

THE EFFECTS OF THIRD-GENERATION ANTIPSYCHOTIC DRUGS ON THE PSYCHOSOCIAL FUNCTIONING OF PATIENTS WITH SCHIZOPHRENIA

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SUMMARY

Background: The degree of cognitive impairment and verbal fluency are more important predictors of a patient's social rehabilitation than the severity of negative or positive symptoms. At the same time, researchers have confirmed and rejected linkages between linguistic functioning and certain cognitive functions in various studies. In several cases these correlations were observed, but did not reach any statistical significance. The aim of this study was to investigate and understand the effects of cognitive decline and impaired fluency on the social functioning of patients with schizophrenia, using a set of experimental psychological techniques on a homogeneous group of patients

Methods: The study involved 30 patients with paranoid schizophrenia. The average age of the patients was around 22 years. All patients received cariprazine in doses of 1.5, 3.0, and 4.5 mg per day. Assessment was performed at baseline and after 8 months using a battery of neurocognitive tests, verbal fluency tests, social functioning scales, PANSS scale and adverse effect scales.

Results: Assessment of higher cognitive functions through verbal fluency may provide a new approach to assessing social functioning. Since social engagement and social involvement usually require considerable effort, the ability of verbal fluency tests may help assess social functioning in a time-constrained clinical setting by both psychologists and psychiatrists, without additional training in clinical psychology. Subsequently, the impact of both antipsychotic treatment and neurocognitive training in improving social outcomes in patients with schizophrenia may be assessed. Comparisons of different antipsychotic medications and combination treatments and a longer-term assessment after 2–3 years of treatment are also needed

Conclusions: Verbal fluency deficits can serve as early indicators of cognitive decline and indicators of the success of psychosocial interventions, characterizing the clinical condition of patients and their social functioning.

Key words: third-generation antipsychotic- schizophrenia- verbal fluency- social dysfunction

Abbreviations: ATP- Antipsychotic; BARS - Behaviourally Anchored Rating Scale; DSST- the Digit Symbol Substitution Test; GLMs- generalized linear models; PANSS – Positive and Negative Syndrome Scale; PSP- scale for assessing social and professional functioning; SARS- side effect assessment scale; SZ –schizophrenia; VFT - Verbal Fluency Test

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INTRODUCTION

Schizophrenia is a group of relatively heteronomous chronic mental disorders that typically begins at a young age and often leads to disability of the patients (Gurovich et al. 2007). About 50% of schizophrenia patients have a disability, most of them are able-bodied young and mature people, that presents a serious burden on the economy of any country (Kitchen 2012). The prevalence of schizophrenia is about 1% (0.77-0.85%) of the world's population (WHO 2022). However, about 14% of patients do not come to the psychiatrist's attention at all. The risk of rehospitalization within two years is quite high and amounts to 40-60%. Schizophrenia reduces the adaptive capabilities of patients, as well as their quality of life, increases the risk of delinquent behavior, as well as premature mortality. Schizophrenia is characterized by a high level of comorbid pathology. In particular, the risk of

alcoholism and drug addiction is as high as 40%. There is also a high proportion of affective disorders (Sofronov 2011). Significant social dysfunction and decreased productivity are largely common for schizophrenia. According to modern concepts, the nuclear symptom of schizophrenia is neurocognitive deficit (Gebreegziabhere 2022). Anomalies of language and its use are also key phenomena in schizophrenia (Bleuler 1950, Brown & Kuperberg 2015, Li et al. 2012). Speech dysfunction occurs at an early stage of the development of the nervous system within disorder (Velham et al. 2009) and predicts both a risk factor for schizophrenia (Bedi et al. 2015) and long-term functional disorder (Green 2006, Lin et al. 2011, Holshausen et al. 2014). Decreased verbal fluency is a characteristic feature of schizophrenia. It includes a combination of mechanisms, such as semantic processing skills (Smirnova 2017) and difficulties using context (Doherty et al. 2011; Vogel et al. 2009). Neuroscientific

research has revealed neural networks underlying both verbal fluency and cognitive skills (Doherty 2013, Skiba 2024). The prefrontal cortex as an area associated with executive functions is particularly involved in these processes. Functional magnetic resonance imaging (fMRI) studies have shown increased activity in the prefrontal cortex during tasks related to verbal fluency and cognitive flexibility, highlighting the neuroscientific basis of their relationship (Mutlu 2021, Lundin 2023, Comparelli 2020).

The degree of cognitive impairment and verbal fluency are more important predictors of a patient's social rehabilitation than the severity of negative or positive symptoms (Suttajit 2015).

The problems of schizophrenia therapy significantly affect the functional well-being, quality and expectancy of patient's life (Nasirova 2022, Huntre 2012, Mendl 2013). To ensure comprehensive, effective, and safe treatment for patients with schizophrenia, we need antipsychotics with a wide range of action that can trigger processes of resocialization, especially for young adults.

The most significant achievement in addressing the challenge of optimizing treatment at the current stage is the use of antipsychotic medications known as the "third generation" (ATPs): aripiprazole, bexipiprazole, and cariprazine.

All of these third-generation antipsychotic medications are included in the Russian clinical guidelines for the treatment of schizophrenia. The present study examines the use of the 3rd generation antipsychotic cariprazine. Cariprazine differs from second-generation antipsychotics by partial agonism of dopamine D2 and D3 receptors. Given the generally favorable tolerability profile, cariprazine is considered a first-line treatment for schizophrenia (Keks 2020). The unique mechanism of action of cariprazine, such as a partial agonist with the highest affinity for dopamine D3 receptors and the longest half-life, makes it effective against all symptoms of schizophrenia (Calabres 2020). Its high affinity for dopamine D2 receptors accounts for its effectiveness in reducing positive symptoms and preventing relapse during long-term treatment. The greater affinity for D3 receptors compared to D2 receptors, along with the high occupancy of both D3 and D2 receptors in vivo, ensure the efficacy of the drug in treating difficult-to-control persistent negative symptoms and cognitive impairment (Girgis et al. 2016). Cariprazine is among the most effective treatments for both positive and negative symptoms, as well as depressive symptoms.

At the same time, researchers have confirmed and rejected linkages between linguistic functioning and certain cognitive functions in various studies. In several cases these correlations were observed, but did not reach any statistical significance. Most studies indicate correlations between linguistic and cognitive functioning to varying degrees in individuals with schizophrenia. This suggests that correlations may be present or absent in individual patients, depending on the circumstances.

In most studies, patient groups were heterogeneous in terms of medication, age, and educational background (Grabias 2012; Crenikiewicz 2004; Sylwia 2025).

The aim of this study was to investigate and understand the effects of cognitive decline and impaired fluency on the social functioning of patients with schizophrenia, using a set of experimental psychological techniques on a homogeneous group of patients.

METHODS

The study used clinical, neuropsychological, and statistical methods. To evaluate the results, we used the PANSS clinical scale (Kay et al. 1987) and the PSP scale for assessing social and professional functioning (Morosini 2000). We also used the SARS side effect assessment scale developed by M. Arda et al. We also used BARS to assess the severity of drug-induced akathisia.

The following psychodiagnostic techniques were used to assess cognitive functioning:

- *To assess memory*, the Benton Visual Retention Test was used (1960).
- *To assess attention*, the Sequential Connections test (parts A and B), Trail Making Test A & B, and the Tapping test were used. These tests were adapted from Reitan R.M. and Wolfson D. (1993), and the method for rapid diagnosis of nervous system properties by psychomotor indicators by E.P. Ilyin was used. The Tapping test and the Digit Symbol Substitution Test (DSST), a modified subtest from the WAIS-IV, were also used.
- *The Verbal Fluency Test (VFT)* is a test used to assess a person's ability to generate words quickly and easily in various categories, such as verbal, semantic, and emotional. The test was developed by Lezak M.D. in 1995.

The initial evaluation of patients was conducted at the start of therapy in the Day care hospital. An additional follow-up study was carried out for 8 months after starting cariprazine treatment.

The data obtained from a comprehensive examination of patients was analyzed on a Pentium Intel Centrino personal computer using SPSS Statistica software version 17.0. A multidimensional analysis was conducted using four generalized linear models (GLMs) to examine the relationship between memory, attention scores (Benton), speech fluency (VFT), and overall cognitive function scores (PSP). These models were chosen because they take into account the limitations of the estimates and allow for more accurate modeling within the given scale.

Age, education (in years), duration of disease, and number of acute episodes were included as independent variables in all four models. Pearson correlation analyses were also conducted to study the relationship between speech fluency and cognitive function. The results were considered statistically significant if the p-value was less than 0.05.

All statistical analyses were performed using Python version 3.11.7.

Table 1. Changes in Clinical and Cognitive parameters in schizophrenic patients treated with Caripazine over 8 months

Category	Baseline	Range	In 8 months	Range
Age (years)	23.2	20–26	23.6	20–26
Duration of education (years)	15.2	12–18	15.3	12–18
Duration of disease (years)	2.3	1–5	2.6	1–5
Number of episodes	1.75	1–3	1.75	1–3
Cariprazine dosage (mg)	3.0–4.5	1.5–4.5	3.0	1.5–3.0
PANSS scale (psychopathology)	84.44 ± 1.82	80–90	66.25 ± 1.95	60–75
PSP scale (functionality)	68.3±	60–75	78.9 ± 1.6	70–82
VFT scale (cognitive functions)	25.86±	20–30	29.4 ± 0.9	26–28
Benton scale (cognitive tests)	3.04 ± 0.54	2.5–3.5	3.8 ± 0.4	3.4–4.8
Maze test	17.62±1.24	17.02-17.91	18.46±1.81	18.03-19,12

Material

The study involved 30 patients with paranoid schizophrenia who were undergoing outpatient treatment at the Neuropsychiatric Dispensaries No. 2 and 3 in St. Petersburg. The average age of the patients was around 22 years, and most of them had active social lives (they were either students or working). All patients received cariprazine in doses of 1.5, 3.0, and 4.5 mg per day as their primary medication in a Day care hospital or hospital setting.

RESULTS

The interaction between verbal fluency and cognitive abilities is a complex and dynamic process, in which each of them influences and shapes the other (Table 1).

The graph shows the results of testing of patients at the beginning and after 8 months of the study. The testing covered such aspects as social and personal functioning, cognitive functions, visual and motor coordination, and verbal fluency. The rates increase of the applied scales directly indicates an increase in the pace of activity, an improvement in concentration, an increase in the adequacy of thinking and the volume of long-term memory (Figure 1, 2).

For young patients, after relief of acute and subacute symptoms, changes in subscales A and B in the PSP were most relevant. Subscale A refers to socially useful activities that involve work, study, and social and group activities. Successful continuation of academic or work activities is important for social functioning, as it allows the patient to go to the university, to get a job, and to switch to more professional and paid positions, despite having a disability. This category correlates with executive functions within a cognitive profile due to the restoration of attention and working memory functions. There is also a connection with speech fluency, particularly semantic and verbal fluency.

Subscale B relates to the establishment of social relationships, including the appearance or expansion of a circle of friends and acquaintances. This is closely linked to emotional fluency and attention.

Indicators of an increase in activity, improved concentration, increased thinking capacity and long-term

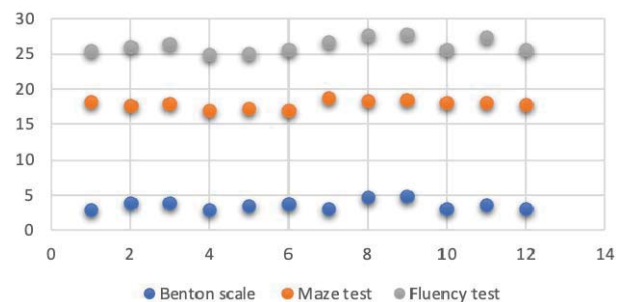


Figure 1. Test results

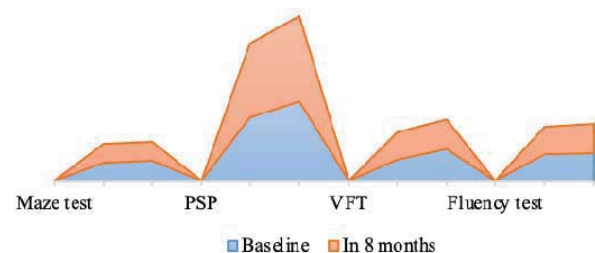


Figure 2. Visualization of rates increase

memory have been observed. Trends towards an increase in short-term operational memory have also been identified. According to the survey data, all indicators have increased up to 36.6%. The maximum improvement was seen in visual memory and attention, while performing functions undergone less change (Table 2).

DISCUSSION

Results showed an improvement in the use of categorical language style in patients during treatment, which can be interpreted as evidence of an improvement in analytical thinking compared to the first point in the study. Lower scores were associated with higher levels of conceptual disorganization and disorganized thinking. Moreover, language style was a stronger predictor of conceptual disorganization than cognitive measures.

According to the data of the Large Academic Dictionary, P, O, S were used in testing. Thus, 6 volumes (16-21 v.) are devoted to the letter "P", 3 volumes (13-15 v.) to the letter "O", 2.5 volumes (24-26 v.) to the letter "S", i.e. a fairly diverse number of words. It is noteworthy that

Table 2. Differences in participants with schizophrenia (SZ) between baseline and 8 months after the treatment in verbal fluency, cognitive strategies, executive functions, and information processing speed

	AV (n = 108)		CC (n = 108)		Task effect type		Group effect		Interaction effect	
	M (AD)	M (AD)	Φ	η^2	Φ	η^2	Φ	η^2	Φ	η^2
<i>Comparison of verbal fluency and cognitive strategies</i>										
Semantic fluency:										
Total words	17.64 (6.28)	22.03 (6.32)	24.22	<0.001	24.22	0.11	242.78	<0.001	11.62	<0.001
Animal Fluency	13.57 (3.98)	15.82 (3.96)								
Fruit Fluency	14.76 (5.34)	17.28 (3.64)								
Vegetable Fluency	0.12 (0.02)	0.10 (0.02)								
Average cluster size	0.14 (0.02)	0.13 (0.02)	28.24	<0.001	28.24	0.11	159.24	<0.001	1.98	0.141
Animal Fluency	0.13 (0.02)	0.11 (0.02)								
Fruit Fluency	0.40 (0.14)	0.42 (0.13)								
Vegetable Fluency	0.44 (0.14)	0.50 (0.13)								
Total switchings	0.45 (0.14)	0.48 (0.13)	10.07	0.002	10.07	0.05	15.23	<0.001	4.78	0.018
Animal Fluency										
Fruit Fluency										
Vegetable Fluency										
Phonemic fluency:										
Total words	13.72 (4.43)	15.56 (4.97)	2.51	0.087	2.51	0.01	243.72	<0.001	10.77	<0.001
Letter P	10.46 (4.07)	10.58 (3.82)								
Letter O	9.21 (3.93)	10.02 (4.07)								
Letter S	0.12 (0.03)	0.11 (0.03)								
Average cluster size	0.13 (0.03)	0.13 (0.03)	0.51	0.406	0.51	0.01	41.55	<0.001	3.36	0.058
Letter P	0.10 (0.03)	0.10 (0.03)								
Letter O	0.51 (0.18)	0.58 (0.14)								
Letter S	0.60 (0.20)	0.64 (0.15)								
Total switchings	0.43 (0.15)	0.52 (0.13)	3.62	0.041	3.62	0.02	3.44	0.045	0.00	0.897
Letter P										
Letter O										
Letter S										
<i>Comparison of executive functions and processing speed</i>										
Concept formation and problem solving:										
Maze test	2.47 (0.52)	2.41 (0.29)	20.54	<0.001	20.54	0.07	1.38	0.174	0.84	0.313
% repeated errors	2.95 (0.55)	2.63 (0.47)								
% non-perservative errors										
Processing speed and cognitive flexibility:										
Trail Making Test	3.67 (0.32)	3.41 (0.26)	101.31	<0.001	101.31	0.27	1428.81	<0.001	5.97	0.009
Completion time	4.56 (0.32)	391 (0.24)								

the number of words for different letters is approximately the same, given the almost 2-fold difference in the number of words in the dictionary between O and S. But the order of typing words for letters also affects the results. The maximum indicators were in the 1st and 2nd rubrics, and exhaustion began by the 3rd rubric. The number of words in categorical subgroups changed similarly. In this study, the sequence of letters and categories changed randomly. This test is a good predictor of cognitive decline in schizophrenia; improvement is noted during therapy, a connection with the level of education.

Tests of speech fluency can predict cognitive decline in patients with schizophrenia, and therapy is associated with improved performance related to the level of education. As therapy progresses, there is a correlation between speech fluency tests and educational level, which is not present in the subacute phase of the disease.

The results showed an improvement in the use of categorical language style among patients during therapy. This can be interpreted as an indication of improved analytical thinking, compared to the beginning of the study. Higher scores were associated with lower levels of conceptual disorganization and better thinking. Furthermore, language style was a stronger predictor of conceptual disorganization than cognitive indicators.

We did not observe any significant side effects from caripazine therapy, except for akathisia, which occurred in 5 out of the 30 patients who participated in the study (17%). These episodes of akathisia mainly occurred at the age of 25 and were quickly relieved by the beta-blocker anaprilin, at a minimum dosage of 20 mg once a day in the morning, under the supervision of blood pressure and heart rate.

Based on the discussions so far, assessment of higher cognitive functions through verbal fluency may provide a new approach to assessing social functioning. Since social engagement and social involvement usually require considerable effort, the ability of verbal fluency tests may help assess social functioning in a time-constrained clinical setting by both psychologists and psychiatrists, without additional training in clinical psychology. Subsequently, the impact of both antipsychotic treatment and neurocognitive training in improving social outcomes in patients with schizophrenia may be assessed. Comparisons of different antipsychotic medications and combination treatments and a longer-term assessment after 2–3 years of treatment are also needed.

CONCLUSIONS

Understanding the relationship between verbal fluency and cognitive skills has important implications for predicting social status. Third-generation antipsychotics can indirectly improve social functioning by positively affecting verbal fluency and cognitive abilities. The favorable profile is also enhanced by reducing negative symptoms

and minimizing extrapyramidal side effects. However, effectiveness depends on individualized therapy and comprehensive rehabilitation. Verbal fluency deficits can serve as early indicators of cognitive decline and indicators of the success of psychosocial interventions, characterizing the clinical condition of patients and their social functioning.

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All authors approved the final manuscript.

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