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THE USE OF AN ANTAGONIST 5-HT2A/C FOR DEPRESSION AND MOTOR FUNCTION IN PARKINSON'S DISEASE

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Abstract – **Objective:** To test the ability of a 5HT2a/c (trazodone) antagonist, to improve depression and motor function in Parkinson's disease (PD). **Method:** Twenty PD patients with and without depression were randomly assigned to receive trazodone (group 1) or not (group 2). They were evaluated through UPDRS and Hamilton Depression Rating Scale (HAM-D). **Results:** For the UPDRS the mean score of group 2 was 33.1±19.7 and 37.1±18.0 at the end. For the group 1, the corresponding scores were 31.4±11.3 and 25.9±13.7. The variations in the Mann-Whitney test were 0.734 at the initial moment and 0.208 at the final moment. The variation in the comparison of the initial moment with the final moment was 0.005 providing statistical significance. For the HAM-D, the mean score went up 4 points in group 2, contrary to a 5.5 points decrease in group 1. **Conclusion:** Data analysis shows that this agent significantly improves depression, but the motor function improved only in the depressed patients. Because of the known anti-dopaminergic property of the 5-HT2c receptors, a possible approach for depression in PD could be the use of 5-HT2c antagonists, similarly to the use of atypical neuroleptics in case of psychotic symptoms.

KEY WORDS: trazodone, depression, Parkinson's disease phases of PD.

Uso de um antagonista 5-HT 2a/c na depressão e na função motora de pacientes com doença de Parkinson

Resumo – **Objetivo:** Avaliar a eficácia de um antagonista 5-HT2a/c (trazodona) na depressão e na função motora de pacientes com doença de Parkinson (DP). **Método:** Vinte pacientes com DP com e sem depressão foram randomizados e divididos em 2 grupos com e sem a trazodona (grupos 1 e 2). Foram avaliados pela escala UPDRS e a de depressão de Hamilton (EDH). **Resultados:** A média inicial do grupo 2 na UPDRS foi 33,1±19,7 no momento inicial e 37,1±18,0 no final. Para o grupo 1 as médias correspondentes foram 31,4±11,3 e 25,9±13,7. As variações no teste de Mann-Whitney foram 0,734 no momento inicial e de 0,208 no final. A variação na comparação entre o momento inicial e o final foi 0,005, caracterizando significância estatística. Para a EDH a média subiu 4 pontos no grupo 2, e desceu 5,5 pontos no grupo 1. **Conclusão:** A análise estatística revelou melhora da depressão, porém o benefício na função motora foi obtido apenas entre os deprimidos. Do mesmo modo que os neurolépticos atípicos atuam nos sintomas psicóticos, a ação secundária dopaminérgica do antagonista 5-HT2c pode ser útil no tratamento da depressão na DP.

PALAVRAS-CHAVE: trazodona, depressão, doença de Parkinson.

Non-motor symptoms make a significant contribution to the morbidity rates of Parkinson's disease (PD). Meta analytic data on the prevalence of depressive symptoms ranks to 31%[1]. Two previous series in Brazil found depression occurring in 38.33% and 24% of parkinsonian patients[2,3]. Surprisingly enough, the first studies on PD-related depression management date back to the end of the fifties, when Sigwald et al.[4] related isolated cases of motor worsening during imipramine treatment in depressed patients with PD. Besides, out of 43 studies carried out during 35 years of research, there were only three randomized trials on this matter[5]. The leuchine-rich repeat kinase 2 (LRRK2) gene mutations are a common cause of familial and sporadic PD (PD). A research showed an association of

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the LRRK2 p.G2019S among Brazilian PD patients[6]. A possible susceptibility to develop depression in PD may be linked to a genetic condition. A recent animal model for PD showed that the engrailed1 gene might be implicated in some cases of PD depressive patients[7].

Selective serotonin reuptake inhibitors (SSRIs) have been used to treat depression in PD. However, study evidence on the efficacy and safety of antidepressants in PD is lacking. There are several 5-HT receptor subtypes, including the 5-HT1a, 5-HT1b, 5-HT2a, 5-HT3 and 5-HT4 receptors. 5-HT2c receptors located to the *substantia nigra* and the ventral tegmental area may affect the dopaminergic activity, possibly interfering with motor control, motivation and rewarding mechanisms in the brain. In keeping with its ability to modulate dopamine (DA) neuron function in the brain, the 5-HT2C is currently considered as a major target for improved treatments of neuropsychiatric disorders related to DA neuron dysfunction, such as depression, schizophrenia, Parkinson's disease or drug addiction. It has been shown that the receptor 5-HT2a increases the dopaminergic activity, contrary to the reduced action evoked by the 5-HT2c receptor activation[8]. Despite these antagonistic actions, the much bigger anatomical, functional expressivity of 5-HT2c on 5-HT2a has become the inhibition of 5-HT2c as representative of the secondary dopaminergic function[9,10].

The objective of this study was to test the hypothesis that oral trazodone, a 5-HT2a/c antagonist/reuptake inhibitor, improve motor phases and depression in PD.

METHOD

This randomized study was approved by the HUCFF-UFRJ ethics committee. Twenty PD patients classified in the category 3 (clinically definite: plastic rigidity, bradykinesia, postural disturbance and rest tremor) according to Calne et al.[11] with and without depression were randomized in two groups. During 5 months (from T0 to T5), apart from usual PD care, group 1 (G1) received 50 mg trazodone orally twice a day, contrary to group 2 (G2), with no trazodone. The individuals all came from the Movement Disorders Sector at the Clementino Fraga Filho University Hospital (Federal University of Rio de Janeiro).

All the individuals were blind examined every month by two examiners: one ranked the scales, without knowing if the drug was applied or not, and the other did the randomizing, not stratified, without knowing the categories of the scales. Subjects were examined every month and ranked by an independent physician according to different scales: Unified Parkinson's Disease Rating Scale Score (UPDRS), Hoehn and Yahr (HY), Schwab and England (SE) and the Hamilton Depression Rating Scale (HAM-D). The UPDRS was carried out for parts II and III. Depressive symptoms were assessed through the HAM-D 17 scale with a cut point of 10 (HAM-D≥10)[4]. No other antiparkinsonian drug was added. Baseline exclusion criteria were: (1) secondary or atypical Parkinsonism; (2) organic mental syndrome related to cognitive and non-cognitive symptoms; (3) PD diagnosis before the age of 45 or after 75. Follow-up exclusion criteria were: (1) change in the dose or type of the antiparkinsonian drug; (2) signs or symptoms potentially interfering with the results.

All the analysis was conducted in observed case type and in a comparison between groups. The p-values were two tailed. Wilcoxon test was used to compare different groups with baseline. The Mann-Whitney test was employed comparing the groups.

RESULTS

Fifteen men (75%) and five women (25%) entered the protocol. Ages ranged between 45 and 75 years old (av-

Table 1. UPDRS of groups with and without medication.

Group without trazodone (n=12)											
	UPDRS scores						Baseline (t0)				
Descriptive statistics	t0	t1	t2	t3	t4	t5	t1–t0	t2–t0	t3–t0	t4–t0	t5–t0
Average	33.1	32.2	35.0	34.8	36.6	37.1	–0.9	1.9	1.7	3.5	4.0
SD	19.7	21.1	19.7	19.4	18.1	18.0	6.1	7.1	6.3	6.5	6.6
Medium	29.5	25.0	30.5	31.10	33.0	34.5	–12.0	–11.0	–8.0	–6.0	–6.0
p-value Wilcoxon test							0.552	0.390	0.458	0.121	0.071
Group with trazodone (n=8)											
	UPDRS scores						Initial evaluation (t0)				
Descriptive statistics	t0	t1	t2	t3	t4	t5	t1–t0	t2–t0	t3–t0	t4–t0	t5–t0
Average	31.4	29.4	30.6	28.1	27.1	25.9	–2.0	–0.8	–3.3	–4.3	–5.5
SD	11.3	12.0	10.3	11.9	12.8	13.7	3.0	6.3	8.0	5.5	5.3
Medium	33.0	28.0	30.5	27.0	22.5	21.0	–2.0	–3.0	–4.5	–3.5	–5.0
p-value Wilcoxon test							0.158	0.387	0.228	0.092	0.034

UPDRS: Unified Parkinson's Disease Rating Scale Score; SD: standard deviation.

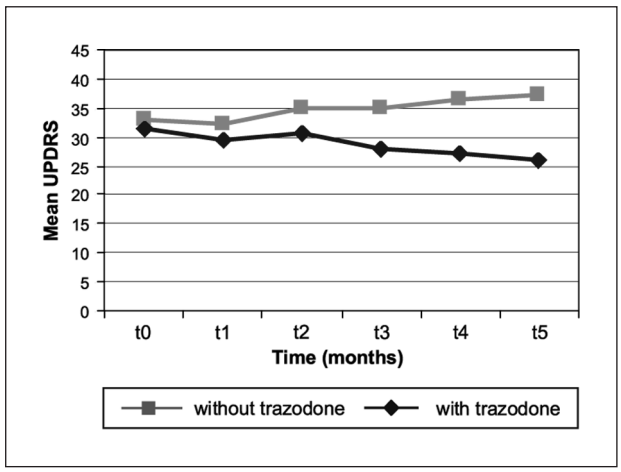

Figure. Mean UPDRS analysis in all patients.

erage 62.3). The length of the illness varied between 1.6 to 16.3 years. Randomization for the use of trazodone selected twelve patients without trazodone (G2) and eight with the drug (G1). The percentage of depressed patients in G1 was 75% (6/8) and 58,3% (7/12) in G2.

The scales of HY and SE provided an average and standard deviation without statistical significance. The illness time span varied from 1.6 to 16.3 years. In the trazodone group three patients left the protocol: Two due to sleepiness and one because of postural vertiginous sensation. These three patients were not included in the analysis performed. All patients took at least one of the following antiparkinsonian drugs: carbidopa + levodopa (250/25 mg), amantadine (100 mg) and/or pramipexole (0.25–1g).

Table 1 shows the UPDRS variation and the corresponding p values for the moment-to-moment comparisons, separating the groups with and without trazodone. To make things clearer the variation was analyzed from an initial time T0 to an ending time T5. The initial average of the group G2 was of 33.1 (SD 19.7) rising to 37.1 (σ=18.0) at the end. The initial average of the group G1 was 31.4 (σ=11.3) ending in 25.9 (σ=13.7). The result was stability in the group G2 and a slight decline in the group G1. The Wilcoxon test of 0.034 only showed results during the last period (T5), even so there was a reduction tendency. Figure shows the average value of the UPDRS by month. The variations in the Mann-Whitney test were 0.734 at the initial moment and 0.208 at the final moment. The variation in the comparison of the initial moment with the final moment was 0.005 providing statistical significance.

A moderate fall in the average of the UPDRS in the group G1was observed, though no variation of this average in the group G2. The variation in the HAM-D from the initial moment until the final moment showed in the group G2 that the average varied from 11.4 (SD=7.2) to 10.2 (SD=7.4). The p-value of the Wilcoxon test was 0.235 in the T5-T0 variation, with statistical significance. In the group G1 the initial average was 12.4 (SD=6.3) and final average 6.0 (SD=4.6). The p-value of the Wilcoxon test was of 0.062 in variation T5-T0. The average of the HAM-D went up by 4 points in the group G2 and went down by 5.5 points in the group G1.

The groups at the initial moment and the final moment were analyzed, showing a fall on average of 12.4 at the initial moment to 6.0 at the final moment in the group G1. The p-value of the Wilcoxon test was 0.115 in the T5-T0 variation, demonstrating a tendency to drop. In the group G2 the patients at the cutting off point of ten points had remained unchanged in the points of the HAM-D until the

Table 2. Statistics of the HAM-D according to time.

Without medication (n=12)											
	HAM–D						Initial evaluation (t0)				
Descriptive statistics	t0	t1	t2	t3	t4	t5	t1–t0	t2–t0	t3–t0	t4–t0	t5–t0
Average	11.4	10.0	11.0	10.8	10.2	10.2	–1.4	–0.4	–0.7	–1.3	–1.3
SD	7.2	7.8	7.7	7.4	6.9	7.4	2.6	2.2	3.0	2.9	3.1
Medium	11.5	7.0	11.0	10.0	10.0	9.5	–0.5	–0.5	–2.0	–2.0	–2.0
P-value Wilcoxon test							0.083	0.486	0.398	0.218	0.235
With medication (n=8)											
	HAM–D						Initial evaluatiom (t0)				
Descriptive statistics	t0	t1	t2	t3	t4	t5	t1–t0	t2–t0	t3–t0	t4–t0	t5–t0
Average	12.4	10.0	8.5	6.6	5.9	6.0	–2.4	–3.9	–5.8	–6.5	–6.4
SD	6.3	6.8	5.7	5.0	4.6	4.6	5.2	6.8	6.7	6.7	6.8
Medium	14.0	8.5	7.5	5.0	4.0	4.0	–1.5	–2.0	–3.5	–6.0	–6.0
p-value Wilcoxon test							0.248	0.104	0.034	0.045	0.062

HAM-D: Hamilton Depression Rating Ssale; SD: standard deviation.

Table 3. Spearman correlation coefficients for UPDRS and HAM-D.

		G2 (n=12)				
		UPDRS			HAM-D	
UPDRS and HAM-D		Initial (t0)	Final (t5)	Variation (Δ)	Initial (t0)	Final (t5)
Final UPDRS	correlation	0.895	1			
	p-value	<0.001				
Δ UPDRS	correlation	–0.140	0.175	1		
	p-value	0.664	0.586			
Initial HAM-D	correlation	0.748	0.695	–0.041	1	
	p-value	0.005	0.012	0.900		
Final HAM-D	correlation	0.867	0.839	0.158	0.881	1
	p-value	<0.001	0.001	0.623	<0.001	
Δ HAM-D	correlation	0.430	0.349	–0.069	–0.016	0.358
	p-value	0.163	0.266	0.831	0.961	0.254
		G1 (n=8)				
		UPDRS			HAM–D	
UPDRS and HAM-D		Initial (t0)	Final (t5)	Variation (Δ)	Initial (t0)	Final (t5)
Final UPDRS	correlation	0.946	1			
	p-value	<0.001				
Δ UPDRS	correlation	0.323	0.530	1		
	p-value	0.435	0.177			
Initial HAM-D	correlation	0.479	0.452	–0.398	1	
	p-value	0.230	0.261	0.329		
Final HAM-D	correlation	0.166	0.238	0.295	0.045	1
	p-value	0.694	0.571	0.477	0.916	
Δ HAM-D	correlation	0.740	0.799	0.744	–0.744	0.423
	p-value	0.036	0.017	0.034	0.034	0.297

UPDRS: Unified Parkinson's Disease Rating Scale Score; HAM-D: Hamilton Depression Rating Scale.

end. In the medicated patients only one, of a total of six, remained unchanged

In Table 2, the group at the initial moment and the final moment is analyzed, showing a fall on average of 12.4 at the initial moment to 6.0 at the final moment in the group G1. The p-value of the Wilcoxon test was 0.115 in the T5–T0 variation, demonstrating a tendency to drop. In the group G2 the patients at the cutting off point of ten points had remained unchanged in the points of the HAM-D until the end. In the medicated patients only one, of a total of six, remained unchanged. Table 3 shows the Spearman correlation coefficients on the variables of the HAM-D and the UPDRS scales. The UPDRS finding of 0,895 is highly correlated and significant as it is so close to 1.

DISCUSSION

From the existing literature, reporting on both in vivo and postmortem data in animal models and in humans, it is apparent that the serotonergic neurotransmitter system is involved in the pathophysiology of PD. The experimental evidence supporting the role of serotonin in motor control was firstly found in 1993[12]. Prospective survey suggested that depression associates psychomotor disturbances to some type of dopaminergic dysfunction[13-15].

A strong correlation between the depression severity and degree of motor dysfunction was demonstrated in PD[16]. The authors speculated that the reduced serotonin levels in PD could be related to the reduced motor activity in depressed patients with PD, which is observed especially when these are compared to the non-depressed patients. They also described an association of depression with the severity of bradykinesia and axial rigidity.

Other studies also associated motor function and depressive symptoms in PD[14,17]. In a revision of these studies Di Giovanni et al.[8] reported that the exposition of striatum and nucleus accumbens to serotonin causes an increase in dopamine release. After checking that drugs acting on the receptors 5-HT2c can diminish the levodopa-induced diskynesias, concluded that these receptors participate in the functions of the basal ganglia and the pathophysiology of parkinsonism.

In animal models of PD serotonergic research has mainly focused on the 5-HT1 and 5-HT2 receptor subtype. According to Scholtissen and cols.[18], the most rele-

vant aspects of the serotonin-dopamine relationship are the following: (A) The 5-HT2a receptor is excitatory for dopamine release, while 5-HT2c is inhibitory; (B) the progressive degeneration of the dopaminergic neurons causes the dopamine synthesis to occur in serotoninergic terminals; (C) Neuroimagings show reduction of serotonin in some cortical and subcortical areas in PD; (D) there is a reduction in 5-HT2a receptors density in the premotorcortex contralaterally to the side of motor symptoms onset in PD. The compensatory reduction of the serotonin secondary to the dopaminergic neuronal loss may contribute to the improvement of the motor function, but this may increase the risk of depression significantly.

Two previous reports[19,20] showed that trazodone may improve tremor in PD. However, these studies were not randomized, not blind, and patients were not submitted to the HAM-D or UPDRS scales. In our study the choice of not doing a double-blind study or not treating the control group with placebo, possibly restricts the significance of the finding. However, studies involving placebo in PD might generate conflicting results. In PD dopaminergic activation of pathways mediating reward may be responsible for a positive placebo response in up to 50% of patients[21]. Same results have been seen in depression, where placebo partially reproduces selective reuptake inhibitor-mediated brain activation.

Trazodone is a serotonin reuptake inhibitor with specific antagonistic action at 5-HT2a/2c receptors. A dopaminergic burst while the system suffers an antagonist action is apparently a paradox. However, Balsara et al.[10] signaled that the antagonistic action of trazodone at receptors 5-HT2c clearly predominates. The trazodone dopaminergic action at 5-HT2c receptors is observed with doses varying from 5 to 20 mg/kg/day. Larger doses determining contrary effects may be related to lower tolerance. This could also occur with antidepressants because of desensitization of serotoninergic autoreceptors at neurons in the raphei nucleus[22].

Di Matteo et al.[23] reported that the disinhibition of the mesocorticolimbic function induced by 5-HT2c receptors antagonism may treat psychotic symptoms in PD, since second generation neuroleptics produce fewer extrapyramidal effects and have an inverse 5-HT2c agonist action. The antidepressive performance of the receptors 5-HT2c could therefore serve as a model for the treatment of depression in PD. Based on the principle that the activation of 5-HT2c receptors increases the activity in the *substantia nigra*, it is possible that the stimulation of these receptors contributes to an increase in basal ganglia output which would favour parkinsonian symptoms. The expression of 5-HT2c receptors in the *substantia nigra pars reticulata* and in the medial pallidal complex supports this hypothesis[24]. Moreover, 5-HT2c receptors binding was increased in a model of parkinsonism developed in rats[25], as well as in parkinsonian patients[26].

In an open study[27], where an average dose of nefazodone for a period of four months on three depressive patients with PD, was used, there were improvements in the motor symptoms submitted previously to fluoxetine. The results showed reduction of tremor in the three patients, and a discrete improvement, at the beginning and in the development of gait in another two.

This comment would be repeated in the following year by Avila et al.[28], who compared motor improvement following nefazodone in nine depressed parkinsonian patients, with a fluoxetine treated control. Motor improvement following nefazodone was reported in parkinsonian patients and not in fluoxetine treated group. According to Avila and colleagues, blocking 5-HT2 receptors promotes dopamine release and a subsequent reduction of D2 receptor blockade, resulting in a reduction of extrapyramidal symptoms.

Experimental studies suggest a primary relationship and the importance of dopaminergic mechanisms in PD and depression. Thus, treatment with dopamine agonists promises to reduce motor complications as well as depressive symptoms, avoiding multiple drug interactions as well as possible antidepressant medication side effects[29]. There are case reports and echocardiographic studies suggesting that the ergot-derived dopamine agonists, pergolide and cabergoline, increase the relative risk of cardiac-valve regurgitation[30]. No cases were attributed to ropinirole or pramipexole, but like antidepressants these non-ergoline substances most commonly causes nausea and sleep disturbances. Also, drug-induced psychosis may complicate the course and management of PD and are associated with dopamine agonists.

Several reports show that non-5-HT2c antagonistic SSRIs may abruptly unleash parkinsonism. However, PD evolves slowly over many years. There is no report on the motor evolution of PD patients under these drugs for a period longer than seven months. The chronic use of SSRIs with this type of action may perhaps lead to a worsening of the motor function in this context.

Based on available data, trazodone significantly improved motor symptoms only in depressed patients. This result also favors the hypothesis that depressed PD patients may gain a benefit in the motor symptoms when treated by antidepressants, and that this effect may be related, at least in part, to the inhibition of the 5-HT2c receptor.

This review demonstrates the overall benefits of continuation- and maintenance-phase treatment of depression in PD with antidepressants and emphasizes the need for additional studies of comparative differences among drugs. Other second-generation antidepressants 5-HT2c antagonists could also have similar effects.

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