-t Test

Table 2. The clinical characteristics of the patients

	Group						t- test	
	Total		TRD		Non-TRD		t	p
	Mean	SD	Mean	SD	Mean	SD		
Number of depressive episodes	3,11	2,1	3,94	2,32	2,28	1,47	4,28	<0,001
Previous suicide attempt	0,81	1,26	1,18	1,52	0,44	0,79	3,06	<0,001
Age of onset	32,33	10,9	32,3	11,87	32,36	9,96	0,03	0,98
Duration of the current episode	29,8	18,42	40,36	17,86	19,24	11,8	6,98	<0,001

	Total (n=100)		TRD (n=50)		Non-TRD (n=50)		Chi-square	
	n	%	n	%	n	%	Chi-square	p
Comorbid medical disorders	43	43	26	52	17	34	3,305	0,069
History of hospitalization	25	25	22	44	3	6	19,253	<0,001
ECT	7	7	7	14	0	0	7,527	0,006
Family history of psychiatric diagnoses	36	36	22	44	14	28	2,778	0,096

Table 3. The distribution of scale scores between groups

Variable	Group	M	SD	t	p*
LEE_total	TRD	26,82	13,696	2,375	0,02
	Non-TRD	20,6	12,467		
LEE_i	TRD	7,34	3,578	1,214	0,228
	Non-TRD	6,52	3,164		
LEE_e	TRD	7,4	4,071	2,594	0,011
	Non-TRD	5,44	3,459		
LEE_a	TRD	5,66	3,978	2,129	0,036
	Non-TRD	4,06	3,525		
LEE_t	TRD	6,42	4,101	1,864	0,065
	Non-TRD	4,92	3,943		
EE_total	TRD	18,56	4,441	3,684	<0,001
	Non-TRD	15,16	4,782		
EE_eo	TRD	8,52	2,092	4,4	<0,001
	Non-TRD	6,84	1,707		
EE_ch	TRD	10,04	4,286	1,546	0,125
	Non-TRD	8,76	3,988		
QIDS-SR16	TRD	20,02	3,384	5,953	<0,001
	Non-TRD	15,54	4,107		

LEE: Level of expressed emotion, LEE_i: Intrusiveness, LEE_e: Emotional response, LEE_a: Attitude toward illness, LEE_t: Tolerance/expectation, EE_eo: Emotional over-involvement, EE_ch: Criticism/hostility, TRD: Treatment resistance depression, Non-TRD: Non-resistance depression, QIDS-SR16: Quick Inventory of Depressive Symptomatology Self-Report
*Student-t Test

score and total EE and LEE scores and all subscale scores ($p < 0.05$).

There was a statistically significant positive correlation between the education level of the patient and the EE_eo subscale ($r = 0.351$; $p < 0.001$).

Regression Analysis

The regression analysis was done for variables predicting EE and LEE scale scores. The multiple linear regression analysis conducted in all participants revealed that only the QIDS-SR16 total score (β=0.381, p<0,001) and male gender (β=0.229, p=0,015) had an effect on the total score of EE [R2=0,186, F=8,522,p<0,001]. The LEE total score were predicted by only the QIDS-SR16 total score (β=0.388, p<0,001), and higher education level of the key relatives (β=0.194, p=0,031) [R2=0,270,F=7,111,p<0,001].

Discussion

In this study, it was aimed to determine whether there is any difference in terms of expressed emotion in resistant and non-resistant major depression patients, and the relationship between the clinical characteristics of depression and severity markers, and the expressed emotion.

In the present study, the mean age of the patient group was 38,75 ± 11,32, and 72% of the patients were women. The age and gender distribution was in line with the literature [14].

There was no significant difference between the groups in terms of sociodemographic data (age, gender, etc.). Factors such as gender and educational status are known to affect EE [15-18]. The lack of significant differences in sociodemographic data between the groups contributed to the comparison of the two groups in terms of EE.

When two groups were compared in terms of EE scales, LEE total score, LEE_e subscale and LEE_a subscale scores were found to be higher in the resistant patient group. In case of a mental illness in one of the family members, relatives of the patients may show some emotional reactions. The more severe the disorder, the more stigmatization and the more the EE take place [19]. Therefore, it can be expected that the EE may be higher in resistant depression, which can be difficult to treat and more likely to be recurrent. It is possible that higher LEE_e and LEE_a subscale scores in the resistant patient group may be due to the symptoms of major depression-related disorders; and also the personality traits and emotion expressions of family members may have contributed to the resistance of major depression.

A negative correlation was found between the family history of psychiatric disease and EE_ch subscale. The greater the number of individuals with a history of psychiatric disease in the family, the more likely the family members are to be experienced about psychiatric illnesses and given psychoeducation on psychiatric disorders. Therefore, it is understandable that family members are less criticizing and hostile towards the individual with the disease.

No statistically significant correlation was found between other sociodemographic variables (age, gender, etc.) and EE and LEE scales.

A significant correlation was found between LEE_i subscale and history of hospitalization. Inpatient treatment may lead to a more intrusive attitude of the relatives because of the interpretations such as the disease is more severe and difficult to treat. Excessive interventionist attitudes may constitute an obstacle to the individual's ability to exhibit his skills as an individual and cause the symptoms of depression to worsen.

In our study, a significant positive correlation was found between the EE_eo subscale and the duration of the current depressive episode. It is observed that the families of patients with long-standing depression have a more protective attitude, while the relatives of patients with a high number of past

depressive episodes behave in the opposite way.

There was a negative correlation between the number of past depressive episodes and the EE_eo subscale. If the disease becomes chronic, it may cause difficulties in the relationships between the patient and the family, and it may also cause an emotional detachment and the protective attitude of the family may decrease.

There was a statistically significant correlation between LEE total score and LEE_e and LEE_t subscale scores and being unemployed among patients in the TRD group. Family members may have some expectations of patients with depression, such as having a profession, contributing to the family economy, or starting to establish their own lives as individuals. Therefore, they may be more reactive and more intolerant towards the individual who has resistant disease.

In the present study, a significant negative correlation was found between the EE_eo subscale and educational status of the relative in the TRD group. Family members with higher education level exhibit a less protective attitude towards the patient, which is compatible with our clinical observations, considering that their sociocultural level and their level of knowledge about mental disorders may be higher.

Significant correlations were found between the key relative other than spouse variable and the emotional overinvolvement subscale of the EE scale. However, in studies carried out with relatives living separately from the patient, conclusions were drawn that the predictive effect of EE is strong [20]. It has been reported that parents who have a mental illness in their children have feelings of guilt for this condition and that they have a more protective and concerned attitude towards the sick child during the disease process [21].

There was a significant correlation between the total score of the QIDS-SR16 scale and the total scores of the EE and LEE scales and their subscale scores, and the level of expressed emotion of the family members increased as the QIDS-SR16 score increased. The relationship between disease severity and EE is a controversial issue. There are contradictory findings about the relationship between the severity of the disease and expressed emotions of the patient's relatives. The reasons for the contradictory results of these studies may be due the differences in factors such as the methods used in evaluating the EE level, sample selection, the disease stage at the point of evaluation, and the proximity of the key relative to the patient [22].

LEE total score increases as the duration of education of the relatives increases in this study. Past studies on depression show that the patients' and the relatives' education levels' effects on the EE has not been examined. Therefore, it is a controversial issue whether the education levels of the family members are related to EE.

In our study, male gender was found to increase EE total score. However, in the literature on EE, the differences between female and male genders have been studied very little. A past study found no relationship between the genders and EE, and it was found that women's relatives were more critical and more protective than men [23].

The results of the present study should be interpreted considering some limitations. The biggest limitation is the cross-sectional nature of the study. It was thought that the possibility of undiagnosed bipolar depression patients taking part among the participants may affect the results of the study. The number of samples can also be specified as another limitation. However, when we consider other EE studies in depression, our sample size is higher [24]. When selecting a sample of depressed patients, relatives who were available for participation in the study were included and patients living alone were excluded. These limitations are factors that prevent the generalization of our results.

Besides its limitations, the present study is the first study comparing the expressed emotion between the TRD and non-TRD patients. There is a need for prospective studies with a large sample size regarding how expressed emotion affects the severity of the disease and its clinical course.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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