

IMPACT OF OLANZAPINE ON COGNITIVE FUNCTIONS IN PATIENTS WITH SCHIZOPHRENIA DURING AN OBSERVATION PERIOD OF SIX MONTHS

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SUMMARY

Objective: The objective of our study was to evaluate the effect of olanzapine treatment on selected cognitive functions in patients suffering from schizophrenia during an observation period of six-months.

Subjects and methods: Twenty patients with a diagnosis of schizophrenia according to ICD-10 criteria for research were examined. One day before initiation of olanzapine a baseline assessment was performed. The neuropsychological examination was repeated 28 days, 60 days, 3 months, and 6 months after the beginning of treatment. Cognitive function measurements were performed using Signal, COGNITRON and RT tests, being a part of the computer-based Vienna Test System (VTS).

Results: Our study showed an improvement in the assessed cognitive functions. Impairments in cognitive domains were observed at baseline as compared to published normative data, and enhancement in achieved results was observed subsequently in all stages of the treatment until the 6th month.

Conclusion: The above results are consistent with a number of other studies on the impact on cognitive functioning in patients with schizophrenia treated with olanzapine.

Key words: olanzapine - schizophrenia - cognitive processes – attention - reaction time

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INTRODUCTION

Schizophrenia is a devastating and multidimensional disease, affecting 0.3-1% of the general population. Because of the complexity of the clinical picture of schizophrenia it manifests in various symptoms: positive, negative, agitation, depression, anxiety and cognitive impairment (Lindenmayer et al. 1994).

Impairment of attention and the deficit of operational memory are thought to be the most prominent cognitive dysfunctions in schizophrenia (Goldman-Rakic 1999). According to Javitt (Javitt 2010) cognitive impairment in schizophrenia is the key symptom of the disease, usually preceding by a few years the first acute episode. These dysfunctions are present in approximately 70% of persons, and can be maintained at a stable level over the rest of their lifetime (Bilder et al. 2000, Rund et al. 2006).

Cognitive impairment in schizophrenia is of major importance among the theories of pathogenesis of schizophrenia. Most of studies indicate that chronic life disability in schizophrenia relates more to cognitive dysfunctions and negative symptoms than to positive symptoms (Kantrowitz & Javitt 2010a, 2010b).

Contemporarily used classical and atypical neuroleptics have revealed a modest influence on the improvement of cognitive dysfunctions in schizophrenia. The aim of our study was to evaluate the effect of olanzapine treatment on selected cognitive functions and schizophrenia symptoms in patients suffering from schizophrenia over an observation period of six-months.

SUBJECTS AND METHODS

Subjects

Twenty patients with a diagnosis of schizophrenia according to ICD-10 diagnostic criteria for research hospitalized in the Department of Psychiatry and Psychotherapy of the Medical University of Silesia in Katowice, Poland were examined. The patients were excluded if they did not have at least high-school education, if they suffered from medical illnesses that may affect brain function and if they underwent electroconvulsive therapy in a period shorter than 6 months prior to the examination. One day before initiation of olanzapine a baseline assessment was performed. The neuropsychological examination was repeated 28 days, 60 days, 3 months, and 6 months after the beginning of treatment. The use of benzodiazepines was interrupted 48 hours before each assessment, and a continuous co-medication with benzodiazepines never lasted longer than 48 hours. No other additional medication was administered.

The protocol of the study was approved by the Bioethics Committee of the Medical University of Silesia in Katowice and written informed consent was obtained from all participants.

Methods

The Vienna Test System (VTS) is a comprehensive motor test battery covering a range of perception, cognitive and psychomotor control tests. Selected tests

from the computer-aided Vienna Test System, product of Dr. Gernot Schuhfried GmbH were used: Cognitron (COG) assessing attention and concentration through the comparison of figures concerning their congruence measuring, Vienna Reaction Test (RT) recording reaction times and also covering the areas of alertness, the ability to repress an inadequate reaction, vigilance and intermodal comparisons, and Signal-Detection (SIGNAL) assessing long-term selective attention, that is the visual differentiation of a relevant signal within irrelevant signals (Schuhfried 1992).

The Positive and Negative Symptom Scale (PANSS) was also used to evaluate general nonpsychotic psychiatric symptoms, positive psychotic symptoms, and negative symptoms. An assessment using PANSS took place on the same days as the neuropsychological examination.

Data analysis and statistics

In order to compare the results of subsequent stages of the examination a one-way ANOVA analysis of variance with repeated measures was conducted.

RESULTS

COG - correct responses results

The analysis of variance was statistically significant $F(4, 76) = 183.42, p < 0.001; \eta^2 = 0.91$. In each stage of the examinations the number of correct responses increased - an average of 23%. The increase in the level of correct responses between the first and last examination reaches 126%. Tukey post-hoc test showed statistically significant differences between all the stages of the examinations ($p < 0.05$). The results obtained are presented in Figure 1.

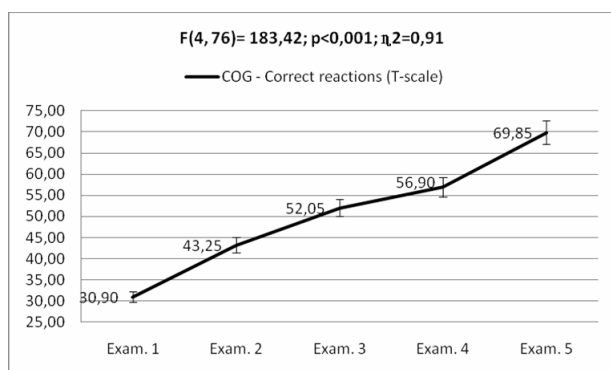


Figure 1. Results of the Cognitron Test. COG – correct reactions (T-score)

COG - incorrect responses

The analysis of variance was statistically significant $F(4, 76) = 12.2, P < 0.001; \eta^2 = 0.39$. The lowest number of incorrect responses occurred in examination 4 and the highest in examination 5 (an increase of 33.5%). Tukey post-hoc test showed a statically significant difference

only between the results obtained in examination 1 and the results of examination 2 ($M1=M2=67.35$ vs. $57.95, P < 0.05$), the results of examination 3 ($M1=67.35$ vs $M3=58.5, P < 0.05$) and the results of examination 4 ($M1=M4=67.35$ vs. $52.9, P < 0.001$). Significant differences also exist between the results obtained in examination 5 and the results of examination 2 ($M5=M2=70.65$ vs. $57.95, P < 0.001$), the results of examination 3 ($M5=M3=70.65$ vs. $58.5, P < 0.01$) and the results of examination 4 ($M5=M4=70.65$ vs. $52.9, P < 0.001$). The results obtained are presented in Figure 2.

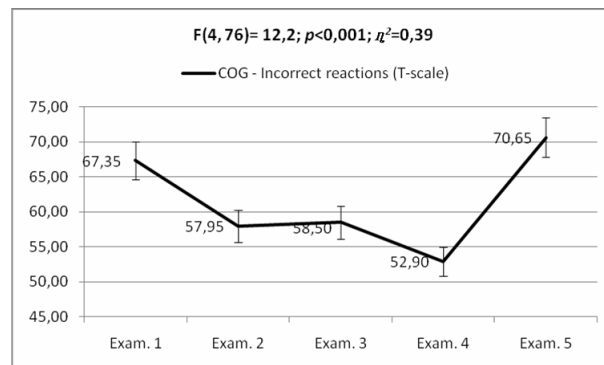


Figure 2. Results of the Cognitron Test. COG – incorrect reactions (T-score)

RT - median reaction time

The analysis of variance was statistically significant $F(4, 76) = 169.48, p < 0.001; \eta^2 = 0.9$. The median value of reaction time increases linearly in each successive trial (on average 24%). The increase in median value of reaction time between the first and last examination reaches 134.9%. Tukey post-hoc test showed statistically significant differences between all the stages of the examinations ($p < 0.01$). The results obtained are presented in Figure 3.

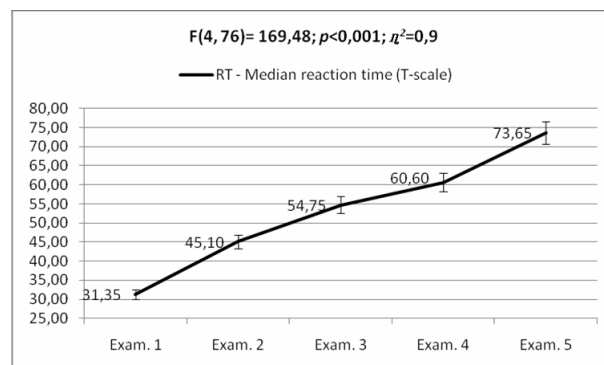


Figure 3. Results of the Reaction Test. Median reaction time (T-score)

SIGNAL – the number of correct and delayed responses

The analysis of variance was statistically significant $F(4, 76) = 95.95, p < 0.001; \eta^2 = 0.83$. The proportion of correct to delayed responses increases linearly in each

successive examination (average of 17.8%). The largest increase of this proportion occurred between examination 1 and the other examinations (on average 60%). The increase in the proportion of correct and delayed reactions between examination 1 and examination 5 reaches 86.3%. Tukey post-hoc test showed no statistically significant differences only between examinations 2 and 3, and between examinations 3 and 4. The results of the other examinations differ significantly at $p < 0.001$. The results obtained are presented in Figure 4.

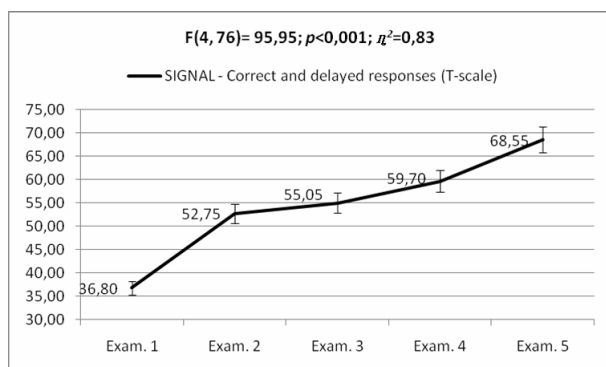


Figure 4. Results of the SIGNAL Test. Correct and delayed responses (T-score)

PANSS - total score

The analysis of variance was statistically significant ($F(4, 76) = 155.32$, $p < 0.001$; $\chi^2 = 0.89$). The number of symptoms decreases linearly in each examination (average of 7.5%). The decrease of symptoms between the results in examination 1 and examination 5 reaches 33.6%. Tukey post-hoc Tukey showed statistically significant differences between the results obtained in all stages of the examinations ($p < 0.01$). The results obtained are presented in Figure 5.

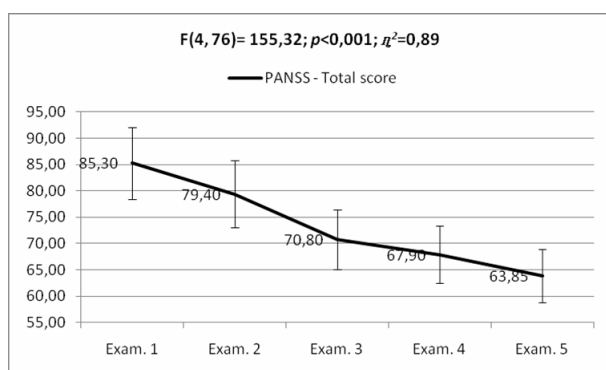


Figure 5. Results of the PANSS Scale. Total score

DISCUSSION

According to the studies conducted on the impact of antipsychotic treatment on cognitive functioning in schizophrenia before 1999, clozapine improved attention and verbal fluency, risperidone improved working memory, executive functioning, and attention, and olanzapine had a positive effect on verbal learning

and memory, verbal fluency, and executive function (Meltzer & McGurk 1999). The advantage of olanzapine in the treatment of cognitive deficits was also confirmed in further studies. In one of them the results of olanzapine versus fluphenazine treatment were evaluated. The patients meeting DSM-IV diagnostic criteria for schizophrenia, were included in the study and assessed with subscales of the Wechsler Adult Intelligence Scale, the Stroop Neuropsychological Screening Test and the Wisconsin Card Sorting Test. Olanzapine, unlike fluphenazine, had a beneficial effect on digit-symbol performance and some aspects of executive function (Ljubin et al. 2000). In another study the efficacy of olanzapine, haloperidol, and risperidone in the treatment of cognitive impairment in the early phase schizophrenia was analysed. According to the results olanzapine had some superior cognitive benefits relative to haloperidol and risperidone (Purdon et al. 2000). Evidence was found of the efficacy of olanzapine on neurocognitive functioning not only in schizophrenia, but also in schizophreniform and schizoaffective disorders (Stip et al. 2003). In a study done by Sharma et al. (2003) similar beneficial effects of olanzapine and clozapine on verbal learning and memory measures in schizophrenic patients were proven.

However a few years later some more critical opinions concerning the impact of olanzapine on cognitive functions appeared. For example a large randomized, double-blind trial on 377 patients assessing effects of olanzapine and risperidone on cognitive functioning in patients with schizophrenia was done by Harvey et al. (Harvey 2003). In this study no previously reported greater benefits of olanzapine over risperidone were confirmed.

Some interesting observations were provided by the studies being the part of the CATIE research project. Perphenazine turned out to be significantly superior to olanzapine and risperidone after 18 months of treatment. In this study it was also found that early cognitive improvement predicted remaining on the initial medication for the whole 18-month period for patients, who were treated with ziprasidone and quetiapine (Harvey 2007). In one of the recent studies it was found that switching between olanzapine and ziprasidone does not improve cognitive outcomes in patients with recent-onset schizophrenia supporting the literature reports that the different antipsychotics have similar impact on cognitive symptoms in schizophrenia (Grootens et al. 2010).

Results obtained in our study confirm the positive impact of olanzapine on attention. McGurk et al. (2004) showed that olanzapine improves the selectivity of attention. In the conclusion the authors conclude that olanzapine selectively improves different cognitive dysfunctions in schizophrenia. Also Keefe et al. (2004) described the positive impact of olanzapine on selectivity of attention in schizophrenia patients treated for 3 months. Harvey et al. (2006) found that olanzapine improves attention together with operational memory

and motor response time. Better reaction time was also present in our study group. In another study by Forbes et al. (Forbes 2009) after 6 weeks of treatment olanzapine improves the reaction time to the stimuli.

CONCLUSION

Altogether, olanzapine reveals its effectiveness both in the improvement of attention and reaction time and other schizophrenia symptoms in long term treatment.

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