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Temperament and character as a predictor of response to selective serotonin reuptake inhibitors in patients with majordepressive disorder

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Abstract

Background: Personality is one of the most important factors affecting the treatment course of patients with psychiatric disorders.

Objective: The present study aimed to find the possible relationship between personality factors and response to selective serotonin reuptake inhibitors treatment for major depression.

Method: One hundred and seven patients with mild or moderate major depression treated with citalopram, sertraline or fluoxetine for two months enrolled in the present prospective study. Every patients were evaluated by Hamilton depression test (as pre-test and post-test) and Temperament and Character Inventory questionnaire (as pre-test) and their response to treatment evaluated base on their Hamilton depression test.

Results: The mean age of the patients was 39.7 years and most of the population were female (71.9%). The results showed that reward dependence (OR=1.18, P =0.05), age (OR=1.07, P=0.002) and cooperativeness (OR=0.76, P <0.001) had significant effect on the likelihood of being non-responsiveness to the treatment. Logistic regression showed that the effect of temperament and character, gender, age, and depression score at the beginning of the treatment indicated that only cooperativeness (B =-0.21, P<0.01) predicted response to treatment.

Conclusion: Temperament and character or at least some of their traits may predispose response to depression treatment.

temperament and character; serotonin reuptake inhibitors; major depressive disorder; personality

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INTRODUCTION

Depression is associated with a considerably high cost of illness among all age groups and also as a comorbidity [1]. This common mental illness is a global public health concern as recent studies demonstrated an approximate 50% rise among 195 countries and regions from 1990 to 2017 [2, 3]. Depressive disorders have a considerable negative impact on quality of life and

are associated with adverse clinical outcomes including increased risk of suicide [4]. Although there is a wide range of pharmaceutical regimens available for the management of depression, however, successful treatment may not be achieved for some individuals [5]. Although the effectiveness of antidepressants in managing depressive symptoms has been widely addressed; however, non-adherence and inappropriate response to treatment is still a problematic issue. Inappropriate and incomplete response to antidepressants could be because various factors including the patient's belief regarding their illness, drug side effects and cultural factors [6]. Different antidepressants have shown to be differently adhered to by the general population [6]. Among these drugs, selective serotonin reuptake inhibitors (SSRIs) are considered as a more favorable treatment that is less frequently abandoned by patients [6]. Temperament and character are among the effective factors on medication adherence and also treatment response in different psychiatric disorders [7-10]. Among several personality models, the Cloninger biosocial model is widely used [8]. Cloninger et al. proposed a Tridimensional Personality Questionnaire (TPQ) as an inventory for personality traits [11]. TPQ operates with three fundamental dimensions: Novelty seeking (NS), harm avoidance (HA), and reward dependence (RD). NS means the tendency to responding actively to novel stimuli leading to the pursuit of rewards and escape from punishment. HA is defined as the tendency to an inhibitory response to signals of aversive stimuli leading to avoidance of punishment and non-reward. RD corresponds to the tendency for a positive response to signals of reward to maintain or resist behavioral extinction. According to this model, the three dimensions have been supposed to be inheritable and independent. Also, NS, HA, and RD have been correlated to a specific central neurotransmitter; for example, NS with basal dopaminergic activity, HA with serotonergic activity, and RD with low basal noradrenergic activity have separated RD in two dimensions isolating persistence (PS) dimension and regrouping the three other subscales in an RD dimension [12]. In Temperament and Character Inventory (TCI) that is an inventory for a personality trait, based on a synthesis of information about social and cognitive development and descriptions of personality development in humanist and transpersonal psychology, recently the model was extended to measure seven dimensions of personality along with three measures of character: self-directedness (SD), cooperativeness (CO), and self-transcendence (ST) [13, 14]. Hansenne et al. defined these three characters as follow: "SD refers to the ability to control, regulate and adapt behavior to fit the situation under individually chosen goals and values; CO account for differences in identification with and acceptance of other people; ST is associated with spirituality, referring generally to identification with everything conceived as essential and consequential parts of a unified whole" [14]. Recent studies suggested that the personality dimensions measured by the TCI can have predictive value in terms of responding to the antidepressant treatment; for instance, high scores on the HA scale can predicate low responses to antidepressant treatment such as tricyclic antidepressants (TCA) and selective serotonin reuptake inhibitors (SSRI) [15]. However, the relationship between personality and depression is very complex and the results are inconsistent and need to be further investigated. Therefore, the present study aimed for evaluating the relationship between personality factors and response to specific treatment with treatment response in major depressive disorder (MDD).

MATERIAL AND METHODS

The present prospective study was approved by Shahid Sadoughi University of Medical Sciences ethic committee. Every new patient with a confirmed diagnosis of MDD based on the Diagnostic and Statistical Manual of Mental Disorders V (DSM-V) criteria who were admitted to any of the three university-affiliated clinics of Shahid Sadoughi University of Medical Sciences (Yazd, Iran) enrolled in the present study. Among these patients, only the patients who were suffering from moderate MDD, with basic minimum education, posing no suicidal thoughts, not being diagnosed with other psychiatric disorders, and receiving treatment with one of the SSRIs were included. Sample size calculation was based on finding a correlaton coefficient of at least 0.3,

with α=0.05 and power of %85, in order to detect this correlation in our population at least 100 patient was needed. Te patients who meeted the inclusion criteria enrolled in the study and completed an informed consent form. These patients completed a Persian version of the 125-item self-report TCI questionnaire and Hamilton depression scale also were filled by clinicians, continued receiving their antidepressant treatment with any type of SSRIs for two months and were visited by a psychiatrist every 2 weeks. The prescribed SSRIs included fluoxetine, citalopram, and sertraline. Paroxetine was not prescribed because of less availability. Some patients received β-Adrenergic Receptor Antagonist or Benzodiazepines like propranolol, clonazepam, Lorazepam, Alprazolam, or zolpidem in addition to SSRIs based on the psychiatric decision for management of their clinical symptoms. During the study period, 23 patients left the study because of interrupting their medications. Finally, 107 patients were followed after two months of treatment and Hamilton depression scale was filled for them again. According to the results, patients were divided into two groups in terms of being responsive (50% Improvement and more) or non-responsive (under 50% Improvement) to SSRIs. To obtain more comprehensive data, we also compared the participants in four groups: no response (0% reduction of initial symptoms, partial response (reduction of initial symptoms are less than 50%), response (reduction of initial symptoms are between 50 to 100%), and complete response (100% symptoms free) [16].

Personality profiles of responsive and nonresponsive patients were obtained through TCI (HA: Harm avoidance, NS: novelty seeking, Reward dependence, PS: Persistence, SD: Self-directedness, CO: Cooperativeness, ST: Self-transcendence) at the beginning of the study and were compared before the treatment to identify personality traits that probably represent responsiveness.

The collected data were entered into the SPSS software (version 21) and analyzed using the Independent t-test, Chi-square, ANOVA with Tukey Post hoc test, Pearson's correlation coefficients, Logistic regression, and ROC analysis.

RESULTS

Results based on 2 outcome categories: Dividing the study population into non-responsive and responsive groups revealed that there was no significant difference among both genders in terms of response to treatment (50% of males and 47% of female patients, P=0.76). The mean (SD) age of the patients in responsive and non-responsive groups was 36.86 (12.39) and 41.41 (10.06) years respectively, and the non-responsive group was significantly younger than the responsive group (P=0.04) (Table 1).

Table 1. The distribution of patient's gender and age in studied categories

		No Response (n=31)	Partial Response (n=25)	Response (n=35)	Complete response (n=16)
Gender	Male (n=30)	0 (0%)	15 (50%)	9 (30%)	6 (20%)
	Female (n=77)	31 (40.3%)	10 (13%)	26 (33.8%)	10 (13%)
Age		41.06 (10.67)	41.84 (9.46)	34.54 (10.82)	41.94 (14.37)

As demonstrated in Table 2, the PS and ST scores were significantly higher among the non-responsive group while the responsive group had significantly higher SD and CO scores (p<0.05).

The backward logistic regression analysis was performed to evaluate the effect of temperament and character, age and gender on treatment response. The results showed that RD (OR=1.18, P=0.05), age (OR=1.07, P=0.002), and CO (OR=0.76, P<0.001) had a significant effect on the likelihood of being non-responsiveness to the treatment.

By performing ROC curve analysis on subscales of Cloninger's temperament and character scales for discriminating responsive and non-responsive patients ST, SD and CO showed a moderate to good discriminating ability (ST: AUC=0.64, 95% CI=(0.53, 0.74); SD: AUC=0.68, 95% CI=(0.58, 0.78) and CO: AUC=0.68, 95%

CI=(0.57, 0.78)). To find the optimum cut point for being able to discriminant responsive from non-responsive patients the following formula was used:

$d = \sqrt{d = (1\text{-senitivituy})^2 + (\text{specificity})^2}$

The optimum cut-point for ST, SD, and CO were 10.5, 8.5, and 16.5, respectively.

Results based on four outcome categories: Changes in depression scores after treatment were higher among male patients (P=0.03). There was a significant difference between responsive and partial responsive subjects regarding the average age. The average age of the partially responsive patients was higher than the average age of the responsive patients (P=0.043). Table 3 shows the correlation between different variables of Cloninger's temperament and character scales indicating a direct significant relationship between PS and ST (r=0.62, P<0/001), SD and CO (r=0.51, P<0.001), RD and PS (r=0.23, P<0.05), RD and NS (r=0.2, P<0.05), and NS and PS (r=0.2, P<0.05). There were significant inverse relationships between CO and HA (r=-0.25, P<0.01), HA and SD (r=-0.21, P<0.05), and SD and ST (r=-0.21 and P<0.05). Moreover, there was a direct relationship between HA, NS, and PS with depression scores before treatment (P<0.001). There was an inverse significant relationship between SD subscale and depression scores before treatment (P<0.001). Before treatment, there was a direct relationship between the age of subjects and PS, SD, CO, and ST (p<0.05). Post hoc tests indicated a significant difference between the four outcome categories in terms of NS, PS, CO, and ST subscales (P<0.001) (Table 2).

Table 2. The distribution of temperament and character scales in studied categories

	Responsive		Non-responsive		P-value	No Response (n=31)		Partial Response (n=25)		Response (n=35)		Complete response (n=16)		P-value
	Mean	SD	Mean	SD		Mean	SD	Mean	SD	Mean	SD	Mean	SD	
HA	13.96	2.96	14.75	3.05	0.18	14.39	3.05	15.2	3.06	14.34	3.24	13.13	2.06	0.2
RD	8.82	2.75	10.55	10.95	0.28	9.55	2.16	11.8	16.31	9.11	2.93	8.19	2.29	0.23
NS	8.73	2.94	8.39	3.8	0.62	9.35	3.09	7.2	4.3	9.74	2.52	6.5	2.58	<0.001
PS	2.63	1.81	3.29	1.6	0.05	3.32	1.6	3.24	1.64	3.31	1.51	1.13	1.5	<0.001
SD	10.57	5.4	7.7	6.59	0.02	6.97	7.57	8.6	5.15	10.14	6.12	11.5	3.29	0.06
CO	17.29	3.77	15.34	2.43	<0.001	15.77	2.75	14.8	1.87	16.63	3.93	18.75	3	<0.001
ST	8.41	3.13	9.95	3.85	0.03	11.35	4.05	8.2	2.77	8.49	3.45	8.25	2.38	<0.001
Pre-treatment depression score	30.84	7.65	31.82	7.21	0.50	32.65	6.02	30.80	8.48	34.54	4.27	22.75	7.19	<0.001

HA: Harm avoidance, NS: novelty seeking, Reward dependence, PS: Persistence, SD: Self directedness, CO: Cooperativeness, ST: Self-transcendence

The outcome category with complete response had higher CO and lower NS compare to the other groups. The non-responsive group had higher PS and ST than other groups. Logistic regression investigated the effect of temperament and character, gender, age, and depression score at the beginning of the treatment and found that only CO (B=-0.21, P <0.01) predicted the response to treatment.

Table 3. Correlation Coefficient subscales' variables

HA	RD	NS	PS	SD	CO	ST		
1	0.16	0.14	0.33	-0.21	-0.25	0.15	Correlation Coefficient	HA
	0.09	0.16	0	0.03*	0.01**	0.12	P-value	

		0.2	0.23	-0.05	0.05	0.11	Correlation Coefficient	RD
		0.04*	0.02*	0.57	0.62	0.28	P-value (2-tailed)	
			0.2	-0.02	0.02	0.07	Correlation Coefficient	NS
			0.04*	0.87	0.82	0.45	P-value (2-tailed)	
				0.01	0.12	0.62	Correlation Coefficient	PS
				0.94	0.21	<0.001**	P-value (2-tailed)	
					0.51	-0.21	Correlation Coefficient	SD
					<0.001**	0.03*	P-value (2-tailed)	
						-0.04	Correlation Coefficient	CO
						0.7	P-value (2-tailed)	

*P<0/05; **P<0.01; ***P<0/001

HA: Harm avoidance, NS: novelty seeking, RD: Reward dependence, PS: Persistence, SD: Self directedness, CO: Cooperativeness, ST: Self-transcendence

Table 4. Correlation Coefficient between variable subscales and pretreatment depression score and age

		HA	RD	NS	PS	SD	CO	ST
Pretreatment Depression Score	Correlation Coefficient	0.33	0.12	0.46	0.41	-0.31	-0.12	0.02
	P-value	*<0.001	0.22	*<0.001	*<0.001	*<0.001	0.22	0.85
Age	Correlation Coefficient	-0.08	-0.02	-0.13	0.34	0.25	0.20	0.38
	P-value	0.41	0.87	0.20	*<0.001	**0.01	0.04	*<0.001

*P<0.001; **P<0.01

HA: Harm avoidance, NS: novelty seeking, RD: Reward dependence, PS: Persistence, SD: Self directedness, CO: Cooperativeness, ST: Self-transcendence

DISCUSSION

The present study demonstrated that the CO could be considered as an appropriate predictor of treatment response among responders and non-responders. The investigation of four groups revealed that those with complete response had higher CO and lower NS while the non-responsive group had higher PS and ST.

Depression is a common psychological disorder with a considerable burden [1]. Despite various treatment regimens for treating MDD, still researchers are looking forward to finding factors affecting treatment response. Up to now, conflicting results are addressing the effect of patients' personality and response to SSRIs. In the present study, we evaluated the relationship between treatment response to SSRIs in MDD patients, and in line with previous studies [17, 18], we could not find a significant difference in terms of treatment response related to MDD patients' gender. Paavonen et al. study from Finland evaluated the relationships between temperament and severity of symptoms as well as

response to depression treatment were assessed [19]. Although temperament disorders and severity of MDD symptoms were related; however, in contrast to our study, there was no relationship between temperament and response to treatment. The aforementioned study demonstrated that the temperament and character inventory were also used and no correlation between gender and treatment to response was found [19]. While Paavonen et al. study applied only a set of temperament components, comparison of our results with their study is difficult [19]. Another study by De Aguiar et al. evaluated the relationship between affective temperaments and response to depression therapy [20]. They demonstrated a significant negative correlation between depressed temperament, anxious temperament, and response to treatment. However, there was a significant direct relationship between hyperthymic temperament and response to treatment [20]. De Aguiar et al. revealed that HA was inversely correlated with RD and directly associated with response to treatment. In our study, the RD determined response to treatment while there was no relationship between HA and response to treatment [20]. As mentioned before and similar to the Paavonen et al study, the discrepancy between our study and two previous studies can be attributed to the intervention of other temperament elements in the response [19, 20]. It should be noted that, for example, in hyperthymic patients, RD temperament along with NS are key factors and the separate evaluation of these two factors cannot be easily achieved. Alongside our results, Kadri et al. concluded that the PS factor is correlated with response to treatment with serotoninergic medicines [21]. The PS factor is related to perseverance and stability of negative traits [21]. Another study addressed more detailed temperament components in temperament and character inventory, investigating their relationship with response to treatment with paroxetine [22]. Regarding the CO transcripts, this study indicated that this factor and even its transcripts can be predictors of response to treatment with serotonergic medicine including paroxetine [22]. Similar to our results, a previous meta-analysis demonstrated that depression before treatment had a direct and significant relationship with HA [8]. As the definitions of this factor suggest, it can be concluded that this factor can have a predisposing role at least in developing depression. A previous study evaluating the relationship between response to antidepressant treatment (Maprotiline) and personality factors revealed a correlation between temperament and response to treatment, demonstrating that character factors including SD and CO could be predictors of response to treatment [23]. In the present study, both temperament and character factors presented predicting capacity and character factors including CO had a more constant and stronger effect. While our study demonstrated that SD could be a predictor of response to SSRIs treatment, other studies determined a predictive role for SD in other therapeutic modalities as well [24]. The Baeken et al. study from Belgium evaluated the predictive ability of temperament factors for response to Repetitive Transcranial Magnetic Stimulation (rTMS). According to their results, high levels of SD could predict response to this particular treatment modality [24]. Even more, it has been reported that personality factors were correlated with the speed of therapeutic response. The Kaneda et al. study from Japan demonstrated that the higher SD and lower HA were correlated with quicker response to therapy [25]. Nevertheless, in patients who had later responses (6 weeks), no relevant personality trait was observed. Moreover, depression before treatment was related to low NS and SD scores [25]. The aforementioned study was inconsistent with our study in terms of the relationship between response to treatment and personality factors. However, this discrepancy is justifiable since the current study investigated the response speed and was conducted on the responsive patients.

One of the limitations mentioned in this study is individual SSRI's are not neccesarly associated with equal efficacy and therefore some of the observed diffrences could be due ro confounding effect of different mediciens usage.

CONCLUSION

The present study demonstrated that some of the temperament and character factors may predict SSRI response in MDD patients. RD temperament factor and especially CO character factor were predictors of response to treatment.

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