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ORIGINAL RESEARCH

Treatment effect on temperament and character in panic disorder: a prospective randomized double-blind study

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OBJECTIVE: The present study aims to analyze the effect of pharmacological treatment for panic disorder on temperament and character dimensions and to compare the effect of imipramine and fluoxetine on this outcome.
METHOD: Temperament and character dimensions were evaluated in panic disorder patients before and after six months of pharmacological treatment with imipramine and fluoxetine, using the Temperament and Character Inventory-Revised. Patients were randomized between groups and both (patient and investigators) were blinded to the intervention drug. Furthermore, 34 non-panic controls answered the revised Temperament and Character Inventory through an Internet survey.
RESULTS: Panic disorder patients showed higher scores for Harm Avoidance and lower scores for Persistence, Self-Directedness, and Cooperativeness than controls at baseline, but only the low Persistence value remained different from controls after treatment. Responder patients presented significant reduction in Harm Avoidance scores and a significant increase in Self-Directedness scores, whereas non-responders showed a significant increase of Harm Avoidance levels. Fluoxetine and Imipramine showed similar effects on the revised Temperament and Character Inventory dimensions.
CONCLUSION: High Harm Avoidance and low Self-Directedness, Persistence, and Cooperativeness are associated with panic disorder. Treatment of acute panic disorder symptoms lead to the reduction of Harm Avoidance and to an increase in Self-Directedness scores. However, there was no difference between treatment with fluoxetine and imipramine for the effect on the revised Temperament and Character Inventory dimensions.

KEYWORDS: Panic disorder; Temperament; Character; Imipramine, Fluoxetine.

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INTRODUCTION

Panic disorder (PD) is a prevalent anxiety disorder that affects 1.6 to 2.2% of the global population.[1] Evidence from naturalistic follow-up studies suggests that at 4-6 years post-treatment, only approximately 30% of individuals achieve full remission.[1] Thus, PD can be considered a chronic and recurrent disorder.

Trait-based studies of personality in patients with PD provide additional diagnostic information, corroborating the identification of more homogeneous subgroups of patients and helping to explain patterns of PD comorbidities. These studies also provide means to identify individuals at risk of developing PD who could benefit from prevention efforts and early intervention. In addition to its importance for diagnostic issues, the study of personality traits in PD patients may also be useful for planning and customizing treatment.[2]

In most studies in which personality characteristics have been evaluated in PD patients, a categorical approach has been utilized in which the interaction between personality disorders or personality traits and PD have been evaluated.[3-5] The high prevalence of comorbid personality disorders and PD suggests a common basis for what the Diagnostic and Statistical Manual of Mental Disorders (DSM) IV used to divide into axis I and II.[6] Therefore, these two diagnostic axis were unified in current DSM-V and dimensional constructs of personality have been suggested to better understand

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the relationship between temperament, character, and the development of psychiatric syndromes.[7] Among the variety of alternative dimensional models proposed, Cloninger's psychobiological model[8,9] has received considerable empirical support.[8] This model consists of four dimensions of temperament (novelty seeking, harm avoidance, reward dependence, and Persistence) and three dimensions of character (Self-directedness, Cooperativeness, and Self-transcendence).[8,9] Temperament is understood as automatic responses to ambient stimuli, which relate to neurobiological predispositions. Character is related to a more complex cognitive process that leads to Self-concept and its relationship to others and the surrounding environment.[8] The *Temperament and Character Inventory* (TCI) was developed to evaluate temperament and character dimensions,[9] which afterwards was revised into the *Temperament and Character Inventory - Revised* (TCI-R).[9]

Cloninger's model has been tested almost exclusively in the acute phase of PD. Most studies have used the *Tridimensional Personality Questionnaire* (TPQ), which refers to the Cloninger's first formulation[10] and evaluates only temperament dimensions. In these studies, high levels of Harm Avoidance were found in PD patients.[11-14]

Two case-control studies were published using the TCI for PD patients.[15,16] Their findings corroborated previous studies in which patients with PD showed higher scores for Harm Avoidance compared with the control group.[12,13] In one of these studies,[16] the patient group also showed lower scores for the Self-directedness character dimension.

It is controversial whether the personality profile in acute PD patients is related to the disorder's symptomatology (state dependent) or is a trait that predisposes an individual to PD or constitutes an intermediate phenotype of this disorder.[17-19] To resolve these questions, longitudinal studies are needed to evaluate personality dimensions before and after PD remission.

To our knowledge, only one previous study has assessed temperament and character dimensions both before and after PD treatment using the TCI-R. This study by Marchesi et al.[20] evaluated 65 PD patients and 71 healthy controls. Patients underwent a year of treatment with paroxetine or citalopram. PD patients showed higher scores for Harm Avoidance than controls both before and after treatment, although for responders, this difference from the controls was reduced after treatment. In this study, data also suggest that the high levels of Harm Avoidance found after remission may depend on subsyndromal residual phobic symptoms. Regarding the character dimensions, only non-responder PD patients differed from the controls both before and after treatment, showing lower scores of Self-directedness and Cooperativeness. A low Self-directedness score before treatment was found to be a predictor of non-remission, and these non-responder patients worsened after treatment.[20]

In its initial phase, Cloninger´s personality model suggested that extreme temperament dimensions could be associated with specific neurochemical pathways, such as the correlation between dysfunctional serotoninergic pathway and low Harm Avoidance scores.[7] However, these assumptions could never be confirmed and Cloninger and his coleguees later on assumed that personality results from a nonlinear and much more complex system that cannot be simplified to specific neurochemical pathways.[9] Still, the comparison between pharmacologically different drugs for their effect on temperament and character may be useful to clarify this issue. Besides that, it may have a clinical importance for treatment drug choice, which is still much understudied.

The aim of the present study is to compare PD patients' TCI-R scores before and after six months of treatment with fluoxetine or imipramine in relation to controls and to compare the difference between the effect of these two drugs on TCI-R scores.

METHODS

Subjects

Forty subjects were included in the study and completed the informed-consent form. They were recruited from out-patients who sought treatment for depression and anxiety disorders at the Institute of Psychiatry of the Federal University of Rio de Janeiro (after institutional ethics committee approval. All subjects included in the study were diagnosed with panic disorder (with or without agoraphobia) according to the *Mini International Neuropsychiatry Interview 5.0* (MINI 5.0).

Patients with major depression, psychotic disorders, organic mental disorders, substance abuse or dependence, or a history of neurological or medical illnesses (i.e., cardiovascular, hematological, liver, respiratory, or endocrinological diseases) were excluded from the study. Electrocardiographic alterations that counter-indicate imipramine use were also considered exclusion criteria. Patients currently using any antidepressant were also excluded.

At the baseline interview, the *Structured Clinical Interview for DSM-IV Axis II Personality Disorders* (SCID II) was applied to exclude patients presenting any personality disorder diagnosed by the DSM-IV.

Assessment

The MINI and the SCID II were applied to recruit subjects according to the inclusion and exclusion criteria described above.

The TCI-R was used for the evaluation of temperament and character dimensions at the baseline and after six months of treatment for panic disorder with one of the

two blind medications (at the end-point). The TCI-R was validated for Brazilian Portuguese with adequate psychometric properties.[21]

The severity and evolution of panic disorder were evaluated by clinical observation and the *Clinical Global Impression Scale* (CGI-S and CGI-I). The CGI scales are commonly used measures of symptom severity and treatment response for psychiatric disorders. The investigator compares the subjects to typical patients in his clinical experience. While CGI-S is a 7-point scale that requires the clinician to rate the severity of the patient's illness at the time of assessment, the CGI-I is a 7 point scale that requires the clinician to assess how much the patient's illness has improved or worsened relative to a baseline state at the beginning of the intervention. Clinical visits were conducted monthly for six months, and the CGI-I was rated at every visit.

Treatment

Patients were treated randomly with imipramine or fluoxetine. There were four possible doses for each tested drug: 25, 75, 150, and 200 mg/day for imipramine and 10, 20, 40, and 60 mg/day for fluoxetine. The drug dose was increased to the point at which symptoms remitted, side effects became intolerable, or the maximum dose was achieved. The patients and the assistant doctor were blinded to the intervention group.

Benzodiazepine use (clonazepam or alprazolam from 0.5 to 2.0 mg/day) was tolerated for the treatment of eventual insomnia and acute anxiety during panic attacks, but not regularly.

Non-panic control group

The control group was composed of 34 subjects from a general population sample. This stage of the study was conducted through an Internet survey in which all subjects answered the TCI-R and the Panic and Agoraphobia Scale (PAS). This last scale consists of five items each of which contains questions about the frequency of panic attacks, intensity of phobic avoidance, anticipatory anxiety, degree of disability, and other health concerns, respectively. Each question is rated on a scale from 0 to 4 according to the aspect investigated (for example, panic: 0 = no panic attack last week, 2 = two or three panic attacks last week 3 = four to six panic attacks last week, 4 = more than 6 panic attacks in the last week). The total score obtained on each item results in a global score ranging from 0 to 52. It was translated to Brazilian Portuguese by Lotufo-Neto.[22]

Subjects who presented panic disorder according to the PAS (4 subjects) were excluded to ensure that the control group would be panic-free. Since we could not exclude potential comorbities in the control group, it is being called "non-panic control group" (or "non-panic controls").

Statistical analysis

Demographic variables were analyzed by a chi-square test. A non-parametric test for independent samples (Mann-Whitney U) was used to compare the TCI-R dimension scores for the PD and non-panic groups at baseline and at the end of the treatment.

To compare the TCI-R dimension before and after treatment, the PD group was divided into two subgroups by the clinical global impression scale (CGI-I score). Patients presenting a final CGI-I equal to 1 or 2 were considered "responders", and those with a final CGI-I from 3 to 6 were considered "non-responders". Wilcoxon signed-rank test was used to analyze the TCI-R scores for responders and non-responders, before and after treatment.

To compare the two intervention groups (imipramine *versus* fluoxetine) before and after treatment, the mean difference between the end-point and baseline in the TCI-R scores was calculated for every dimension for both groups, and a Mann-Whitney U test was performed. In this study, $p < 0.05$ was considered statistically significant.

RESULTS

Demographic and clinical features

Two patients were excluded from the initial sample for presenting new clinical or psychiatric comorbidities (severe diabetes and psychotic symptoms, respectively), and ten patients discontinued the follow-up. Thus, 28 patients completed the study; 14 of them taking fluoxetine (mean dose = 32.14 mg/day), and 14 taking imipramine (mean dose = 125 mg/day). There were no significant differences between the PD and non-panic control groups for demographic features, with the exception of years of education, for which the panic group had a lower mean (10.1 *versus* 13.2 years, $p < 0.01$). Comparing the two intervention groups, there were no differences for all the demographic features (gender, age, and years of study).

PD severity measured by the CGI-S was similar between the imipramine and fluoxetine groups (4.79 *versus* 4.93, $p > 0.05$) as well as for the drop-outs *versus* the completers (4.40 *versus* 4.86, $p > 0.05$). Among the drop-outs, 40% were on fluoxetine, and 60% were on imipramine (not significantly different from the completers, $p > 0.05$). Non-responders had higher PD severity at baseline than responders ($p = 0.019$).

Clinical improvement was measured by the CGI-I and was similar between both intervention groups (1.93 ± 0.91 for fluoxetine and 2.00 ± 0.87 for imipramine, $p > 0.05$). Responders and non-responders were equally distributed between these groups, as was benzodiazepine use. A total of 10 patients used benzodiazepines along the six months of treatment, 5 for each of the intervention groups.

Temperament and character dimensions

The mean scores and standard deviations of the TCI-R dimensions are presented for the panic and non-panic groups as well as for the two intervention subgroups (the fluoxetine and imipramine subgroups) in Table 1.

PD patients *versus* non-panic control group

When compared to the non-panic control group at baseline, panic patients showed significantly higher scores for Harm Avoidance (p = 0.004) and lower scores for Persistence (p = 0.004), Self-directedness (p = 0.002), and Cooperativeness (p = 0.014). At the end-point, the Harm Avoidance and Self-directedness scores were no longer significantly different from the non-panic group, but Persistence and Cooperativeness maintained the differences (p = 0.026 and p = 0.046, respectively); Self-transcendence which was similar between groups at baseline, became different from the non-panic control group (p = 0.045).

PD group before and after treatment

Panic responder patients had a significant reduction of Harm Avoidance (p = 0.003) and an increase in Self-directedness (p = 0.013) and Persistence (p = 0.025) scores during treatment, whereas non-responders only showed a significant change for Harm Avoidance, which, surprisingly, was an increase in scores. Other TCI-R dimensions did not change significantly during the six-month treatment for both responders and non-responders (Table 2). Comparing the responders and non-responders at baseline and at the end-point, there was no significant difference between the groups for any dimension.

Fluoxetine *versus* imipramine

Comparing PD patients who were taking fluoxetine with those taking imipramine in terms of changes during treatment in the TCI-R dimensions (mean difference end-point-baseline), no statistically significant differences were found for any dimension. Changes on TCI-R dimensions for the two intervention groups are illustrated in Figure 1.

DISCUSSION

A previous study from our department has shown that aerobic training may produce favorable alterations in the PD, as measured through the Panic and Agoraphobia Scale, the Cardiac Anxiety Questionnaire, the Anxiety Sensitivity Index and in the Body Sensations Questionnaire scores.[23]

Our study showed that before treatment, PD patients differed significantly from non-panic controls both in temperament (Harm Avoidance and Persistence) and character dimensions (Self-directedness and Cooperativeness). Harm Avoidance was higher, and Persistence, Self-directedness, and Cooperativeness were lower than in the non-panic group. This temperament and character profile in patients presenting PD is consistent with previous literature.[16,20,24] After treatment, patients and controls were no longer different for harm avoidance and Self-directedness, showing that the changes in these dimensions approached patients to controls. When evaluating temperament and character dimensions before and after treatment in responding patients, we see that clinical improvement lead to a significant reduction in Harm Avoidance scores and to an increase in Self-Directedness and Persistence scores.

In contrast, for non-responders, there was an unexpected increase in Harm Avoidance from baseline to end-point. Changes for Self-directedness were not significant for this last subgroup. The mean score for this character dimension increased much less for non-responders vs. responders. We observed that for patients who did not achieve an important improvement in clinical symptoms, not only they did they not reduce symptoms, but they also showed a tendency toward reinforcing the inhibited behavior after the six-month treatment.

Thus, we can say that different responses to treatment lead to different changes in temperament and character dimensions and that Harm Avoidance and Self-directedness

Table 1 - Means and standard deviation for TCI-R dimensions and CGI-S scores for PD patients and Controls

TCI-R Dimension	Controls (N = 34)	PD patients (N = 28)		Fluoxetine Group (N = 14)		Imipramine Group (N = 14)	
		Baseline	End-point	Baseline	End-point	Baseline	End-point
Novelty Seeking	57.79 (13.94)	56.20 (8.53)	56.81 (6.58)	57.18 (7.92)	56.71 (7.19)	55.22 (9.28)	56.90 (6.28)
Harm Avoidance	60.62 (12.65)	70.13 (10.58)	66.04 (11.97)	70.69 (10.00)	65.67 (13.96)	69.56 (11.47)	66.40 (10.11)
Reward Dependence	67.98 (12.60)	66.40 (10.08)	66.88 (8.56)	65.42 (9.40)	66.24 (6.53)	67.38 (10.97)	67.52 (10.42)
Persistence	69.07 (10.50)	62.71 (7.45)	63.78 (9.32)	62.85 (7.35)	64.13 (10.06)	62.57 (7.82)	63.47 (8.94)
Self-Directedness	70.97 (11.15)	62.25 (8.44)	66.00 (10.33)	60.71 (7.98)	63.77 (8.94)	63.78 (8.88)	68.07 (11.40)
Cooperativeness	77.56 (7.64)	72.83 (8.43)	73.89 (8.59)	72.02 (8.21)	71.31 (6.71)	73.65 (8.86)	76.67 (9.75)
Self-Transcendence	52.40 (15.28)	57.25 (11.80)	59.81 (12.72)	56.31 (10.05)	58.85 (10.96)	58.18 (13.65)	60.76 (14.63)
CGI-S	-	4.86 (0.143)	2.24 (0.194)	4.79 (0.214)	2.28 (0.285)	4.93 (0.195)	2.50 (0.272)

TCI-R: Temperament and Character Inventory Revised; PD: Panic disorder; CGI-S: Clinical Global Inventory - Severity.

Table 2 - TCI-R dimensions before and after treatment for responders and non-responders patients

	Mean Differences (end-point-baseline)		Wilcoxon Signed Ranks Test			
	Responders (N = 20)	Non Responders (N = 8)	Responders (N = 20)		Non Responders (N = 8)	
TCI-R Dimensions			Z	p	Z	p
Novelty Seeking	1.0571 (± 6.98)	0.6667 (± 6.70)	-0.523	0.601	-0.946	0.344
Harm Avoidance	-8.6970 (± 10.42)	7.4242 (± 7.93)	-2.963	0.003*	-2.100	0.036*
Reward Dependence	0.5333 (± 4.49)	0.333 (± 8.66)	-0.561	0.575	-0.568	0.570
Persistence	2.1053 (± 5.92)	-1.8571 (± 6.37)	-2.235	0.025*	0.980	0.327
Self -Directedness	4.7368 (± 7.53)	1.2500 (± 3.62)	-2.496	0.013*	-0.851	0.395
Cooperativeness	0.4678 (± 7.11)	1.0417 (± 6.41)	-0.262	0.794	-0.338	0.735
Self-Transcendence	3.2308 (± 10.28)	0.8654 (+/11.30)	-1.553	0.120	-0.140	0.889

TCI-R: Temperament and Character Inventory Revised; Z score: Wilcoxon Signed Tanks Test result; p: p-value. *statistically significant results.

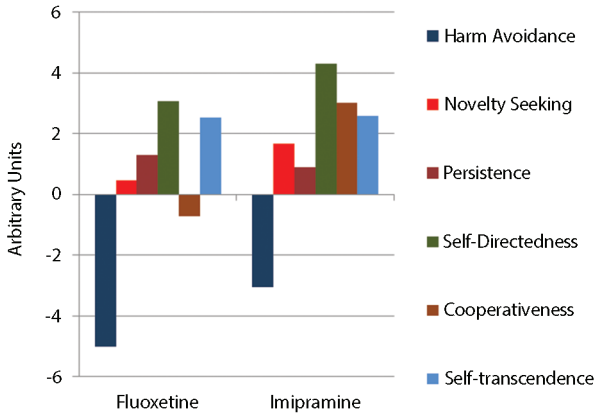

Figure 1 - Mean difference from baseline to end-point of TCI-R dimensions scores for fluoxetine and imipramine groups. TCI-R: Temperament and Character Inventory Revised.

are most closely related to treatment response to PD. There is an interesting parallel between these results and those found in a meta-analysis by Kampman et al.[25] relating temperament, character, and depression. In this study, Harm Avoidance also appeared as the temperament dimension most closely related to treatment response in depressed patients. Character traits were not evaluated in this article.[25] Although Persistence also showed a statistically significant reduction during treatment for R patients, it can considered less clinically significant than Harm Avoidance and Self-directedness changes.

Concerning TCI-R dimensions other than Harm Avoidance and Self-directedness, the literature offers less consistent data relating these dimensions to panic disorder. Persistence is a temperament dimension that serves as a modulator between intentions and drives, holding representations of goals and values in memory while delaying responses to affective stimuli so that a person can make choices that consider both past conditioning and expectations of future outcomes.[24] As postulated recently by Cloninger et al.,[26] Persistence modulates the influence of the temperament trait Harm Avoidance and the character trait Self-directedness on the lifetime risk of developing anxiety and/or mood disorders. Although it is said that high Persistence can lead to anxiety disorders because it increases compulsive behavior,[26] for PD patients, the literature shows a tendency toward low Persistence, remarkably so for drug-resistant patients.[20] Our study found that Persistence was significantly lower than the non-panic controls before treatment, and this difference remained at the end-point. For responders, scores increased significantly during treatment, whereas for non-responders, it tended to decrease. For both groups, however, the size of the clinical effect was considered small.

Self-transcendence mean scores in PD patients did not differ from the non-panic controls before treatment, but became different after treatment. However, Self-transcendence scores did not change significantly between responders or non-responders. Our data show no significant association between PD and novelty seeking and reward dependence levels, corroborating findings described in previous studies.[16,20]

A vast amount of research has been conducted on the association of temperament with psychiatric disorders. Much of this research aims to evaluate if there is a causal relationship between them or if they consist in epiphenomena of a common process. When it comes to PD, literature is scarce and there are no cohort prospective studies, so it is not possible to affirm if Harm Avoidance (or any other temperament dimension) acts as a predisposition factor for PD development. As suggested by Brown et al.,[19] our findings also emphasize that personality traits are modulated by clinical state and pharmacological treatment. However, the temperament and character profile of PD patients was clinically different from that of the non-panic control group before and after treatment, although, this difference was reduced at the endpoint and turned out to be not statistically significant for all dimensions. Thus, it is possible to hypothesize that high Harm Avoidance and

low Self-directedness, Persistence and Cooperativeness constitute premorbid personality traits in patients with PD, which increase during the disorder acute phase, and, for responding patients, and which are reduced after pharmacological treatment with antidepressants, tending to return to a premorbid pattern.[20]

Comparing the two intervention drugs (fluoxetine and imipramine) to their effects on TCI-R dimensions, we did not observe a significant difference for any of them. For all dimensions, the mean difference was similar from baseline to end point for both drugs. Because the patients were randomized between intervention groups and the patients and the researcher were blinded to the randomization, we can say that the probability of this result being due to confounding factors or observer bias is minimal. Both intervention groups were similar in terms of demographic factors, panic severity, and symptom improvement. Because an important association was found between clinical state and temperament and character dimensions, it is not possible to distinguish whether the similarity found between the effects of the drugs was due to similar effects on PD symptoms.

In conclusion, our study corroborates previous reports suggesting that symptomatic PD patients present higher levels of Harm Avoidance and lower levels of Self-directedness, Persistence, and Cooperativeness and that pharmacological treatment with antidepressants, if efficient, leads to a reduction of Harm Avoidance and an increase of Self-directedness and Persistence scores. Based on our data, we can hypothesize that this personality profile is premorbid but is exacerbated by acute symptoms, tending to return to the former pattern after efficient pharmacological treatment. The two tested drugs (fluoxetine and imipramine) show similar effects on temperament and character dimensions.

To our knowledge, this is the first controlled study to compare the effect of treatment with two different drugs on temperament and character in patients presenting panic disorder. Thus, it can be seen as a pilot study for further investigation on the issue.

LIMITATIONS

Our study has some limitations that should be considered. The small sample size all but impedes the generalization of results, and the short length of follow-up may not have allowed for more significant changes in temperament and character dimensions. Thus, further studies with a larger sample and a longer follow-up period are needed to confirm the present data.

In addition, the number of drop-outs in this study was high (36%). Although clinical severity was similar between dropouts and study completers, it is not possible to ensure the absence of selection bias when comparing responding and non-responding patients before and after treatment. Dropouts were equally distributed between both intervention groups. Thus, follow-up losses did not influence their comparison.

It was not possible to collect data concerning potential comorbidities in the control group, which was the reason we preferred to call this group "non-panic control group".

Finally, the non-panic controls had significantly more years of formal education than the patients did. Although it is reported that formal education is not associated with temperament and character scores,[27] we cannot exclude confounding factors related to educational and cultural aspects that may influence the comparison of the PD and control groups.

Conflicts of Interest and Source of Funding

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EFEITO DE TRATAMENTO SOBRE TEMPERAMENTO E CARÁTER NO TRANSTORNO DE PÂNICO: ESTUDO RANDOMIZADO PROSPECTIVO DUPLO-CEGO

OBJETIVO: O presente estudo tem como objetivo analisar o efeito do tratamento farmacológico do transtorno do pânico nas dimensões de temperamento e caráter, comparando os efeitos das medicações imipramina e fluoxetina neste desfecho.

METODOLOGIA: As dimensões de temperamento e caráter foram avaliadas em pacientes com transtorno do pânico antes e depois de seis meses de tratamento com imipramina ou fluoxetina, utilizando-se o "Temperament and Character Inventory- Revised" (TCI-R). O estudo foi randomizado e duplo-cego. Além disso, 34 controles sem transtorno do pânico responderam ao TCI-R via internet.

RESULTADOS: Pacientes com transtorno do pânico apresentaram maior pontuação para "Harm Avoidance" e menor pontuação para "Persistence", "Self-Directedness" e "Cooperativeness" que os controles antes do tratamento, mas apenas "Persistence" manteve a diferença após o tratamento. Pacientes respondedores apresentaram redução significativa da pontuação para "Harm Avoidance" e aumento significativo para "Self-Directedness" após o tratamento, enquanto os não-respondedores mostraram aumento

significativo na pontuação para "Harm Avoidance". A fluoxetina e a imipramina apresentaram efeitos semelhantes nas dimensões do TCI-R.

CONCLUSÃO: Alta pontuação para "Harm Avoidance" e baixa para "Persistence", "Self-Directness" e "Cooperativeness" estão associados ao transtorno do pânico. O tratamento sintomático do transtorno do pânico leva a redução da pontuação para "Harm Avoidance" e aumento de pontuação para "Self-Directedness". No entanto, não há diferença entre os efeitos da imipramina e da fluoxetina nestas dimensões do TCI-R.

UNITERMOS: Transtorno do pânico, Temperamento, Caráter, Imipramina, Fluoxetina.

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