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Research Article

Experience Of Combined Use of Risperidone with Nootropic Drugs in Complex Therapy of Patients with Paranoid Schizophrenia with An Ideation Pattern of Non-Suicidal Auto-Aggressive Behavior

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Abstract

Paranoid schizophrenia is characterized by polymorphism of clinical manifestations and the difficulty of curing negative disorders. To increase the effectiveness of therapy, it is theoretically justified to simultaneously prescribe antipsychotic and nootropic drugs. Based on the example of the combined use of risperidone, memantine and choline alfoscerate in various combinations, data were obtained on increasing the effectiveness of therapy in relation to positive and negative disorders, including non-suicidal auto-aggressive behavior (NAAB). At the same time, the first-line therapy in such patients is the simultaneous administration of all three drugs included in the study - risperidone, choline alfoscerate and memantine.

Keywords: risperidone; choline alfoscerate; memantine; paranoid schizophrenia; non-suicidal auto-aggressive behavior

Introduction

Schizophrenia remains a disease with an unclear etiology and pronounced polymorphism of clinical manifestations. Antipsychotic drugs retain their leading role in the treatment of such patients. However, if they demonstrate high effectiveness in relation to positive disorders, then in relation to the correction of negative manifestations their effect is not enough. In turn, discussions continue in the scientific community regarding the etiology and pathogenesis of negative disorders themselves, including neurocognitive changes. An additional clinical problem is the clinical pathomorphosis of the schizophrenic process. In particular, the proportion of affective and behavioral disorders, including non-suicidal auto-aggressive behavior or "NAAB", is steadily increasing [1]. To solve these clinical problems, combination therapy regimens are increasingly being used, where nootropic drugs act as adjuvant drugs to neuroleptics. Among them, the first line includes drugs whose mechanism of action is associated with an effect on the glutamatergic and cholinergic systems. Thus, the drug Memantine has a multimodal effect in relation to the hypothetical pathogenetic links of the schizophrenic process. In addition to its main function as an antagonist of NMDA receptors, memantine prevents oversaturation of the intracellular space with calcium ions, modulates the activity of the cholinergic, serotonergic and dopaminergic systems, as well as providing an immunomodulatory effect [2,3,4,5,6,7,8,9, 10,11,12,13,14,15,16]. Disturbances of the cholinergic system are observed in almost all mental disorders, including schizophrenia. This predetermines the active use of drugs with cholinergic activity in the treatment of schizophrenia spectrum disorders [17,18,19,20]. In practice, encouraging results were obtained when combining antipsychotics with individual nootropic drugs [21,22,23,24]. A natural continuation of the work of researchers to optimize the

treatment of patients with schizophrenia was the attempt to combine antipsychotics with several nootropic drugs. Among the latter, preference has traditionally been given to memantine and galantamine, as the most studied pharmacological agents [25,26,27,28,29]. This study is an attempt to continue the clinical search for combined treatment regimens with neuroleptics and nootropic drugs for the correction of leading psychopathological manifestations including non-suicidal auto-aggressive actions (NAAA) in patients with paranoid schizophrenia.

Purpose of the study: to study the effectiveness of the combined use of risperidone with nootropic nootropic drugs in patients with paranoid schizophrenia with the ideation pattern of NAAB.

Objectives of the study: 1) to study the effect of nootropic drugs on the nature of clinical and psychopathological manifestations in patients with paranoid schizophrenia with NAAB; 2) to study the effect of nootropics on social adaptation in patients with paranoid schizophrenia with NAAB; 2) study the effect of nootropic drugs on the frequency of NAAA in such patients.

Material and research methods. A total of 81 patients with paranoid schizophrenia were studied in a comparative, non-randomized manner. The average age of the subjects was 35.2±1.3 years, the duration of the disease was 15.6±2.2 years. All examined were men. Type of course of the schizophrenic process: continuous - progressive. The inclusion criteria were: 1) compliance of the diagnosis of paranoid schizophrenia with the criteria of the ICD-10 revision (F20.0); 2) a state of drug remission, with signs of an increasing procedural personality defect; 3) implementation of NAAD by patients with a history of paranoid schizophrenia. Non-inclusion criteria were: 1) psychotic level of disorders at the time of inclusion in the study; 2) auto-aggressive actions in the form of self-strangulation as a means of obtaining sexual satisfaction (asphyxiophilia); 3) taking the drugs included in the study less than 6 months before the start of the study itself. By remission was meant "the weakening and mitigation of all symptoms, ensuring, to one degree or another, the social and labor adaptation of the patient, and embracing a wide range of conditions from those bordering on practical recovery to those in which the symptoms of the defect are already clearly visible" [30]. A schizophrenic defect, or in the modern interpretation – neuro-cognitive procedural changes, was understood as "the consequences of a mental illness that occur in conditions of a complete stop of the process, lead to a persistent (and non-progressive) loss or dissociation of mental functions with a change in personality and are accompanied by a decrease in its functioning" [30]. The definition of "NAAA" included a variety of actions directed against one's health and accompanied by a violation of the integrity (functions) of organs or organ systems. At the same time, there was no demonstration of intention to commit suicide [31]. The study included a main group and a comparison group. The main group consisted of subjects (21 people) who were on monotherapy with risperidone, the average daily dose of which was 7.8±0.4 mg. The comparison group consisted of patients taking combination therapy regimens, including risperidone, choline alfoscerate and memantine. Next, the comparison group was divided into 4 subgroups. The first subgroup (17 people) took risperidone and choline alfoscerate in average daily doses: risperidone - 7.7±0.3 mg, choline alfoscerate 800 mg. The second subgroup (21 people) took risperidone and memantine in average daily doses: risperidone - 7.8±0.3 mg and memantine 10 mg. The third subgroup (22 people) took risperidone, choline alfoscerate and memantine simultaneously, in average daily doses: risperidone -7.8±0.3 mg, choline alfoscerate 800 mg, memantine 10 mg. The choice of drugs for the study was determined by their most frequent use in practical work with this category of patients. The assessment of the mental state of the examination was carried out using a clinical method at the time of inclusion in the study (1 week), then at weeks 12 and 24 of the study. The clinical effectiveness of therapy was determined by comparative analysis of the frequency of exacerbation of psychotic symptoms and committed acts of non-suicidal auto-aggression for a period of 24 weeks before and after inclusion in the study. To objectify the data obtained, the Scale of Negative Psychopathological Symptoms (SANS) was used. Fisher's test was used for statistical evaluation. The clinical and psychopathological picture of the course of the disease consisted of a combination of positive and negative disorders. A retrospective analysis showed that the prodromal period averaged 4.8 ± 0.3 years. During this period, there were causeless mood swings, predominantly of the hypothymic type; Occasionally, patients experienced a feeling of protopathic anxiety. Unmotivated outbursts of aggression with self-harm were noted, including both NAAA (burning the skin, scratching the skin) and impulsive suicide attempts. The patients themselves noted that "during this period of time it became more difficult to assimilate new educational material, thoughts were sometimes "confused." During the 6-12 months preceding the first psychotic episode, depression increased, interspersed with outbursts of irritability and openly displayed aggression (they broke things, fought with relatives). They impulsively began to consume psychoactive substances, immediately reaching high doses; The intake was carried out continuously, and their consumption was also abruptly interrupted. At the same time, no manifestations of withdrawal syndrome and subsequent mental and physical dependence were observed. Outside the stage of drug intoxication, transient illusions of perception and mental automatisms were experienced. Thus, patients "heard their name being called, someone looking at their back. Sometimes passers-by tried to "get into my head and forbade me to communicate with family and friends" (according to the subjects). Productive social activity declined sharply. Patients either stopped communicating with all their acquaintances or did not leave the house. Or they made impulsive trips to unfamiliar places, they could monotonously follow the same route, for example, riding the subway for many hours in a row, which "calmed their nerves." The psychotic episode consisted of psychomotor agitation, uncontrolled anxiety, and clinical manifestations of hallucinatory-delusional syndrome." During the interictal period, negative personality changes increased against the background of a decrease in adaptive-compensatory functions. The patients became lacking in initiative, their range of interests narrowed to satisfying the simplest everyday needs. They were dependent on relatives. They often complained of somatic discomfort, weakness, and diffuse pain in the body, which was not confirmed by objective research data. They showed unmotivated aggression towards loved ones, while, as the patients themselves noted, "they liked to watch the suffering of their close relatives." Occasionally they experienced feelings of anxiety, depression, and abstract thoughts about death. They had no permanent interests, no plans for the future. There was no criticism of one's condition or determination to seek treatment. Such changes in the domestic (Russian) school of psychiatry are considered as manifestations of negative disorders of the tonic type [30]. Any deviation from the habitual way of life caused protest from the patients. Such a trigger could be the desire of relatives to expand the range of household responsibilities, for example, maintaining personal hygiene, daily routine, cleaning the house, as well as the need to regularly take medications, and participate in psychotherapy. The patients' mood of protest, irritability, and conflict increased. To resolve a conflict situation, patients inflicted superficial self-cuts on themselves, less often inserted various objects under the skin, or burned the skin. At the same time, the actual NAAA were applied impulsively, according to the "last straw" principle, which served as an emotional release and was accompanied by formal regret about what they had done. These characteristics of NAAA, in combination with negative changes of the tonic type, formed the ideational pattern of NAAB.

Research results. The frequency of exacerbation of psychotic symptoms in patients taking risperidone monotherapy was 2.3 cases in the retrospective period and 1.2 cases in the prospective period (F1.92, $p<0.05$). In patients taking combination therapy "risperidone + choline alfoscerate" this indicator was 2.2 and 1.0 cases (F2.2, $p<0.05$). Among

patients taking combination therapy “risperidone + memantine”, the frequency of psychotic episodes was 2.3 and 0.9 cases (F2.3, p<0.05). Finally, for patients taking combination therapy “risperidone + choline alfoscerate + memantine” this figure was 2.3 cases in the retrospective period and 0.9 cases in the prospective period (F2.56, p<0.01). The ability of all drugs included in the study to reduce the severity of negative disorders, which differed in severity, was established. In patients on risperidone monotherapy, the reduction in the severity of negative disorders was at the trend level throughout the study (Table 1).

The effectiveness of therapy according to the scale for assessing negative symptoms in patients taking risperidone monotherapy (in points). TableN1

Psychopathological manifestations	Steps to evaluate therapy		
	1 week	12 week	1 week
Flattening and rigidity of affect		Flattening and rigidity of affect	
Speech disorders		Speech disorders	
Apato-abulic disorders		Apato-abulic disorders	
Anhedonia – asociality		Anhedonia – asociality	
Attention		Attention	

* p≤0,05

The decrease in the severity of negative disorders observed in patients taking combination therapy “risperidone + choline alfoscerate” was at the level of trends throughout the study (Table 2). The effectiveness of therapy according to the scale for assessing negative symptomsin patients taking combination therapy with risperidone and choline alfoscerate (in points). Table N2

Psychopathological manifestations	Steps to evaluate therapy		
	1 week	12 week	24 week
Flattening and rigidity of affect	33,3	28,0 (F1.19, p>0,05	23,1 (F1.44, p>0,05
Speech disorders	22,2	19,1 (F1.16, p>0,05	18,0 (F1.23, p>0,05*
Apato-abulic disorders	19,2	15,3 (F1.25, p>0,05	12,8 (F1.5, p>0,05
Anhedonia – asociality	15,2	13,2 (F1.15, p>0,05	12,3 (F1.24, p>0,05
Attention	12,3	11,1 (F1.11, p>0,05	8,3 F1.48, p>0,05

* p≤0,05

Among patients taking combination therapy “risperidone + memantine”, the greatest effect was achieved in terms of reducing psychopathological manifestations associated with apatho-abulsic manifestations, reaching statistically significant values by week 24 of the study. Positive changes in relation to other negative disorders remained at the trend level throughout the study (Table N3).

The effectiveness of therapy according to the scale for assessing negative symptoms in patients taking combination therapy with risperidone and memantine (in points). Table N3

Psychopathological manifestations	Steps to evaluate therapy		
	1week	12 week	24 week
Flattening and rigidity of affect	33,1	27.3 (F1.21, p>0,05	21,0 F1.58, p>0,05
Speech disorders	22,1	18,2 (F1.21,	14,1 F1.57,

		p>0,05	p>0,05
Apato-abulic disorders	19,1	14,0 (F1.36, p>0,05	9,7 (F1.97, p<0,05*
Anhedonia – asociality	15,4	13,0 (F1.18, p>0,05	9.2 F1.18, p>0,05
Attention	12,6	10.2 (F1.24, p>0,05	7.1 F1.77, p>0,05

* p≤0,05

Finally, in patients who took combination therapy "risperodone + choline alfoscerate + memantine," the greatest effect was achieved in relation to psychopathological manifestations in the form of flattening and rigidity of affect, a decrease in apatho-abulsic disorders, as well as anhedonia and concentration. Statistically significant changes in these indicators occurred by week 24 of the study (Table 4).

The effectiveness of therapy according to the scale for assessing negative symptoms in patients taking combination therapy with risperodone + choline alfoscerate + memantine (in points). Table N4

Psychopathological manifestations	Steps to evaluate therapy		
	1week	12 week	24 week
Flattening and rigidity of affect	32,6	26,2 (F1.24, p>0,05	18,0 (F1.81, p<0,05*
Speech disorders	22,1	17,1 (F1.29, p>0,05	13,2 (F1.67, p>0,05
Apato-abulic disorders	19,0	13,0 (F1.46, p>0,05	8,9 F2.13, p<0,05*
Anhedonia – asociality	15,0	10,2 (F1.47, p>0,05	8,1 (F1.85, p<0,05*
Attention	12,8	9,9 (F1.29, p>0,05	6,8 F1.88, p<0,05*

* p≤0,05

The incidence of NAAA in patients taking risperidone monotherapy was 3.3 cases in the retrospective period and 1.6 cases in the prospective period (F 2.06, p<0.05). In patients taking combination therapy "risperidone + choline alfoscerate" this figure was 3.2 and 1.5 cases (F 2.13, p<0.05). Among patients taking combination therapy "risperidone + memantine", the incidence of NAAA was 3.3 and 1.4 cases (F 2.36, p<0.05). Finally, for patients taking combination therapy "risperidone + choline alfoscerate + memantine" this figure was 3.3 cases in the retrospective period, and 1.1 cases in the prospective period (F 3, p<0.01).

Discussion. As part of a comparative analysis, all declared drugs confirmed their effectiveness. At the same time, differences in the effectiveness of therapy on different elements of the clinical picture of the studied individuals were revealed. It was established that all used treatment regimens contributed to reducing the risk of exacerbation of psychotic symptoms, the effectiveness of which decreased in the following order: "risperidone + choline alfoscerate + memantine" < "risperidone + memantine" < "risperidone + memantine" < "risperidone". Moreover, in all comparison groups, the observed positive changes became statistically significant by the end of the study. With all other treatment regimens, positive changes remained at trend levels throughout the study. It can be assumed that combination therapy, including the use of all three drugs included in the study, can significantly enhance the antipsychotic effect of the base drug (risperidone), due to the effect on different parts of the pathogenesis of a single schizophrenic process. For example, by enhancing the dopaminolytic effect, reducing the hyperfunction of the glutamatergic and cholinomimetic systems, as well as stopping immunodestructive processes [32]. It was established that all used treatment regimens contributed to a decrease in the severity of negative disorders, the effectiveness of which decreased in the following order: "risperidone + choline alfoscerate + memantine" < "risperidone + memantine" < "risperidone + memantine" < "risperidone". As a theoretical basis for the results obtained, the following can be assumed: 1) all the declared drugs individually can have a positive clinical effect, acting on various links in the pathogenesis of processual neurocognitive changes [33]; 2) risperidone has a low anticholinergic potential, which reduces the potential risk of deterioration of cognitive functions [34.]; 3) risperidone is able to act as an agonist of serotonin receptors of the 5-HT1A type, which, according to some researchers, can reduce neurocognitive impairment in schizophrenia [35,36]; 4) memantine modulates the action of the cholinergic system, which, in combination with the use of the cholinomimetic pharmacological agent itself (choline alfoscerate), enhances the phenomenon of neuroplasticity, increasing the conductivity of the nerve impulse. At the same time, choline alfoscerate can act as a protector of the negative effects of memantine, including in the prevention of the so-called "Olney's lesion" [37]. It was found that all antipsychotics included in the study reduced the severity of behavioral disorders, including a decrease in the frequency of NAAA, in terms of

effectiveness, arranged in the following order: “risperidone + choline alfoscerate + memantine” < “risperidone + memantine” < “risperidone + memantine” < “risperidone”. Such results have an ambiguous explanation. It can be assumed that in some cases NAAAs appear in the structure of behavioral disorders associated with the group of positive disorders. At the same time, forming a stable model of behavior, NAAB reflect a radical restructuring of mental activity and a decrease in the functions of social adaptation. The pathogenetic basis of such changes are procedural neurocognitive changes. Both hypotheses require further research. At the same time, within the framework of the empirical approach and knowledge of the pharmacodynamic profile of the drugs included in the study, one can expect a positive clinical effect from their use in relation to both hypotheses of the origin of NAAB. The results obtained cannot be considered final. This is hampered by a small sample, the non-randomized nature of the studies, a limited period of observation of the subjects, and the use of a limited number of drugs.

Conclusions. The use of combined treatment regimens, including risperidone and nootropic drugs (choline alfoscerate, memantine), is clinically justified in patients with paranoid schizophrenia with the ideation pattern of NAAB. Combination therapy is superior to antipsychotic monotherapy in reducing the severity of positive and negative disorders, including non-suicidal autoaggression. As part of the actual combination therapy, simultaneous administration of risperidone and two nootropic drugs (memantine and choline alfoscerate) is preferable.

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