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EFFECT OF TIANEPTINE ON COGNITIVE FUNCTIONS IN PATIENTS WITH DEPRESSIVE DISORDERS DURING A 3-MONTH OBSERVATION

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SUMMARY

Objective: *The authors put forward the hypotheses that during a three-month treatment with tianeptine in patients with depressive disorders there is an improvement in the short-term memory, reaction time and attention.*

Subject and methods: *20 patients suffering from depression, were included in the study. During the entire research period all patients were treated with monotherapy with tianeptine. Cognitive function measurements were performed using the Vienna Test System.*

Results: *Our study showed an improvement in the all the assessed functions: patients treated with tianeptine had better performance in tests measuring short term memory and learning processes as well as reaction time and attention.*

Conlusion: *In conclusion, the study shows that tianeptine improves cognitive functions in depressed patients.*

Key words: *affective disorders – antidepressants – cognitive functions - conflict of interest - none declared*

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INTRODUCTION

In patients suffering from depression, neuropsychological deficiencies of attention, memory, psychomotor speed and executive functions are observed. Evidence is found that global neuropsychological deficiencies are present in non-treated patients, and that they partially normalize upon successful treatment (Gualtieri et al. 2006). Cognitive disturbances are often diagnosed in individuals with unipolar affective disorder, mostly regarding elongation of the reaction time (Pardo et al. 2006). They are also found in patients with bipolar disorder. Soon as after the first episode of bipolar disorder patients show distinct deficiencies as compared to healthy people with regard to executive functions, attention span, psychomotor speed and intelligence quotient (IQ) (Nehra et al. 2006).

A relationship between the improvement of cognitive functioning upon treatment and the effect of antidepressant drugs is observed. In one study, attention and memory functions during a major depressive episode and in remission were evaluated in 50 patients treated with fluoxetine and reboxetine. The control group consisted of 15 healthy volunteers. Partial improvement in the studied cognitive functions was achieved, and no differences between patients treated with fluoxetine and reboxetine were found. In the opinion of the authors, the observed cognitive deficiencies are characteristic of both trait and condition (Galassi et al. 2006).

The improvement of cognitive function during antidepressive treatment is probably related to the phenomenon of neuroplasticity. This new approach to the physiopathology of depression might better explain or become a basis for a new hypothesis regarding the mechanism of action of antidepressive drugs, particularly tianeptine. Tianeptine has a specific neurotropic action, and its antidepressive capabilities have been quite well described. Tianeptine results in early subsidence of anxiety symptoms without sedation in depressive patients (Costa e Silva 2004). An important structure involved in neuroplasticity processes is the hippocampus, consequential for certain types of learning and memory. Another important structure, related with anxiety conditioning is the corpus amygdaloideum, which is also stress-sensitive. Long-term tianeptine treatment may prevent adverse changes in the hippocampus and corpus amygdaloideum (McEwen & Chattarji 2004). And treatment with tianeptine may block the adverse effects of stress on cognitive functions of the hippocampus (Campbell et al. 2008).

An improvement in cognitive function was observed in clinical studies with patients treated with tianeptine, comparable in this extent to the effect of paroxetine (Nickel et al. 2003). Beneficial effect of tianeptine on cognitive function was also found in animal studies (Ramanathan et al. 2006). Tianeptine results in an improvement in attention disturbances in cats (Delagrange et al. 1990, Kamoun et al. 1989), and has a beneficial effect on both short- and long-term memory in mice. Literature reports suggest that the neurobiological effect of tianeptine is related to the dynamic cooperation of various neurotransmitter systems, as well as with the structural and functional plasticity of the brain structures responsible for expressing emotions, which is also clinically related to the positive effect of the drug on anxiety and memory processes (McEwen & Olie 2005).

The objective of the present research was to compare the selected cognitive functions (memory, reaction time and attention) in patients with diagnosed depressive disorders treated with tianeptine during a three-month pharmacological treatment.

SUBJECTS AND METHODS

Subjects

20 Patients meeting the ICD 10 criteria of depressive disorders (F32, F33), aged between 18 and 50, were recruited. Patients with mild-to-moderate depression as measured by HDRS score were included in the study. During the entire research period, all patients were treated with tianeptine as monotherapy. The research project was granted approval by the Bioethics Committee of the Medical University of Silesia in Katowice.

In neuropsychological examinations performed with the patients' consent using the Vienna Test System, the following procedure was kept to: the first examination on the day before the first dose of tianeptine, the second examination a month after the first dose of tianeptine, and the third examination three months after the first dose of tianeptine. The authors aimed to maintain monotherapy with tineaptine for the entire treatment period, hence all patients received the tianeptine dose of 37.5 mg/day during the entire three-month pharmacological treatment period.

Methods

Cognitive function measurements were performed using Signal, CORSI and RT tests, being a part of the computer-based Vienna Test System (VTS), developed by Dr Schuhfried Ges.m.b.H. The system was adapted to Polish by Alta s.c. The VTS allows the investigator to standardize the test conditions and the presentation of instructions to patients, rules out computational errors and performs measurements with a 0.1 s precision. Based on the demographic data (age, education, sex) and the tested individual's score, the Vienna Test System generates the crude results and recalculates them to be presented in percentage and T-score scales. The interpretation of the results is based on statistical analysis of the T-score scale scores. The Signal Detection Test is used in applied and clinical psychology to measure the capability of visual discrimination and diagnose the perception lateralization (Brickenkamp 1986). It is based on signal detection theory (Green & Swets 1996).

The Corsi Block-Tapping Test was developed as a diagnostic tool to measure the short-term visual-spatial memory span. The Block-Tapping Test for the immediate block span (UBS) tests the limit capacity of the visual-spatial subsystem of the short-term (recent) memory. On the other hand, the Block-Tapping Test for the supra block span (SBS) reaches beyond the control of the short-term memory (Schufried 1992).

Using individual modules of the Reaction Test (RT) allows the investigator to: measure the reaction time (the reaction time and the motor time are determined independently) to simple and complex light and sound stimuli and measure the attention disturbances (Schufried 1992).

The Hamilton Depression Rating Test (HDRS) was also used to assess the severity of depression.

Significance of the differences between individual tests was evaluated using Friedman's non-parametric test with multiple comparisons. A significance level of 0.05 was assumed. The analysis was performed using the SAS v. 8.2 software (SAS Institute, Cary, NC).

RESULTS

The following indices were measured in the memory function test (CORSI): Immediate Block Span (the variable reflecting the short-term memory capacity) and the Supra Block Span (the variable reflecting the mechanisms of the learning process).

In the first Immediate Block Span test, the patients achieved the average of 5.1, with the standard deviation of 1.1. In the second test, performed a month after the first one, the average was 6.3, with the standard deviation of 0.9. In the third test, which took place 3 months from the first dose of tianeptine, the average was 8.3, with the standard deviation of 0.7 (Table 1). The statistical analysis revealed that the difference of the average values between the first and the second, the second and the third and the first and the third test was statistically significant with the significance level $p=0.05$ ($p<0.001$).

Table 1. Immediate Block Span test results in patients treated with tianeptine during a three-month pharmacological treatment (CORSI)

Test no.	N	Minimum	Maximum	Median	Average	Stand. Dev.	F(p)
1	20	4	7	5	5.1	1.1	
2	20	5	8	6	6.3	0.9	p<0.001
3	20	6	9	8	8.3	0.7	

In addition, an increase in the median value was observed. The median value was 5 in the first test, 6 in the second test, and 8 in the third test. The median value increase is also indicative of the increase in group results.

The other analyzed variable of the CORSI was Supra Block Span – SBS (a variable representing the mechanisms of the learning process). In the first Supra Block Span test, the patients achieved an average of 3.5, with a standard deviation of 1.2. In the second test, the average was 4.3, with a standard deviation of 0.9. In the third test, the average was 5.0, with a standard deviation of 1.3 (Table 2).

Table 2. Supra Block Span test results in patients treated with tianeptine during a three-month pharmacological treatment (CORSI)

Test no.	N	Minimum	Maximum	Median	Average	Stand. Dev.	F(p)
1	20	2	6	3	3.5	1.2	
2	20	2	5	4	4.3	0.9	p<0.004
3	20	2	7	5	5.0	1.3	

The statistical analysis revealed that the difference of the average values between the first and the second and the second and the third test was statistically significant with the significance level p=0.05 (p<0.004).

An increase of the median value was also observed in the Supra Block Span test. The median value was 3 in the first test, 4 in the second test, and 5 in the third test. The median value increase is also indicative of the increase in group results.

The second neuropsychological test used in the study in patients subject to a three-month pharmacological treatment with tianeptine was the Signal Detection Test.

In the first test of selective attention function, measured by the ratio of accurate to delayed responses on the T-score scale, the subjects achieved the average score of 36.4 T, with standard deviation of 10.2. In the second test, performed a month after the first one, the average was 54.3 T, with the standard deviation of 4.1. In the third test, which took place 3 months from the first dose of tianeptine, the average was 65.7 T, with the standard deviation of 3.9 (Table 3).

Table 3. Statistics of the selective attention function test results in patients treated with tianeptine during a three-month pharmacological treatment (Signal Detection)

Test no.	N	Minimum	Maximum	Median	Average	Stand. Dev.	F(p)
1	20	20	50	38	36.4	10.2	
2	20	49	60	55	54.3	4.10	p<0.001
3	20	60	70	64	65.7	3.90	

The statistical analysis revealed that the difference of the average values between the first and the second, the first and the third and the second and the third test was statistically significant with the significance level p=0.05 (p<0.001).

Median values were also determined. In the first test the median was 38, in the second 55, and in the third 64. The median value increase is also indicative of the increase in group results.

In the first test of alertness, measured by signal detection score (on the T-score scale), the subjects achieved the average score of 41.9 T, with standard deviation of 11.0. In the second test, performed a month after the first one, the average was 54.3 T, with the standard deviation of 7.3. In the third test, after 3 months of pharmacological treatment, the average was 68.1 T, with the standard deviation of 7.5 (Table 4).

Table 4. Statistics of the alertness test results in patients treated with tianeptine during a three-month pharmacological treatment (Signal Detection)

Test no.	N	Minimum	Maximum	Median	Average	Stand. Dev.	F(p)
1	20	33	80	39	41.9	11.0	
2	20	41	73	54	54.3	7.3	p<0.001
3	20	61	80	65	68.1	7.5	

The statistical analysis revealed that the difference of the average values between the first and the second, the first and the third and the second and the third test was statistically significant with the significance level p=0.05 (p<0.001).

Taking into account the median values, it was shown to be 39 in the first test, 54 in the second test and 65 in the third test. The median value increase is also indicative of the increase in group results.

The third and last test used in the 20 patients subject to a three-month pharmacological treatment with tianeptine was the Reaction Time (RT) test to measure the time of reaction (the reaction time and the motor time are determined independently) to simple and complex light and sound stimuli.

In the first test of the reaction time, measured by the median reaction time normalized to the T-score scale, the subjects achieved the average score of 24.7 T, with standard deviation of 7.4. In the second test, the average was 46.6 T, with the standard deviation of 5.1. In the third test, the average reached 73,2 T, with the standard deviation of 8.5 (Table 5).

The statistical analysis revealed that the difference of the average values between the first and the second, the first and the third and the second and the third test was statistically significant with the significance level p=0.05 (p<0.001).

Table 5. Reaction time test results in patients treated with tianeptine during a three-month pharmacological treatment (RT)

Test no.	N	Minimum	Maximum	Median	Average	Stand. Dev.	F(p)
1	20	20	39	20	24.7	7.4	
2	20	37	53	47	46.6	5.1	p<0.001
3	20	47	80	76	73.2	8.5	

The assessment of the median values for the three consecutive tests showed that the median was 20 for the first test, 47 for the second test and 76 for the third test. The median value increase is also indicative of the increase in group results.

All patients subject to a three-month pharmacological treatment with tianeptine were assessed three times using the Hamilton Depression Rating Scale (HDRS) to determine the intensity of depression during neuropsychological tests (CORSI, RT and Signal Detection). The HDRS scores of the patients were separately analyzed for correlations with the results of each of the neuropsychological tests (Table 6).

Table 6. Correlation between CORSI, RT and Signal Detection test parameters and Hamilton Depression Rating Scale (HDRS) in patients treated with tianeptine during a three-month pharmacological treatment

	Test number	Spearman Correlation Coefficient	p Value
CORSI - UBS	1	-0.34	0.139
	2	-0.44	0.054
	3	-0.01	0.972
CORSI - SBS	1	-0.13	0.597
	2	-0.38	0.095
	3	0.01	0.965
RT – Reaction Time	1	0.29	0.215
	2	-0.16	0.502
	3	0.39	0.085
Signal detection	1	0.32	0.169
	2	0.05	0.832
	3	-0.05	0.835
Signal detection – Accurate vs delayed	1	0.20	0.408
	2	-0.46	0.044
	3	0.06	0.786

The statistical analysis, performed using the Spearman Correlation Coefficient with the significance level for the differences set to 0.05 showed that the only statistically significant correlation between the intensity of depression and the neuropsychological tests results was between the Signal Detection test variable (ratio of accurate to delayed responses), responsible for selective attention function. The correlation was negative (-0.46), which allows us to conclude that the higher the intensity of depression, the lower the selectivity of attention. The degree of correlation reaches the value characteristic of a significant correlation.

The remaining parameters of individual neuropsychological tests (CORSI, RT and Signal Detection) showed no dependence on the intensity of depression as measured by the HDRS Scale. Hence we may conclude that the intensity of depression is not directly related with the tested cognitive processes.

DISCUSSION

Reports in the literature suggest a beneficial effect of antidepressants on cognitive functions in depressive patients (Galassi et al. 2006). Likewise our study using the neuropsychological test system showed an improvement in the assessed cognitive functions. On the treatment start day, before the first dose of tianeptine, we found deviations from the available published standard values in the tested patients; in the following months, the patients achieved improving results. Our results are in agreement with the literature reports to date, based on the studies of tianeptine conducted using a different methodology (Nickel et al. 2003). They are also in agreement with the findings from animal studies (Delagrange et al. 1990, Kamoun et al. 1989).

Compared to certain studies lasting up to and above 6 months (Galassi et al. 2006), our observation period was relatively short. However, it is worth noticing, that an improvement of cognitive functioning took place as early as after one month. It is interesting that the cognitive processes studied by the authors showed no significant correlation with the depression scores (HDRS). Lack of such correlation may suggest that the cognitive function improvement in patients treated with tianeptine is not effected exclusively by the subsidence of depression symptoms.

The interpretation of the above conclusions should however be very cautious, as accessible empirical data show that there is a direct correlation between the duration of the depressive episode and the intensity of cognitive deficits. One of such example is the research of Gorwood et al. (2008) where this correlation could be

observed. The fact that their research embraced a large population of patients makes their observation very convincing.

Our study plan and methodology had numerous advantages. Thanks to the fact that we were studying patients prescribed with tianeptine for clinical indications, the patients received their optimal treatment, which allowed for an effective improvement in clinical symptoms. Benefits of such approach are also suggested by other authors (Good et al. 2002). The frequency of neuropsychological assessments performed allowed for both the short- and long-term analysis of changes. As shown by the literature data, the choice of an optimal test frequency is a very important factor (Harvey 2001). The test frequency was also optimal with regard to potential problems in motivating the patients to more frequent tests.

Our study, however, has also had certain limitations. The first limitation is the lack of a control group (or a group of patients treated with another antidepressive drug). It cannot be unambiguously ascertained to what extent the results obtained by us are due to a "practice effect". Similar limitations are also pointed out by other authors conducting neuropsychological tests without control groups (Good, 2002, Harvey & Keefe 2001). On the other hand, our results require to be confirmed by studies in larger patient groups.

The obtained results are another important proof of the beneficial effect of tianeptine on the neuroplasticity of the brain, already observed by other authors (Costa e Silva 2004, McEwen & Chattarji 2004).

CONCLUSION

There is an improvement in the short-term memory, in the reaction time and in the attention mechanism in patients with diagnosed depressive disorders during a three-month pharmacological treatment with tianeptine. This suggests that tianeptine not only improves depression but also affects the improvement of cognitive functions.

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