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Original Study

The Influence of Typical and Atypical Antipsychotics on Neurocognitive Functions in Patients with Psychotic Disorders

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SUMMARY

Introduction: Although before, the prioritization of positive and negative symptoms of schizophrenia over neurocognitive impairment was of the highest importance, recent scientific achievements suggest that the disrupted neurocognitive functions are the core clinical feature of schizophrenia. Both general and specific cognitive functions are impaired. Earlier studies promoted atypical antipsychotics as the ones with the pro-cognitive effect, but an increasing number of recent studies do not demonstrate their superiority on neurocognitive improvement over typical antipsychotics.
Aim: The aim of this study was to compare the effects of atypical antipsychotics and a combination of typical and atypical antipsychotics on cognitive functions in patients with psychotic disorders. Furthermore, the effects on gender and duration of disorder on the cognitive functioning of patients on different types of antipsychotic therapy were evaluated, as well as the effect of anticholinergic biperiden in patients receiving combined antipsychotic therapy.
Subjects and Methods: This academic IV phase quasi-experimental clinical study included 50 hospitalized patients at the Clinic for Psychiatry at the Clinical Center of Vojvodina, who were divided into two groups of 25 subjects-one consisted of patients who had been on treatment with atypical antipsychotics for six weeks at least, while the second group included patients who had been on combined therapy with typical and atypical antipsychotics for minimum of six weeks. Within the second group, two subgroups could have been recognized; one with 12 patients who were co-medicated with anticholinergic biperidine, whilst the rest of 13 patients were using only combined antipsychotic therapy. All patients' cognitive functions were tested using the *Mini-Mental State Examination* (MMSE) and the results have been analyzed and compared using t-test.

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Results: There were no statistically significant difference in cognitive functioning between patients using atypical or combined antipsychotic therapy ($p>0.05$). There is no statistically significant effect on gender or duration of disorder on cognitive functioning in the two compared groups ($p>0.05$). There is a statistically significant negative effect on cognition due to the co-medication with biperiden during combined antipsychotic therapy ($p<0.05$).
Conclusions: Atypical antipsychotics did not show superiority in the improvement of neurocognitive functions over combined therapy with atypical and typical antipsychotics. Further investigations should be carried out in order to determine the exact effect of antipsychotics on cognitive functions.

Keywords: atypical antipsychotics, typical antipsychotics, Mini-Mental State Examination, schizophrenia, psychosis, cognition

INTRODUCTION

Up to several decades ago, the impairment of neurocognitive functions in psychotic disorders was of a secondary significance, in contrast to the positive and negative symptoms, which were the most important in both diagnostics and therapy of disorders. Throughout numerous and comprehensive research, it was established that not only have these disorders been accompanied by cognitive impairment, but that impaired neurocognitive functions are the core feature of psychotic disorders [1,2], mainly due to their central role in affecting an individual's functional status across different outcome domains, such as self-care, independent living, social and interpersonal functioning, and vocational functioning [3].

In patients with psychotic disorders, the generalized cognitive deficit is dominant, with the possibility of differentiating certain specific cognitive functions (attention, working memory, short-term and long-term memory, information processing speed, execute functions) that are more dominantly damaged than other cognitive functions (language, non-expressive memory) which have been preserved, but still remain deficient in comparison to the healthy population [4,5].

In the pharmacotherapy of psychotic disorders, both typical and atypical antipsychotics are used. The first generation of antipsychotics (typical, classical) was introduced into therapy in the middle of the last century when the main attention was not focused on cognitive impairment; the purpose of their use was primarily for the mitigation of positive symptoms of schizophrenia, such as agitation, hallucinations, and mania. These drugs are associated with the development of extrapyramidal motor symptoms. The above mentioned side effects can be treated with anticholinergics, which can further aggravate cognitive functioning. Additionally, some studies, using rat models, as well as healthy human volunteers, indicate that typical antipsychotics can have a negative effect on cognitive functioning on their own [6].

Replacement of typical antipsychotics in therapy with atypical was initially motivated by less extrapyramidal adverse effects, lower risk for tardive dyskinesia, a greater effect on the negative and positive symptoms, and also due to the possible pro-cognitive effects of atypical antipsychotics [7]. Numerous studies from the end of the previous and beginning of this century have indicated that atypical antipsychotics have a more emphasized positive effect on cognitive functioning than treatment with typical antipsychotics [8-10]. However, many of these studies have had significant limitations, such as: a small test sample, a short duration of therapy; the statistical analyses that were performed were not always preplanned; a lack of a comparative group, not taking in account some important clinical factors, such as the correlation between cognitive improvement with the change in symptoms that patients experienced; anticholinergic co-medication and changes in extrapyramidal symptoms [11]. Additionally, in many of these trials as the comparator was used a relatively high dose of the first-generation antipsychotic drug, which led to impairment of motor performance and required anticholinergic drugs, which in turn may have impaired cognitive performance [12]. Finally, many of these studies were funded by companies that manufactured those medications, a fact cited by some investigators as a possible source of bias [13].

Two large, prominent studies (CATIE and EUFEST), evaluating the effect of typical and atypical antipsychotics on cognitive functioning in patients with schizophrenia, suggested that, although there was slight to modest improvement in cognitive function for all treatments, there were no differences among medications, regardless of the generation of the antipsychotics [14]. Findings like this have been confirmed in some recent studies, thus, there is an ever-growing opinion that any differences in cognitive improvement between atypical antipsychotics and their older predecessors are actually negligible [6,15], but this statement needs to be proven in the future investigations.

AIM

The aim of this study was to compare the therapeutic effect of atypical antipsychotics on cognitive functions in patients with psychotic disorders with the effect achieved by applying a combination of typical and atypical antipsychotics. The additional objectives were to compare the effects of the two previously mentioned pharmacotherapeutic approaches in terms of patient's gender and duration of the disease, as well as to examine cognitive performance in patients on combined antipsychotic therapy who used anticholinergic biperiden due to extrapyramidal adverse effects of typical antipsychotics.

SUBJECTS AND METHODS

The academic IV phase study was conducted at the Clinic for Psychiatry at the Clinical Center of Vojvodina during the first three months of 2018, with the Permission of the Ethics Committee of the Clinical Center of Vojvodina (№00-20/153). All patients signed the Informed consent. The examined sample consisted of 50 hospitalized patients under the diagnosis of some of the psychotic disorders (F20-F29), of which 20 were hospitalized at the Department for Schizophrenic and Schizotypal Disorders, and 30 patients from the Department for Delusional and Undifferentiated Psychotic Disorders, who had the need for oral antipsychotic therapy. The study was conducted as a quasi-experimental clinical study, in which patients participants in study were deployed in two investigated groups. The first study group consisted of 25 patients who had been continuously hospitalized at the Psychiatric Clinic for at least 6 weeks and who were on oral therapy with atypical antipsychotics, whether monotherapy or a combination of several atypical antipsychotics. A six-week period was selected according to the findings from the previous studies, where the period of 2 months of therapy was sufficient to observe changes in cognitive functioning. The second study group consisted of 25 patients who had been hospitalized at the Psychiatric Clinic for at least 6 weeks, and who were on combined oral therapy with typical and atypical antipsychotics. Within the second study group, two subgroups could have been recognized; one subgroup with 12 patients who were co-medicated with anticholinergic biperidine, which was introduced into therapy with the goal of reducing extrapyramidal adverse effects of typical antipsychotics, while the rest of 13 patients were using only combined antipsychotic therapy.

All patients' generalized cognitive functioning was evaluated using the Mini-Mental State Examination (MMSE). In clinical psychiatric conditions, Mini-mental testing can be used to evaluate cognitive functions in a number of psychiatric disorders, including mental retardation, delirium, manic-depressive disorder, schizophrenia and other psychotic disorders [16]. It assesses the orientation in time and space, attention, working and delayed memory, speech and ability to perform simple spoken and written commands. Each task carries the appropriate number of points and the maximum score is 30. Considering that there were no patients with a completed higher (faculty) education, on the basis of the accomplished score, the patients were classified into one of three possible categories of global cognitive functioning:

- from 24 to 30 – there is no cognitive deficit;
- from 18 to 23 – there is a moderate cognitive deficit;
- less than 18 – severe cognitive deficit is present.

Methods of descriptive and analytical statistics were used to analyze the obtained data. The data are represented by arithmetic means, standard deviations, absolute and relative frequencies. Student's t-test was used for the analytical statistics method. Statistical significance was determined at a level of $p<0.05$. The results are shown in tables, using the Microsoft Office 2013 package.

RESULTS

Of the 50 tested examinees, 19 were females (38%) and 31 males (62%). The age range was from 20 to 68, with an average age of 42.96 years. 12 of these patients (24%) were hospitalized due to the first episode of a psychotic disorder, while 38 (76%) had a chronic disease and multiple previous hospitalizations. Within the group treated with atypical antipsychotic, there were 10 females (40%) and 15 male patients (60%). The age range was from 21 to 68 years of age, the average age of 46.28 years. 8 patients (32%) have been hospitalized due to a first psychotic episode, while the remaining 17 (68%) had previously been hospitalized due to psychotic symptoms. In a group of patients treated with a combination of atypical and typical antipsychotics, there were 9 females (36%) and 16 males (64%). The average age of patients was 39.64 years, ranging from 20 to 65 years. Of the total number of patients in this group, 3 (12%) had the first and 22 (88%) repeated psychotic episode. Within this group, there were also 12 patients (48%) who, in addition to combining antipsychotics, also used anticholinergic therapy with biperiden to mitigate extrapyramidal symptoms.

The results of the study showed that patients treated with atypical antipsychotic achieved on Mini-mental testing an average overall score 25.1 out 30, which ranked them among the group of patients with preserved cognitive functions. Patients treated with combined therapy with atypical and typical antipsychotics achieved an average score of 24.8 points, which also ranked them in the group of patients without cognitive impairment. By comparing the average scores of these two groups, no statistically significant difference in cognitive functioning was found (p=0.3602, p> 0.05).

Analyzing the cognitive performance assessed by the MMSE test among the different genders, regardless of the form of the applied antipsychotic therapy, no statistically significant difference in cognitive functioning was found (p=0.1, p>0.05), although male subjects had 1.2 points higher overall score on the MMSE test than female ones. Results of this study also showed that there was no statistically significant difference in cognitive performance in relation to sex in patients on different types of antipsychotic therapy. Those results are shown in Table 1.

By comparing the average values of overall MMSE score of patients who were hospitalized for the first time due to a psychotic episode with those who had been hospitalized multiple times, without taking into account the therapeutic antipsychotic approach, patients with the first psychotic episode had 0.1 points higher total MMSE score compared to those with repeated hospitalization, and this difference was not statistically significant (p=0.46, p>0.05). Patients with the first psychotic episode did not show statistically significant difference in cognitive functioning, regardless of whether they consumed atypical therapy or were on a combination of typical and atypical antipsychotics (p=0.25, p>0.05). The same results were obtained analyzing the cognitive functions in patients with a chronic disorder, with no statistically significant difference demonstrated between the effect of atypical and combined antipsychotic therapy (p=0.48, p>0.05).

An analysis of the effect of anticholinergic biperiden on cognitive functions showed that patients who received combined antipsychotic therapy and were also co-medicated with anticholinergics had statistically significant (p=0.009, p<0.05) lower scores on MMSE, compared to those who received combined antipsychotic therapy, without anticholinergics. Results are shown in Table 2.

DISCUSSION

After the expiration of the selected time interval of at least 6 weeks, the study indicated that patients receiving either atypical or combined antipsychotic therapy achieved an aver-

Table 1. A relationship between gender and cognitive functioning on different antipsychotic approaches

Gender	Type of antipsychotic therapy	Number of patients	Arithmetic mean of MMSE score	Standard deviation	T-test	p
Female	Atypical	10	24.6	3.3	+ 0.62	0.27
	Combined	9	23.6	3.2		
Male	Atypical	15	25.5	3.3	+ 0.14	0.44
	Combined	16	25.4	2.8		

Type of therapy	Number of patients	Arithmetic mean of MMSE score	Standard deviation	T-test	p
Combined antipsychotics with anticholinergics	12	23.41	3.2	-2.51	0.009*
Combined antipsychotics without anticholinergics	13	26.15	2.1		

Table 2. The effect of anticholinergics on cognitive functioning

* statistically significant difference at the level of 0.05

age score in MMSE testing of more than 24, which put them in the category of preserved cognitive functioning. Although the majority of studies agree that cognitive impairment is the central feature of untreated psychotic disorders, the normal cognitive functioning of the subjects of this study can be explained by the previous use of antipsychotic therapy for a minimum of six weeks. The results of the conducted study indicate that there is no statistically significant improvement in cognitive function after six weeks of administration of atypical antipsychotics compared to the combined antipsychotic therapy taken at the same time interval.

Atypical antipsychotics have been earlier most frequently associated with pro-cognitive effects. Harvey et al. stated that treatment with atypical antipsychotic was associated with a wide spectrum of benefits in cognitive functioning [17]. Barkic et al. also demonstrated an improvement in cognitive functioning following the replacement of typical antipsychotics with atypical risperidone. In their study, the cognitive improvement was explained by the withdrawal of typical antipsychotics from the therapy and the consequent inhibition of secondary cognitive impairment, as well as the reduction of the dose of anticholinergics and the decrease in the number of patients requiring anticholinergic therapy with risperidone [18]. Numerous studies demonstrated a positive effect of atypical antipsychotics on cognitive functioning [9,11,19].

However, one of the most prominent, randomized, double-blind studies, CATIE study (*Clinical Antipsychotic Trials of Intervention Effectiveness*) [20], in which the effect of perphenazine, as a representative of typical antipsychotics, was compared to the several drugs from the group of atypical antipsychotics (olanzapine, quetiapine, risperidone) during therapy of 18 months, showed that after two months of therapy all compared groups displayed little but significant improvement in neurocognitive functioning. However, there was no statistically significant difference between any of the investigated groups, including those in which the typical antipsychotic perphenazine was used. Furthermore, after 18 months of therapy, the neurocognitive improvement was higher in the group treated with perphenazine than in those with olanzapine and risperidone.

Another randomized, open-label trial, named EUFEST (*European First Episode Schizophrenia Trial*) [21] was conducted in order to overcome some limitations of CATIE study, such as only including chronically ill patients or using perphenazine instead of haloperidol, which is the most prescribed first-generation antipsychotic. The mentioned study compared the cognitive performance of first-episode patients randomly assigned in an open-label design to haloperidol or one of four second-generation antipsychotics (amisulpride, olanzapine, quetiapine, and ziprasidone) after 6 months of therapy. Compared with the scores at baseline, composite cognitive test scores improved for all five treatment groups at the 6-month follow-up evaluation. However, there were no overall differences among the treatment groups. These results were in agreement with the findings from CATIE study, and could be correlated with the results obtained in our study, in which atypical antipsychotics did not show a better cognitive effect over combined typical and atypical therapy. Results similar to those from previously mentioned studies are being confirmed in many recent investigations [14,15]. When nine studies investigating long-term effect (over 6 months) of atypical antipsychotics were meta-analyzed, olanzapine and quetiapine emerged as superior [22] but when all studies longer than 8 weeks were considered, there were no clear differences between antipsychotics [23].

One of the possible modulating factors that could affect cognitive performance is gender. Our study showed that there was no statistically significant difference in cognitive functioning among psychotic patients of different sexes, both in atypical or in combined antipsychotic therapy. Also, the influence of gender on cognition, regardless of the applied therapy, has been monitored, and the obtained

results showed no statistically significant difference in the comparison. Other studies that had been investigating the relationship between gender and cognition came to the opposite results. Some of them suggested that men with schizophrenia have greater cognitive impairment than women, especially in the domain of attention, language, execute functions and intelligence [24-26]. In contrast, some earlier studies suggested that women exhibit greater cognitive impairment [27]. Lastly, some studies showed no statistically significant difference in cognition between patients of different gender, which correlates with the results of this study [28-30]. This inconsistency of the results is probably due to different strategies in sampling patients, their inadequate pairing or inadequate sample size.

This study has shown that there is no statistically significant difference in cognitive functioning between patients during the first psychotic episode and patients who have previously been hospitalized because of the same or similar psychotic symptoms. Such results are in correlation with the results of other studies that proved that the cognitive impairment is present pre-morbidly and tend to persist throughout the course of the illness [14,31]. Even before the first psychotic episode is clinically detected, generalized cognitive deficits can be detected among the population of a high risk of developing psychosis [32]. When patients develop the first psychotic episode, their cognitive deficit is even more stable and more emphasized. They show a generalized cognitive deficit as well as damage to a number of specific cognitive functions [33]. In the chronic stage of the disease, there is no correlation between the aging process and the acceleration of cognitive decline, so patients with the first episode of psychosis can be as damaged in different cognitive domains as patients with chronic schizophrenia [11].

Obtained results of this study showed that co-medication with biperiden in patients on combined antipsychotic therapy has a statistically significant negative effect on cognitive functioning, compared to average MMSE scores of patients receiving combined therapy without biperiden co-medication. This negative effect of anticholinergics on cognitive functioning has been demonstrated in a numerous of previously conducted studies [34-37], with individuals with schizophrenia particularly susceptible to these effects [38]. This, however, does not mean that anticholinergics should be excluded from therapy in order to improve cognition because the target sites of their action are precisely extrapyramidal symptoms, which are also associated with additional impairment of cognitive performances [39].

The limitations of this study should be taken into account when interpreting the results. The main disadvantages are the lack of prospective monitoring of cognitive functioning, a small number of patients, as well as an uneven gender and age structure. Also, patients are not homogeneous in terms of diagnosed psychotic disorder. Furthermore, this study examined the effect of the certain group of antipsychotic drugs, without considering the individual selected drugs within the group, as well as the applied therapeutic dose.

CONCLUSION

This study showed that using MMSE, there is no statistically significant difference in the cognitive functioning in patients on treatment with atypical antipsychotic, compared to patients treated with combined therapy with atypical and typical antipsychotics. Furthermore, gender, age and duration of disease do not have a statistically significant part in cognitive functioning. Finally, medication with anticholinergic biperiden causes deterioration in cognitive functioning.

Lately, an increasing number of studies do not demonstrate the superiority of atypical antipsychotics on neurocognitive improvement over typical antipsychotics, as it was believed previously. In order to overcome the high heterogeneity of the results obtained in the studies investigating this matter, it is necessary to conduct new ones where the majority of unwanted sources of heterogeneity should be eliminated, with an emphasis on those of methodological characteristics.

CONFLICT OF INTEREST

The authors have no conflicts of interest that are directly relevant to the content of this study.

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Efekti tipičnih i atipičnih antipsihotika na kognitivne funkcije kod pacijenata sa psihotičnim poremećajima

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KRATAK SADRŽAJ

Uvod: Iako se ranije pozitivnim i negativnim simptomima shizofrenije pridavao najveći značaj, novija naučna dostignuća ukazuju na to da su poremećene neurokognitivne funkcije centralna klinička karakteristika shizofrenije. Oštećeno je globalno kognitivno funkcionisanje, baš kao i pojedine specifične kognitivne funkcije. Ranije sprovođene studije su ukazivale na prokognitivni efekat atipičnih antipsihotika u odnosu na tipične, međutim novije studije ne potvrđuju dominantost atipičnih antipsihotika u kognitivnom poboljšanju.
Cilj: Cilj ove studije bio je da se uporedi efekat atipičnih antipsihotika na kognitivne funkcije kod psihotičnih pacijenata sa efektom kombinovane terapije tipičnim i atipičnim antipsihotikom. Takođe, ispitan je uticaj pola i dužine trajanja bolesti na kognitivno funkcionisanje pacijenata na atipičnoj i kombinovanoj antipsihotičnoj terapiji, kao i uticaj komedikacije antiholinergikom biperidenom na kognitivno funkcionisanje kod psihotičnih pacijenata na kombinovanoj antipsihotičnoj terapiji.
Materijal i metode: U ovoj akademskoj kvazi-eksperimentalnoj studiji učestvovalo je 50 pacijenata hospitalizovanih na Klinici za psihijatriju Kliničkog centra Vojvodine, koji su bili raspodeljeni u dve grupe od po 25 ispitanika. Jednu grupu su činili pacijenti koji su minimum šest nedelja unazad bili na terapiji atipičnim antipsihoticima, a drugu pacijenti koji su minimum šest nedelja unazad bili na kombinovanoj terapiji tipičnim i atipičnim antipsihoticima. Unutar druge grupe mogle su se izdvojiti dve podgrupe – jedna sa 12 pacijenata koji su bili na komedikaciji sa antiholinergikom i druga sa preostalih 13 pacijenata koji su primali samo kombinovanu antipsihotičnu terapiju. Svim pacijentima su testirane kognitivne funkcije pomoću Mini-mental testa (MMSE), a dobijeni rezultati analizirani pomoću t-testa.
Rezultati: Nema statistički značajne razlike u kognitivnom funkcionisanju kod pacijenata na atipičnoj i kombinovanoj antipsihotičnoj terapiji($p>0,05$). Nema statistički značajnog efekta pola i dužine trajanja bolesti na kognitivno funkcionisanje u dve poređene grupe ($p>0,05$). Postoji statistički značajan negativan efekat na kogniciju usled komedikacije biperidenom u toku kombinovane antipsihotične terapije ($p<0,05$).
Zaključak: Rezultati ovog istraživanja su pokazali da atipični antipsihotici nemaju bolji kognitivni efekat u odnosu na kombinovanu terapiju atipičnim i tipičnim antipsihoticima. Istraživanja u budućbosti bi trebala da dokažu nedvosmislieni efekat antipsihotika na kognitivno funkcionisanje.

Ključne reči: atipični antipsihotici, tipični antipsihotici, Mini-mental test, shizofrenija, psihoza, kognicija

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