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PERSONALITY CHANGES DURING ANTIDEPRESSANT TREATMENT

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SUMMARY

Objectives: *We have investigated the changes of Temperament and Character Inventory (TCI) dimensions of personality in outpatients during 6 months of antidepressant treatment.*

Subjects and methods: *30 outpatients were treated for mild or moderate depressive episode, current mild or moderate episode of reccurent depressive disorder or mixed anxiety and depressive disorder (ICD-10). The intensity of depression was assessed by the Montgomery-Asberg Depression Rating Scale (MADRS) at the beginning of treatment and then after the 1st, 3rd and 6th month of treatment. The TCI dimensions were assessed by the Temperament and Character Inventory-Revised (TCI-R) at the same time periods as the MADRS. The mean scores of the TCI-R dimensions and MADRS were processed by Wilcoxon pair test.*

Results: *We have observed a significant decrease in harm avoidance (HA) score after 6 months of treatment ($p<0.05$), between the 1st and 6th month ($p<0.05$), between the 3rd and 6th month, ($p=0.033$), significant increase in persistance (P) between the 1st and 6th month ($p<0.05$) and a significant decrease in self-transcendence (ST) score after 3 months ($p<0.05$) and after 6 months ($p<0.05$). In the MADRS total score we have observed a significant decrease after the 1st ($p<0.001$), 3rd ($p<0.001$) and also 6th month ($p<0.001$).*

Conclusions: *Our findings showed changes of personality dimensions HA, P and ST in outpatients during antidepressant treatment.*

Key words: *antidepressant – character – depression – treatment - temperament*

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INTRODUCTION

Depressive disorder is one of the most frequently occuring mental disorders. Major depression is the most common reason for worldwide disability and affective disorders affect approximately one fifth of the population (Kessler et al. 2005). These facts should be the reason for early diagnostics, adequate treatment and prevention of depression and advancement of new antidepressant agents. Currently, antidepressants of first choice are selective serotonine reuptake inhibitors (SSRIs) or serotonine noradrenaline reuptake inhibitors (SNRIs). Application of these agents in clinical practice has made significant progress in the treatment of depressive disorder. Antidepressants cause clearly better conditions in 60-70% of patients and are significantly more efficient than placebo (Schatzberg & Nemeroff 1998). Despite such progress, there is still the problem of antidepressant choice strategy and the decision about when to finish the treatment. In common clinical practice, the rating scales such as the MADRS (Montgomery Asberg Depression Rating Scale) or HDRS (Hamilton Depression Rating Scale) are often used to assess the intensity of standard depressive symptoms. Using the rating scale total score, there is also a possibility to assess efficacy of antidepressant treatment indirectly. In general, the disadvantage of a rating scale is, that it often evaluates classic depressive symptoms, which could already have been relieved after an

acute phase of treatment. Thus, use of depression rating scales could be profitably supplemented by detection of personality changes for more complex assessment of the course of antidepressant treatment. It could be favourable to consider changes of personality dimensions according to Cloninger´s theory during long-term antidepressant treatment.

This theory created the biosocial model of temperament and character**,** according to Cloninger, which comes from biological, neurophysiological, genetic and psychological studies (Cloninger & Svrakic 2000). It describes the relationships between the biogenetic structure of personality and psychiatric disorders. According to Cloninger, personality is a complex stepped system which comprises different psychobiological dimensions of temperament and character.

Temperament is largely genetically determined and configures automatic behavior responses. It consists of four hereditary dimensions that are observable even from early childhood and include procedural and unconscious learning. They are designated as *novelty-seeking* (NS), *harm-avoidance* (HA), *reward-dependence* (RD) and *persistence* (P). NS is the system of behavioral activation with dopamine as it's neurotransmitter. Individuals high in NS show exhilaration in response to novel stimuli and intuitive decision making. HA is the system of behavioral inhibition with GABA and serotonin neurotransmitters. Individuals high in HA show worry, pessimism, easy fatigue and shyness with strangers. RD is the system for maintenance of ongoing behavior and noradrenalin and serotonin are it's neurotransmitters. Individuals high in RD are affectionate and dependent upon the approval of others. P is the system of partial reinforcement and active behavior despite fatigue and frustration with glutamate and serotonin as it's neurotransmitters. Individuals high in P are tenacious and determined.

Character develops in the course of ontogenesis and it is mostly affected by social learning. Character regulates the cognitive processes of sensory perception and emotion provoked by temperament. It consists of *self-directedness* (SD), *cooperativeness* (CO) and s*elf-transcendence* (ST) dimensions (Cloninger & Svrakic 2000). These are determined more by environment than heredity. SD refers to identification with the autonomous self and ability to solve situations according to individual goals and values. Individuals high in SD show high self-esteem and responsibility. CO indicates the extent to which individuals view other people as a part of the self. Individuals high in CO are socially tolerant and helpful. ST responds to identification with a unity of all things in the world. Individuals high in ST are fulfilled, intuitive and spiritual. Cloninger has suggested that mutual interactions of all dimensions may influence the vulnerability to depression. Consequently, many studies have been investigating its clinical application in patients with major depression. These studies have demonstrated that high HA is associated with depression and anxiety (Abrams et al. 2004, Farmer et al. 2003, Joffe et al. 1993, Jylhä & Isometsä 2006). Another consistent finding from previous studies is that low SD is associated with depression (Farmer et al. 2003, Hirano et al. 2002). Some of these studies also suggest, that some dimensions (especially HA, RD and SD) may be related to the response to antidepressant treatment in patients with major depression (Joyce et al. 1994, Nelson & Cloninger 1995, Nelson & Cloninger 1997).

Dimensions of personality can be detected as well as measured with the help of a special questionnaire called the TCI (Temperament and Character Inventory). It was developed by Cloninger and associates as a self-rating personality questionnaire. This inventory has been shown to have a sufficient factor validity in the general population (Cloninger et al. 1993, Cloninger et al. 1994). Recently, Cloninger et al. have developed a new version of this questionnaire, The Temperament and Character Inventory-Revised (TCI-R) and only a few published studies have employed the revised version (Gutierrez-Zotes et al. 2003, Jylhä & Isometsä 2006).

The purpose of the present study was to apply the TCI-R for detection of personality changes during 6 months of antidepressant treatment in subjects with depressive episode or current episode of recurrent depressive disorder in mild or

moderate intensity or mixed anxiety and depressive disorder (ICD-10 research criteria), who were treated with antidepressants. The TCI-R dimensions were assessed repeatedly during treatment at the same time periods as MADRS in order to find an association between the response to antidepressant treatment and TCI-R dimensions changes. The TCI-R assessment in healthy controls also enables a comparison of natural changes of TCI-R scores in non-depressive subjects with TCI-R changes in depressed individuals during treatment.

SUBJECTS AND METHODS

A total of 30 acutely ill patients met the criteria for a mild or moderate depressive episode (17 patients), a mild or moderate current episode of reccurent depressive disorder (2 patients) or mixed anxious-depressive disorder (11 patients) according to ICD-10 research criteria and undertaken by our open-label prospective study. Only patients who reached ≥ 7 in the MADRS total score at the beginning of treatment were included (mild depression 7-19, moderate depression 20-34 in the MADRS total score). Patients with mild depression who did not respond to the previous psychotherapy underwent psychopharmacological treatment. All of the patients were presented with research instructions which they fully understood. Participation in the study was voluntary and informed consent was obtained. Subjects with a past history of manic or hypomanic episodes or with brain-organic etiology and also patients suffering from severe depression (MADRS total score ≥ 35) were excluded. No patient fulfilled the criteria for a personality disorder. The diagnostic assessments were performed by two independent psychiatrists. The control group consisted of 25 healthy volunteers. In order to detect dynamics of both personality changes and intensity of depression during the acute and maintenance phase of the treatment, we have completed assessments 4 times-at the beginning of treatment, after 1 month and after 3 and 6 months of treatment. This study was approved by the local medical research ethics committee. All of the 21 females and 9 males with a mean age (±S.D.) of 37.9 (±7.6) years were treated with SSRI or SNRI agent in monotherapy. The control group comprised 19 women and 6 men with a mean age (±S.D.) of 36.1 (±9.1) years. Over 6 months of clinical trial assessments of depression intensity and dimensions of personality were performed repeatedly. The efficacy of treatment and intensity of depression were assessed by the MADRS during the 1st visit of patient (baseline assessment-MADRS 0) and then after the 1st, 3rd and 6th month (MADRS 1, 3, 6) of treatment. A change in the total MADRS score indicates the efficacy of an agent and the treatment response was defined as a 50% reduction in the MADRS total score at the beginning of the treatment. The remission was defined as < 7 in the MADRS total score. The changes of personality were assessed with the help of the TCI-R questionnaire in its computerised 240 item version. Using TCI–R, dimensions of personality were assessed in patients and also in the control group at the same time periods as the MADRS (Table 1). The MADRS was performed by a psychiatrist at an outpatient clinic and the TCI-R was completed by the patients and healthy controls, using a personal computer and processing the TCI-R dimensions by software. Because of a relatively small number of patients were obtained mean scores of the TCI-R and MADRS processed by non-parametric Wilcoxon pair test.

RESULTS

We have observed a significant decrease in mean total MADRS scores after the 1st month of treatment - MADRS 0 vs MADRS 1 (p=0.000049), after the 3rd - MADRS 0 vs MADRS 3 (p=0.000053) and also in the 6th month - MADRS 0 vs MADRS 6 (p=0.000002). The significant decrease of depression´s intensity was also observed between the 1st and 6th month - MADRS 1 vs MADRS 6 (p=0.016401) and between the 3rd and 6th month - MADRS 3 vs MADRS 6 (p=0.013760). There were no significant differences in MADRS 1 vs MADRS 3 (Table 1, 2).

Table 1. Descriptive statistics of all measurements in patients (mean total scores and standard deviations of MADRS and TCI dimensions)

		X ± SD			X ± SD
MADRS	0	16.13 6.28	P	0	116.87 13.63
	1	8.87 6.16		1	115.30 13.94
	3	8.47 7.23		3	116.00 13.65
	6	6.03 6.03		6	119.07 12.61
NS	0	92.93 12.14	SD	0	137.30 16.90
	1	92.67 12.15		1	139.97 14.62
	3	93.90 13.12		3	136.77 16.45
	6	94.93 12.07		6	139.53 15.71
HA	0	108.87 15.72	CO	0	135.97 11.87
	1	106.50 16.90		1	134.40 13.53
	3	106.03 15.39		3	133.93 10.61
	6	101.40 18.63		6	133.37 12.57
RD	0	105.83 13.28	ST	0	73.40 14.78
	1	103.63 9.00		1	70.23 18.42
	3	102.90 11.54		3	70.00 16.04
	6	103.73 11.88		6	69.87 17.85

X – mean score, SD – standard deviation, MADRS – Montgomery Asberg Depression Rating Scale, NS – Novelty Seeking, HA – Harm Avoidance, RD – Reward-dependence, P – Persistence, SD – Self-directedness, CO – Cooperativeness, ST – Self-transcendence; 0 – the first visit of patient, 1 – visit after 1 month of treatment, 3 – visit after 3 months of treatment, 6 – visit after 6 months of treatment

Table 2. Dynamics in MADRS and TCI dimensions total mean scores in patients (Wilcoxon pair test)

Comparison between scores		Z	p	Comparison between scores		Z	p
MADRS	0 vs 1	4.060	0.000049***	P	0 vs 1	1.060	0.289
	0 vs 3	4.042	0.000053***		0 vs 3	0.717	0.473
	0 vs 6	4.782	0.000002***		0 vs 6	0.695	0.487
	1 vs 3	0.714	0.475056		1 vs 3	1.003	0.316
	1 vs 6	2.400	0.016401*		1 vs 6	2.098	0.036*
	3 vs 6	2.464	0.013760*		3 vs 6	1.708	0.088
NS	0 vs 1	0.184	0.854	SD	0 vs 1	1.412	0.158
	0 vs 3	0.936	0.349		0 vs 3	0.309	0.758
	0 vs 6	1.490	0.136		0 vs 6	0.786	0.432
	1 vs 3	1.162	0.245		1 vs 3	1.537	0.124
	1 vs 6	1.633	0.103		1 vs 6	0.324	0.746
	3 vs 6	0.672	0.502		3 vs 6	1.362	0.173
HA	0 vs 1	1.092	0.275	CO	0 vs 1	1.002	0.316
	0 vs 3	1.471	0.141		0 vs 3	1.357	0.175
	0 vs 6	2.337	0.019*		0 vs 6	1.903	0.057
	1 vs 3	0.387	0.699		1 vs 3	0.041	0.967
	1 vs 6	2.097	0.036*		1 vs 6	0.823	0.411
	3 vs 6	2.129	0.033*		3 vs 6	0.541	0.589
RD	0 vs 1	1.795	0.073	ST	0 vs 1	1.687	0.092
	0 vs 3	1.742	0.082		0 vs 3	2.129	0.033*
	0 vs 6	1.213	0.225		0 vs 6	2.201	0.028*
	1 vs 3	0.717	0.473		1 vs 3	0.228	0.819
	1 vs 6	0.239	0.811		1 vs 6	0.576	0.565
	3 vs 6	0.603	0.546		3 vs 6	0.057	0.955

X – mean score, SD – standard deviation, MADRS – Montgomery Asberg Depression Rating Scale,
NS – Novelty Seeking, HA – Harm Avoidance, RD – Reward-dependence, P – Persistence, SD – Self-directedness,
CO – Cooperativeness, ST – Self-transcendence; 0 – the first visit of patient, 1 – visit after 1 month of treatment,
3 – visit after 3 months of treatment, 6 – visit after 6 months of treatment; *p < 0.05, **p < 0.01, ***p < 0.001;
Z-test statistics value

The treatment response (≥50% decrease in total MADRS score) was seen in 12 patients (40%) after the 1st month, 17 patients (56.7%) after 3 months and 21 patients (70%) after 6 months. The remission (MADRS<7) was achieved by 14 patients (46.6%) after the 1st month of treatment, 16 patients (53.3%) after the 3rd month and 19 patients (63.3%) after the 6th month. We have also found significant changes in the TCI-R temperament dimension scores in the study sample during treatment. The significant decrease in the mean HA score was observed after 6 months of treatment-HA 0 vs HA 6 (p=0.019), between the 1st and 6th month-HA 1 vs HA 6 (p=0.036) and between the 3rd and 6th month-HA 3 vs HA 6 (p=0.033) (Table 1, 2). There were no significant changes in NS score between any measurements (Table 2). Also, no significant changes were found in RD scores (Table 2). In the P dimension, we have observed a significant increase between the 1st and 6th month-P 1 vs P 6 (p=0.036) (Table 1, 2). In the TCI-R character dimensions, we have observed a significant decrease in ST scores after 3 months- ST 0 vs ST 3 (p=0.033) and also after 6 months-ST 0 vs ST 6 (p=0.028) (Table 1, 2). There were no significant changes found in CO and SD dimensions (Table 2).

As shown in Table 3, several significant changes in character dimensions and also one in P dimension were detected in the control group. There were significant decreases observable after 3 months (146.32±11.71 vs 142.52±11.79, p=0.011) and after 6 months (146.32±11.71 vs 140.80±12.81, p=0.001) in the SD mean score, a significant decrease between the 1st and the 3rd (135.56±13.22 vs 131.60±14.13, p=0.005) and between the 1st and 6th month (135.56±13.22 vs 132.80±13.71, p=0.038) in the CO mean score and also a significant decrease in the ST mean score between the 1st and the 3rd month (68.84±14.99 vs 66.52±14.32, p=0.011). Surprisingly, a significant increase was detected in the P mean score between the baseline measurement vs measurement after the 1st month (122.16±17.14 vs 126.20±18.00, p=0.009).

Table 3. Dynamics in TCI dimensions total mean scores in healthy controls (Wilcoxon pair test)

	0 vs 1		0 vs 3		0 vs 6		1 vs 3		1 vs 6		3 vs 6	
	Z	p	Z	p	Z	p	Z	p	Z	p	Z	p
NS	0.228	0.820	0.715	0.475	0.932	0.932	0.297	0.297	0.143	0.886	0.973	0.330
HA	1.217	0.224	0.400	0.689	0.135	0.893	0.745	0.456	1.600	0.110	1.125	0.260
RD	0.982	0.326	1.943	0.052	0.052	0.092	0.821	0.411	0.700	0.484	0.471	0.637
P	2.629	0.009**	0.877	0.381	1.257	0.209	1.329	0.184	1.426	0.154	0.319	0.749
SD	0.912	0.362	2.557	0.011*	3.458	0.001**	1.588	0.112	1.840	0.066	0.043	0.966
CO	1.243	0.214	1.507	0.132	0.601	0.548	2.829	0.005**	2.078	0.038*	0.629	0.530
ST	1.557	0.119	0.186	0.853	0.143	0.886	2.529	0.011*	1.293	0.196	0.973	0.330

NS – Novelty Seeking, HA – Harm Avoidance, RD – Reward-dependence, P – Persistence, SD – Self-directedness, CO – Cooperativeness, ST – Self-transcendence 0 – the first visit, 1 – visit after 1 month, 3 – visit after 3 months, 6 – visit after 6 months, *p < 0.05, **p < 0.01, ***p < 0.001; Z-test statistics value

DISCUSSION

Our findings showed statistically significant changes of personality temperament in the HA, P dimensions and character ST dimension in patients during 6 months of antidepressant treatment. We have observed a significant change in the HA score after 6 months of treatment, between the 1st and 6th month and between the 3rd and 6th month. The significant change in the P score was observed between the 1st and 6th month. In the character ST dimension we have observed significant changes after 3 and 6 months of treatment. The changes of personality dimensions were detected by the TCI-R in the course of treatment, during which we observed a continuous decrease in the intensity of depressive symptomatology assessed by the MADRS. Our results could be supported by outcomes of other studies showing that a high score of temperament dimension HA is associated with anxiety and depression and it could decline after antidepressant treatment (Farmer et al. 2003, Joffe et al. 1993, Jylhä & Isometsä 2006). In contrast to some previous studies (Farmer et al.

2003, Hirano et al. 2002), we did not find any significant changes in the SD character dimension. In addition to the decrease in the HA score, we have observed a significant increase in the P temperament and significant decrease in the ST character dimension in the study sample. Interesting findings were changes in the P, SD, CO and ST dimensions in the control group. The temperament dimension HA is characterized as a heritable tendency to respond intensely to aversive stimuli and to learn to avoid punishment (Cloninger 1987). HA quantifies individual differences in the extent to which a person is anxious, pessimistic and shy versus risk-taking, optimistic, and outgoing (Cloninger 1986). Persistence could be characterized as perseverance in behavior despite frustration and fatigue. The TCI character dimensions also provided a way to quantify aspects of mature mental self-government, thereby providing a reliable way to measure the higher cognitive processes that modulate emotional conflicts (Cloninger et al. 1993). SD is characterized as the ability to control, regulate and adapt behavior to fit the situation and individually chosen goals, while ST is characterized as identification with everything conceived as essential and consequential parts of a unified whole (Cloninger 1987). The familial vulnerability to major depression is predicted most strongly by high HA and low SD. NS and RD also decreased the risk whereas P, CO and ST did not influence the familial risk (Farmer et al. 2003). High HA and low SD are also predictive of poor response to antidepressants (Joyce et al. 2003, Tome et al. 1997). Also it is supposed that low SD and high HA can occur as a consequence of depressive episodes (Farmer et al. 2003, Hirano et al. 2002).

However, one recent study with a large number of participants demonstrated, using hierarchical multiple regression analyses, specific depression was predicted by lower RD, P and lower scores in all of the character dimensions. Specific anxiety was predicted by higher NS, HA, P and ST and lower SD. The association between specific anxiety and ST was a unique finding (Matsudaira & Kitamura, 2006). This finding supports the character cube model in which the melancholic character, as indicated by lower SD, CO, and ST scores, is the prototype of unipolar depression (Cloninger et al. 1998). Our data indicates the changes of HA, P and ST are connected with antidepressant treatment in the study sample. These dimensions could be associated with anxiety and depression as mentioned above. However, we have observed significant alterations in all character dimensions and the P temperament dimension as well, in the control group.

The alterations in temperament dimensions may reflect that personality mechanisms involved in pathogenesis of depression were affected. The changes in character dimensions could reflect the way that personality reacts to depressive disorder, using psychological mechanisms and higher cognitive functions. It seems likely that it would be useful to distinguish between temperament and character for effective treatment planning. Temperament has a tendency to remain with relatively stable characteristics and it is rather resistant to psychotherapeutic treatment. Character, on the other hand, develops during adulthood and it can distinctively react to psychotherapeutic interventions. Because of these differences, in the case of the impulsivity conditioned mainly by temperament would, we expect be more likely to be affected by psychopharmacological treatment (e.g. antidepressants), whereas psychotherapy would be beneficial in affecting self-control and interactions with people which emerge mostly from the character (Gabbard 2000).

The human capacity for creative self-organization appears to have an unpredictable influence on mood and personality development (Cloninger 2004). It is possible that character dimensions could be strongly affected by psychological reactions and thereby show a high variability over time.

The alteration in the P dimensions in the control group was a surprising finding. The P dimension perhaps shows less stability over time in comparison to other temperament dimensions, but it is also possible that this outcome is an aberration caused by a relatively small number of healthy controls.

We hypothesize that depression could lead to a limited natural fluctuation of TCI character dimensions, which we have observed in the control

group. In contrast, there were more expressive alterations of TCI temperament dimensions (especially in HA) in the study sample. The possible explanation of this finding could be, that temperament dimensions are mostly affected by basic pathophysiologic mechanisms underlying the course of depression and targeted by antidepressant treatment. Consequently, character dimensions show a lower fluctuation as a consequence of depression experienced by personality.

The changes of personality in depressive patients are probably caused by complex mechanisms. The relationship between personality and depression is also complex. Enns and Cox have identified several possible models of such interactions (Enns & Cox 1997). It could possibly involve intense interactions of personality dimensions, environmental factors and depressive disorder itself. Moreover, another possible factor is that antidepressant therapy contributes to the differences in personality scores.

There are only a few studies investigating the effects of antidepressants on personality traits and the findings are inconsistent (Gelfin et al. 1998, Knutson et al. 1998). One recent study suggested that SSRIs can exert effects on personality characteristics that are independent of treatment response (Brody et al. 2000).

The limitations of our study are a relatively small study sample of 30 patients and a non-homogeneous structure of the sample with patients suffering from depressive episode, recurrent depressive disorder and mixed anxious-depressive disorder. Another possible confounding factor is that the study sample consists of outpatients. Outpatients usually do not suffer from severe depression and could, in comparison to inpatients, face different conditions. Therefore, the changes of personality dimensions in outpatients could reflect more „real life“ situations with distinct treatment response.

CONCLUSION

Our findings indicate that the changes of personality characteristics occur at least several months after commencement of antidepressant treatment. It could possibly confirm the necessity of long-term antidepressant treatment even when clear depressive symptomatology has retreated. We suggest that the TCI-R could be an applicable tool for detection of these changes during treatment. The progress of such personality changes could probably help with the decision about the duration of antidepressant treatment after extinction of depressive symptomatology. The TCI-R could also be suitable for analysis of these changes and their potential advantages or disadvantages for patients.

The changes of temperament and character dimensions may reflect alterations in various neuromediator systems taking part in the pathogenesis of anxious and depressive disorders. Therefore, Cloninger´s theory may be of potential importance in developing an integrated understanding of the wide range of biological and psychosocial processes underlying the etiology, course and treatment of depression.

Further long-term studies with a larger number of patients and homogeneous structure of cohorts are necessary to answer, whether the TCI-R is methodologically appropriate and valuable for clinical utility in depressed patients. It could be potentially used to detect the changes of personality characteristics in both inpatients and outpatients suffering from major depression, mixed anxiety and depressive disorder or other types of affective disorders.

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