The influence of antipsychotic therapy on the cognitive functions of schizophrenic patients

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Summary

Aim: The aim of the present study was twofold: 1. to compare the efficacy of three antipsychotics (ziprasidone, olanzapine and perazine) in schizophrenia 2. to compare the improvement in cognitive functioning between groups treated with the three different neuroleptics.

Method: A total of 58 Caucasian patients diagnosed with paranoid schizophrenia were recruited into the study group. We used the Polish version of the CIDI (Composite International Diagnostic Interview) to obtain ICD-10 diagnoses. The intensity of psychopathological symptoms was examined using the PANSS. The patients were randomly assigned to treatment with perazine, olanzapine or ziprasidone administered as monotherapy for 3 months. The treatment efficacy was measured as a change in the PANSS (Positive and Negative Syndrome Scale) total score from baseline (T0) to 3 months (T1). The WCST (The Wisconsin Card Sorting Test) was used to measure working memory and executive functions in the evaluated patients. Wilcoxon's and Kruskal-Wallis tests were applied to compare changes in the PANSS scores between the treatment groups. To analyze the cognitive functions, Kruskal-Wallis test for the WCST parameters was used.

Results: The three antipsychotics similarly reduced the total PANSS score. The WCST parameters in the 3 groups of examined patients using the Kruskal-Wallis test revealed some differences between the three administered antipsychotics.

Conclusions: Results suggest that the short-term efficacy of the atypical (olanzapine, ziprasidone) and typical (perazine) antipsychotic drugs did not differ. Based on the analysis, a conclusion can be drawn that the three neuroleptics provided similar improvements in cognitive functioning.

Key words: cognitive functions, schiyophrenia, neuroleptics

Introduction

Currently, numerous studies subcategorize the symptoms of schizophrenia into dimensions (positive, negative but also cognitive symptoms, aggressive symptoms

and affective symptoms). The cognitive dimension is not recognized as a part of the diagnostic criteria for schizophrenia in the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders) or the ICD-10 (International Statistical Classification of Diseases and Related Health Problems), and it is not included by expert groups in the proposed criteria for the ICD-11. However, the cognitive dimension is being considered for inclusion in the DSM-V as a part of the diagnostic system [1-4].

According to scientific studies, schizophrenic patients examined neuropsychologically exhibit cognitive dysfunctions. Deficits may influence several domains including attention, working memory and executive functions. Impairments are primarily due to dysfunction of the frontal cortex, temporal cortex, and hippocampus. Working memory is also connected with neurotransmission in the brain, especially with dopamine activity [5-10]. This indicates that neurostructural changes underlie schizophrenia, and these can be treated in the same way as neurodegenerative and neurodevelopmental diseases [11]. Cognitive dysfunctions are currently regarded to be endophenotypical markers indicative of a predisposition to schizophrenia. These deficits may precede the onset of psychosis and can be stable throughout the course of the illness in some patients. Recent pharmacological and behavioral studies suggest the malleability of cognitive deficits [12]. Many studies suggest that atypical neuroleptics can improve cognitive function in schizophrenic patients. This improvement is a consequence of the association between the dopaminergic, serotonergic and noradrenergic systems [13]. As the awareness of the functional importance of neurocognitive impairments in schizophrenia has increased, interest in treatments to improve cognition has also been growing.

In spite of the fact, that neuroleptic drugs have been applied for many years, no algorithm of procedure has been created which would guarantee therapeutic success. In this study the whole attention is focused on the therapeutic aspect. However, the authors are aware of the value of that subject and signalizes the necessity of further investigations in that direction.

Perazine is a typical neuroleptic, phenothiazine derivative that is widely used in some European countries, including Germany and Poland, and it is thought to provide potent antipsychotic and sedative effects with a relatively low risk of extrapyramidal side effects [14]. At the time of the study design, perazine and olanzapine were the two most-widely used antipsychotic drugs in the recruiting center, and ziprasidone had been introduced to the Polish market. Interestingly, recent naturalistic studies have shown that the effectiveness of some typical and atypical antipsychotics did not differ in real-life clinical settings [15-18].

The purpose of the present study was to examine the effect of treatment with olanzapine, ziprasidone and perazine on cognitive functions in schizophrenic patients in two contexts: improvement of psychotic symptoms and improvement of cognitive functions. To realize this aims patients were assessed with the Positive and Negative Syndrome Scale (the most popular scale to examine patient with schizophrenia symptoms) and with The Wisconsin Card Sorting Test (method measured a few dimensions of cognitive functions). We expected that atypical neuroleptics would provide better results than typical neuroleptics, especially for cognitive function improvement.

Materials and methods

Patients

Our study was a naturalistic, unblended, conducted at the Pomeranian Medical University between June 2006 and May 2010. A total of 58 Caucasian patients of Polish descent (28 men and 30 women; mean age: 36.2±12.0 years) with paranoid schizophrenia were recruited in a daily department, ambulatory care clinics and also when patients were hospitalized. The mean age at the time of the first psychotic episode was 26.9±6.9 years. The Polish version of the CIDI (Composite International Diagnostic Interview) and the ICD-10 criteria were used to confirm the diagnosis of paranoid schizophrenia [19].

The exclusion criteria included serious neurological and/or somatic disorders (e.g., stroke, hepatic insufficiency, diabetes). Informed consent was obtained from each participant after providing the patients with both written material and a verbal description. The study was performed in accordance with the Declaration of Helsinki, and its protocol was approved by the Ethics Committee of the Pomeranian Medical University.

Patients were assigned to the treatment groups (olanzapine, n=19; ziprasidone, n=20; perazine, n=19) according to the simple randomization method [20]. The range of doses of ziprasidone (120-160 mg), olanzapine (10-20 mg), and perazine (300-600 mg) used in the present study were in accordance with the Polish standards of schizophrenia treatment and followed the manufacturer's recommendations [21]. All patients were previously medicated with antipsychotic drugs, but none of the patients was treated with olanzapine, perazine or ziprasidone before inclusion in the present study. Before the start of the study, the patients remained free of antipsychotic medications for 3-7 days. The intensity of psychopathological symptoms was assessed with the aid of the PANSS (Positive and Negative Syndrome Scale) at the time of admission (T0) and after 3 month (T1) of monotherapy with olanzapine, perazine or ziprasidone [22].

The Wisconsin Card Sorting Test (WCST) used in present study was developed in 1948 by Berg and Grant. This test assesses abstract thinking and the ability to shift cognitive strategies in response to environmental changes. Currently, the WCST is used to measure working memory and executive functions. Many parameters in the WCST can be measured and analyzed: the total number of used cards, the number of errors and right answers, perseverative responses and errors connected with working memory and plasticity of thinking disturbances, nonperseverative errors connected with attention disturbances, the number of completed categories, the conceptual level of the responses, failure to maintain set and learning to learn [23]. In the present study, a computer version of the WCST was used to measure cognitive functions [24]. This part of study was conducted by a neuropsychologist after a special preparation course.

Statistical analysis

Data analysis was performed using Wilcoxon's test and the Kruskal-Wallis test. The level of statistical relevance (p) was set at 0.05 or less. Wilcoxon's and Kruskal-

Wallis tests were used to identify differences between the treatment groups in baseline PANSS scores and age and to compare changes in the total PANSS scores between the treatment groups. The Kruskal-Wallis test of the WCST parameters were used to analyze cognitive function.

Results

At the time of admission, the total PANSS score did not differ between the patients assigned to the olanzapine (102.0±17.1), perazine (102.2±16.4) and ziprasidone (100.6±13.9) treatment groups (p=0.94) (Table 1). The mean age (ziprasidone: 37.1±10.9 years, olanzapine: 35.5±13.5 years, perazine: 35.9±12.1 years; p=0.91) and the percentage of patients treated with the investigated drugs (olanzapine: 32.8%, ziprasidone: 34.5%, perazine: 32.8%; p values > 0.050) did not differ between the treatment groups.

At the beginning of the study, the total PANSS score did not differ between the patients treated with the different drugs (Kruskal-Wallis test; Table 2). A significant reduction in the PANSS score was observed over time in the entire study group. However, the PANSS score reduction did not differ between the three antipsychotic treatment groups (PANSS after 3 months: olanzapine - 64.8±18.9, ziprasidone - 75.2±27.1, perazine - 68.0±28.3) (Tables 1 and 2). Similarly, analysis of three psychophatological dimensions of PANSS (positive, negative and general) not revealed differences between therapeutic groups.

Table 1. **PANSS score reduction from baseline (T0) to 3 months (T1)
in patients treated with the three different neuroleptics (Wilcoxon's test)**

| | PANSS | | | | | | | | | |
| | N | Baseline (T0) | | | | After 3 months (T1) | | | | |
			Aver.	SD	Min.	Max.	Aver.	SD	Min.	Max.	p
Olanzapine	19	102.00	17.11	63.00	136.00	64.79	18.90	39.00	111.00	0.00065
Ziprasidone	20	100.60	13.86	72.00	132.00	75.25	27.15	41.00	132.00	0.00222
Perazine	19	102.22	16.41	72.00	143.00	68.47	28.26	42.00	143.00	0.00098

SD – standard deviation N – number of patients Aver. – average PANSS score
Min. – minimal PANSS score Max. – maximal PANSS score

Table 2. **Kruskal–Wallis test for the total PANSS score – at the time of admission
and at the end of the study**

| | | Kruskal-Wallis test | | | | | |
| | N | Baseline (T0) | | | After 3 months (T1) | | |
		Rank sum	H	p	Rank sum	H	p
Olanzapine	19	582.00			559.00		
Ziprasidone	20	574.00	0.1359	0.9343	645.50	1.0817	0.5823
Perazine	19	555.00			506.50		

N – number of patients, H – variance of the ranks among groups

Cognitive functions were evaluated with the WCST, both at the beginning of the experiment and again after sixty days. The Wisconsin Card Sorting Test parameters in the three antipsychotic treatment groups were analyzed with the Kruskal-Wallis test, and two statistically significant differences were identified between the groups: the "trials in first category" and "conceptual responses" parameters. However, a post-hoc analysis did not confirm such a dependence. Based on the statistical analysis, we can conclude that there were no differences in cognitive function improvement between the groups of patients treated with olanzapine, ziprasidone and perazine (Table 3 – *on next page)*.

Discussion

Our main hypothesis was that atypical neuroleptics would improve significantly the cognitive functions in compare to perazine - the typical neuroleptic but our study results did not confirm the advantage of atypical neuroleptics when compared with typical neuroleptics such as perazine in the 3 months period. Previous studies have shown that results of similar investigation often are controversial. For example Woodward et al. present that although haloperidol may cause deleterious effects at very high doses, or in specific cognitive domains, these effects are not likely to explain the broader range of cognitive improvements observed with atypical drugs and when used a low dose of haloperidol (<10 mg) [25]. In newer study provided by McGurk et al. not any cognitive test was worsened by olanzapine treatment. Improvements in the BPRS Total and Positive Symptom Subscale scores were noted. Improvements in verbal learning and memory, sustained attention, and psychomotor tracking were independent of improvement in psychopathology [26]. Harvey et al. showed significant improvement in verbal skills and global score following the switch from conventional antipsychotics, olanzapine, or risperidone to ziprasidone what mean that patient requiring a change in antipsychotic therapy may exhibit cognitive improvement following a switch to ziprasidone [27].

It is possible to find more similar studies - that is search for clinical proofs of improvement and benefits for patient chosen therapy is valuable in our opinion.

In the present naturalistic, unblinded study, patients with an exacerbation of paranoid schizophrenia were randomly assigned to olanzapine, perazine or ziprasidone monotherapy, i.e., to antipsychotic drugs with different binding profiles and clinical characteristics [1]. The total PANSS score was obtained at the time of admission (T0) and at the end of a 3-month follow-up period. No difference in the reduction of the total PANSS score was found between the three studied groups. The results of our study are in agreement with the recent naturalistic studies, which also identified no major difference between the typical (perazine) and atypical (olanzapine, ziprasidone) antipsychotic medications [28-35]. To the best of our knowledge, this is the first study to compare olanzapine and ziprasidone to perazine, the old phenothiazine derivative with potent antipsychotic effects and a relatively low risk of extrapyramidal symptoms [14, 31].

Table 3. **The Kruskal-Wallis test scores for the Wisconsin Card Sorting Test by pharmacological treatment (olanzapine, ziprasidone, perazine) described by mean values and standard deviations**

| Treatment | Ziprasidone | | | | Olanzapine | | | | Perazine | | | | | |
| | Baseline | | 3 months | | Baseline | | 3 months | | Baseline | | 3 months | | | |
WCST parameters	Mean value	SD	Mean value	SD	Mean value	SD	Mean value	SD	Mean value	SD	Mean value	SD	H (2. N=50)	p
Total cards	107.8	24.05	102.8	23.22	106.7	20.11	96.50	22.02	117.3	20.01	106.5	22.73	1.61	0.4470
Total correct	66.32	12.79	72.74	14.01	69.50	16.82	66.65	9.85	72.55	18.34	62.18	16.09	1.90	0.3872
Total correct	41.47	27.86	30.05	24.67	34.95	27.99	29.85	26.16	44.73	24.84	44.36	32.60	2.0	0.3586
Total errors	41.47	27.86	30.05	24.67	29.85	27.99	27.25	26.16	44.36	24.84	38.27	32.60	2.44	0.2951
perseverative responses	29.00	28.24	15.63	13.27	30.35	30.36	17.20	15.49	33.09	34.46	26.55	20.98	2.08	0.3529
perseverative errors	24.05	22.21	14.26	11.04	25.00	25.82	15.70	13.69	26.91	22.30	22.64	17.39	1.44	0.4864
nonperseverative errors	17.42	15.35	15.79	18.20	12.20	11.91	14.15	13.26	17.45	11.86	21.73	22.47	5.67	**0.0588**
conceptual responses	53.89	18.52	66.95	18.11	59.65	24.11	58.30	17.75	58.73	26.92	52.73	24.03	1.84	0.3982
categories completed	4.32	1.92	4.95	1.84	4.30	2.41	4.90	1.97	3.55	2.38	3.82	2.64	5.99	**0.0501**
trials in first category	15.79	8.45	24.68	27.75	20.95	26.50	13.35	4.96	32.55	47.70	36.73	40.52	0.70	0.7043
failure to maintain set	1.21	2.55	1.05	1.75	1.45	2.01	0.55	0.76	2.09	2.59	0.82	1.54	1.11	0.5736
learning to learn	-6.61	11.40	-5.87	7.93	-3.53	9.94	-5.87	12.68	-7.20	4.89	-4.08	12.34		

SD – standard deviation, N – number of patients, H – variance of
the ranks among groups

In the present study, there was no difference in the short-term treatment response to ziprasidone, olanzapine, and perazine in patients with an acute exacerbation of schizophrenia.

The Wisconsin Card Sorting Test is a very popular tool for assessing cognitive functions such as attention and working memory. Treatment with first-generation antipsychotics influences cognitive functions in patients with schizophrenia, but the data are controversial [31, 35-36]. First-generation drugs can be associated with worse results in working memory, speed processing and motor skills. Additionally, the anticholinergic effect of these drugs is associated with decreases in simple attention, complex attention, short-term memory, delayed recall, semantic memory, working memory and executive functions [37].

Cognitive functioning is perhaps associated with the dose of antipsychotics administered. Low doses of the classical neuroleptics have been observed to increase the cognitive dimension, while higher doses decrease the same function [38].

Many studies suggest that atypical neuroleptics can improve cognitive functions in schizophrenia [27, 39-41]. This improvement is a consequence of the associations between the dopaminergic, serotonergic and noradrenergic systems. Such a mechanism of action is shared by atypical neuroleptics such as olanzapine and ziprasidone. Our study results did not confirm the advantage of atypical neuroleptics when compared with typical neuroleptics such as perazine. Multiple studies have shown the other results (but none have evaluated perazine) [42-46].

Our study has some limitations, including the short observation time, especially in the context of cognitive functions, we analyzing only part of schizophrenia dimensions with only two but common tests . The study group was relatively small, but the statistical power was sufficient to exclude false-negative results and positive error. Hence, our results may require further replication in large multicenter studies and administered other antipsychotic medications. Although our study did not indicate significant difference, it included small number of patients, we can still proof hints of further changes in cognitive functions. There is more published studies from this area but very often small number of investigated subject, short time of observation, different methodology not allow us to establish final conclusions but as we mentioned this is the way to elaborate clinical consensus [47-55].

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