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Research Article

A Differential Approach to the Improvement of Prevention and Correction of Neuroleptic Side Extrapyramidal Disorders with Pantogam Active in Patients with Schizophrenia

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Abstract

Objective: The Objective of the study was to assess the efficacy and safety of pantogam active (PA) in prevention and correction of neurological side-effects during the course neuroleptic treatment of acute endogenous psychoses.

Materials and Methods: Eighty schizophrenic patients (mean age 33 years) with acute psychosis were examined. All patients received 28-day course treatment with typical and atypical neuroleptics. Two equal groups were studied: patients of the first group were treated with trihexyphenidyl (THP) in dose of 0,002 - 0,012 mg and patients of the second group received in addition PA in dose 0,9 mg/day. Clinical-observation, psychometric scales (PANSS, CGI-S, UKU) were used at baseline and on 1st, 3rd, 7th, 14th, 21st, 28st days.

Results: PA in the combination with THP improved tolerability to neuroleptic therapy in whole and exerted the better correction effect on neuroleptic extrapyramidal disorders (EPD) as compared to THP monotherapy. The number of patients with ERD reduced 1.5 times and prevention of EPD was observed 3 times more frequent in the group treated with PA. In the THP group, other adverse effects (AE) were 1,7 times more frequent and the total AE score was 2,5 times greater in comparison with the PA group (131 vs 50). Correction and preventive effects of the combined treatment with THP and PA on the clinically severe symptoms of EPD (akathisia, muscle dystonia) were more frequent in patients treated with typical neuroleptics. A less amount of THP (by 1,2 times) was used to stop EPD in the PA group.

Conclusion: PA in the combination with THP demonstrated the clear neuroprotective effect on the development, frequency and clinical manifestations of neurological side-effects. The PA can be recommended as a drug of choice for correction and prevention of neuroleptic side-effects, it promotes their tolerability and improves quality of life during the course treatment.

Keywords: *Side Extrapyramidal Disorders; Typical and Atypical Neuroleptics; Trihexyphenidyl; Pantogam Active; Neuroprotective Action*

Introduction

The wide use of psychopharmacological agents in medical practice has expanded the possibility of optimizing the treatment of mental illnesses, but in 50 - 60% of cases, the use of such agents leads to the development of side effects that significantly impair the quality of life of patients. Therefore, the search and improvement of methods for the correction of adverse events (AE) of psychopharmacotherapy for

the entire period of its history, up to the present, have not lost their relevance and are the subject of scientific research. This is especially true for treatment with antipsychotics, the prescription of which is accompanied by the development of severe neurological disorders in the form of extrapyramidal disorders (EPR) up to tardive dyskinesia. Their occurrence is associated with impaired axonal transport and synaptic transmission of neurotransmitters (dopamine, acetylcholine, norepinephrine, GABA, etc). Based on the assumption of impairment in the functioning of the gabaergic system, which regulates the activity of the dopamine system, when developing corrective therapy for antipsychotic EPR more than 40 years ago, the choice was made of drugs of the nootropic series. It was established, that the first and basic representative of this class of compounds, Nootropil, being close in chemical structure to GABA, enhances the synthesis of dopamine, increases the density of cholinergic receptors and, owing to the activation of cortical-subcortical bonds, increases the stability of brain tissue to toxic effects (including antipsychotics), which led to its use in case of poor tolerance to psychotropic drugs.

Already the first clinical studies of nootropil demonstrated, that its introduction into the psychotherapy regimen significantly improved the tolerance to psychotropic drugs, avoids their side effects and complications (from somatovegetative to neurological and mental) and ensures the prevention of intolerance to psychopharmacological drugs. The efficacy of the piracetam (which is an analog of nootropil) was found to be an adjuvant in the treatment of persistent neurological (extrapyramidal) impairments up to their complete relief during the treatment of endogenous psychoses with various neuroleptic drugs [1,2]. It is not accidental, that the elimination of neurological complications of antipsychotic drugs and their poor tolerance are included in the indications for the use of nootropil [3].

Subsequently, similar pharmacotherapeutic properties were revealed in pantogam, the domestic nootropic drug. By its chemical structure, the active substance of pantogam is calcium hopantenate (calcium salt of D-pantoyl-gamma-aminobutyric acid) and has similar pharmacological effects to GABA and pantothenic acid. The above data substantiated the indications for its use as a therapeutic and prophylactic agent in subcortical hyperkinesis, drug parkinsonism, tremor and neuroleptic syndrome with EPR [1,4,5].

In the search for new nootropic drugs for cessation of undesirable side effects of neuroleptic antipsychotics, the attention of the researchers was drawn to the domestic innovative pantogam active, the active substance of which is rac-hopantenic acid - a mixture of equal amounts of D- and L-stereoisomers of hopantenic acid. Owing to the presence of the L-isomer of hopantenic acid in its composition, rac-hopantenic acid not only interacts with GABA-B receptors, but also has a great affinity for non-benzodiazepine GABA-A receptors, as well as a unique ability to interact with D2-dopamine receptors [6,7]. This provides rac-hopantenic acid with a qualitative novelty of pharmacological properties and an ability to increase the resistance of the central nervous system to the effects of toxic substances, thereby reducing the frequency of side effects of antipsychotics.

Up to date, clinical studies have made it possible to establish the neurovegetotropic and light anxiolytic properties of rac-hopantenic acid, its ability to improve integrative indicators of cognitive functions [8,9]. The action of rac-hopantenic acid as a corrector of the side effects of antipsychotic therapy in patients with schizophrenia (dystonic hyperkineses, muscle dyskinesias, extrapyramidal symptoms) was also studied by using the clinical and psychometric methods, which showed its ability to reduce 4 times the frequency and intensity of adverse events of antipsychotic therapy [10,11]. These data determined the choice of rac-hopantenic acid (Pantogam Active) as a protector and/or corrector of adverse extrapyramidal disorders in a case of active antipsychotic therapy of psychotic conditions in patients with schizophrenia and argued for its further study in this direction.

Objective of the Study

The objective of the study was to determine the efficacy and the safety of use of PA as a neuroprotective agent for the prevention and cessation of side ESR during neuroleptic therapy of acute psychotic conditions in patients with schizophrenia.

Materials and Methods

The study was conducted in the Department of Endogenous Mental Disorders and Affective States (Head - Academician A.S. Tiganov RAS) of the Mental Health Research Center.

In accordance with the study protocol, 80 patients, 33 males and 47 females, aged 18 to 51 years (average - 33 years) underwent complete course of therapy. All patients were examined in hospital during an acute psychotic state with a clinical picture of paranoid, catatonic-hallucinatory-delusional, affective-delusional (manic-delusional or depressive-delusional) psychoses within the framework of shift-like schizophrenia (28 patients), exacerbation of continuous paranoid schizophrenia (23) and schizoaffective psychosis (29). According to ICD-10, their diagnosis corresponded to F20.x (1-2); F20.x0 and F25. (0-1-2). The average total score on the PANSS scale for one patient, included in the study was 82.4, which corresponded to the moderate severity of the acute psychotic state.

During the study all the patients received basic therapy with antipsychotics of different generations in adequate daily doses, prescribed in accordance with the specificities of psychotic states. In 20 (25%) patients, these were typical neuroleptics (TN) - haloperidol, zuclopentixol, trifluoperazin, truxal, chlorprotixene, chlorpromazine, propericiazine, moditen; in 31 (30.7%) - atypical antipsychotics (ATN) - olanzapine, risperidone, asenapine, clozapine, aripiprazole, quetiapine, serdolect, amisulpride; 29 (36.3%) patients received TH in combination with ATN. As an additional to antipsychotics and concomitant therapy, prescription of normothymics (according to indications) was allowed (except carbamazepine), as well as antidepressants and somatic treatment it excluded the use of other than PA, nootropics and other correctors, except trihexyphenidyl (THF), benzodiazepine tranquilizers and hypnotics, barbiturates. Obtaining informed consent of the patient to participate in the study was obligatory.

As research tools clinical observation methods were used, as well as international PANSS rating scale with a rating of 0, 14th and 28th days of treatment, a UKU side-effect scale and a CGI-S scale for assessment of the severity of ESR. All the results of assessment of the condition of patients were recorded in an individual medical record.

Each of the patients was observed for 28 days (4 weeks). From the first day of inclusion in the study protocol, all the patients simultaneously with the prescription of antipsychotics with prophylactic for EPR aim, were prescribed a THF corrector at a dose of 0.002 mg. With the development of EPR, its daily dose was increased every day and brought to the active relief dose (to the maximum of 0.012 mg). Its value was determined by clinical indications. EPR was assessed on days 0, 3, 7, 10, 14, 21 and 28 (from the first day they appeared in patient status until complete reduction).

The study was conducted as a prospective, comparative, naturalistic and was carried out in two groups of patients consisting of 40 people each. These groups were formed depending on the introduction of corrective ESR agents-only THF, or its combination with PA into the regimen of neuroleptic therapy. Group 1 (n = 40) included patients, who from the first day of the study and until its end, as an additional to antipsychotic therapy, received only THF as correctors for the prevention and correction of adverse ESR, starting with a daily dose of 0.002 mg on the 1st day of treatment with a gradual increase in a case of the development of EPR to the optimal relief (up to a maximum of 0.012 mg). Group 2 (n = 40) - all patients during the period of antipsychotic therapy, starting from the first day of treatment, also received a THF corrector in a daily dose of 0.002 for prevention of side EPR, but in combination with 0.9 mg PA daily. In a case of development of EPR, as in the 1st group, the dose of THF increased up to relief dose, while the daily dose of PA remained constant, regardless of changes in daily doses of THF during experimental course treatment.

In the formed groups of patients, no statistically significant differences were found for such indices as gender, average age of patients, diagnosis of the disease, total score for PANSS. During the study and assessment of its results, all clinical and psychometric indices in their dynamics in the 1st and 2nd groups of patients were compared with each other. The significance of differences between the obtained indices (p) was determined by the criterion of Student t.

Results and Discussion

In the treatment of acute psychotic conditions in patients with schizophrenia with antipsychotics of different generations, clinical improvement with remission by the 28th day of treatment was noticed in both groups. The dynamics of psychotic disorders according to

the PANSS assessment at days 0, 14 and 28 according to the indices of the mean total score of their intensity in the 1st and 2nd groups of patients was approximately the same and did not statistically differ: the mean total PANSS score in one patient from 0 to 28 days of assessment, respectively, varied from 80 to 58.5 and from 84.7 to 63.8.

During treatment, antipsychotic EPR developed in 76.25% of patients, at the same time in group 1, who received only THF for corrective purposes, EPR occurred in 35 (87.5%) of 40 patients, in group 2, where THF was prescribed in combination with 0.9 PA daily, ESR developed less frequently: in 25 (65%) of 40 patients (differences were significant, p = 0.05). Besides, in the 1st group, repeated episodes of EPR occurred in 40% of patients during treatment; in the 2nd group, repeated episodes of EPR were also less common: in 30.8% of patients. It should be noted, that in the process of antipsychotic and corrective therapy, side EPR did not develop in 12.5 and 35% of patients of the 1st and 2nd groups, respectively, i.e. almost 3 times more often, they were absent in patients of the 2nd group receiving THF in combination with 0.9 PA daily.

The established specificities of development and correction of neuroleptic EPR are consistent with the results of their assessment on the CGI-S scale: the total number of patients with EPR, observed on all days of therapy in the 1st group was equal to 109, in the 2nd group it was 82. Accordingly, the average number of patients with EPR for one day of therapy in the 1st and 2nd groups was 3.9 and 2.9 people, i.e. these indices in the 2nd group of patients were also almost 1.5 times less than in the 1st group.

According to the CGI scale for corrective monotherapy of THF (group 1) on the first day of the assessment, the number of patients with ESR was more than 1.5 times higher than the indices of group 2 patients, who received THF in combination with PA (12, 5% and 7.5%, respectively). Subsequently, the frequency of patients with EPR in the 1st group increased sequentially and by the 3rd and 7th days of the assessment became more than 5.5 times higher as compared to 1st day (up to 70%) and then slowly decreased by the 28th day, but remained at a higher level than on the first day: 22.5%. In the 2nd group, the number of patients with ESR, starting from the 3rd day of the assessment, also steadily increased, but with lower rates of frequency than in the 1st group; they reached their maximum frequency by the 21st day of treatment (up to 57.5%) and according to that day indices they were equated to the 1st group indices. However, after the 21st day, the frequency of patients with EPR in the 2nd group sharply reduced by the 28th day of assessment (up to 10%) and almost from the 25th day of therapy no signs of EPR in patients of the 2nd group were observed at all (differences in the days of assessment are significant at 5.0 and 0.1% levels) (Figure 1).

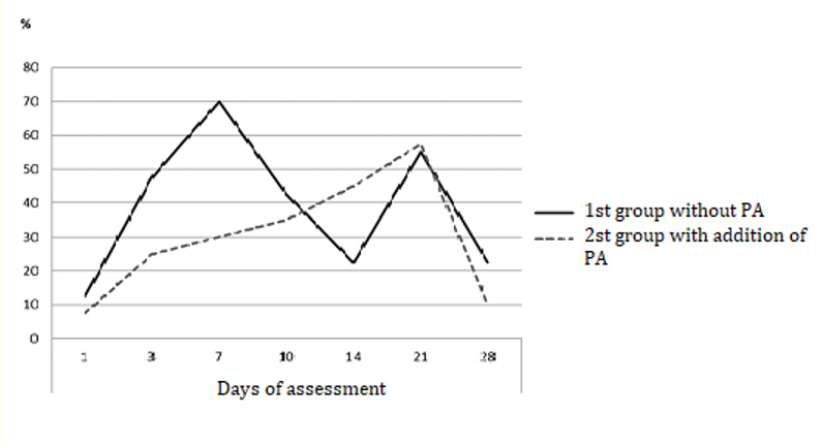

Figure 1: *Frequency dynamics (in % to the total number of patients) of ESR in patients of the 1st and 2nd groups with antipsychotic therapy according to CGI.*

The differences in the time of formation and reverse development of EPR in both groups of patients could rightly be associated with different values of the daily dose of received antipsychotics: in the 1st group of patients, when using only THF, EPR developed more often already on the 1st day of the prescription of still minimal initial daily doses of neuroleptics, whereas in the 2nd group of patients receiving THF in combination with PA, later (from the 3rd day of treatment) development of EPR occurred under conditions of taking already higher daily doses of antipsychotics and their increase in the following days.

Days of assessment

According to the regimen of antipsychotic therapy, they increased since the 1st up to 7th days from the minimum to the optimal therapeutic dose (or, accordingly, reduced at the stage of 21 - 28th days of course treatment). It was established, that in the 1st group of patients, an increase or decrease in the daily doses of antipsychotics in the indicated periods occurred in 81 and 43.1% of cases, respectively, in the 2nd group it took place in 75.4 and 33.3% of cases. These trends were more represented in patients treated with TH in comparison with those, who received ATN (there were no statistically significant differences between the indices in the groups).

For the entire period of the course treatment in the 1st group of patients in total 150 EPR signs were found and on average, 1 patient accounted for 4.3 EPR symptoms; in the 2nd group, these indices respectively amounted to 74 and 2.8 symptoms, i.e. they were 2 and 1.5 times less. In the 1st group of patients, the frequency of EPR signs on the 1st day of course therapy was almost 5 times higher than that in the 2nd group (12% versus 2.7% of signs), then it increased by the 7th the day of therapy and began to reduce only from the 10th day of treatment. In the 2nd group, the greatest frequency of EPR symptoms was observed only during the period from the 3rd to the 7th - 10th days of the assessment, but on the 7th day it was 1.5 times lower than the higher indices in the 1st group (24.7% versus 16.2% of symptoms) and remained relatively stable at this level until the 10th day. When assessing the 28th day of treatment, the frequency of EPR symptoms in the 1st group was more than twice higher than the indices in the 2nd group. At the same time in the 2nd group, as noted above, from the 25th day of the course EPR treatments were not observed at all (Table 1).

Type of antipsychotic	1st group of patients							Total	2nd group of patients							Total
	Valuation day								Valuation day							
	1st	3rd	7th	10th	14th	21st	28th		1st	3rd	7th	10th	14th	21st	28th	
TN																
abs.	1	9	6	7	4	3	-	30	2	8	9	7	6	2	-	34
%	0,7	6	4	4,7	2,7	2	-	20	2,7	10,8	12,2	9,4	8,1	2,7	-	45,9
ATN																
abs.	9	16	21	11	4	5	4	70	-	3	2	2	5	3	-	15
%	6	10,7	14	7,3	2,7	3,3	2,7	46,7	-	4,1	2,7	2,7	6,7	4,1	-	20,3
TN+ATN																
abs.	8	12	7	4	1	13	5	50	-	1	1	2	8	11	2	25
%	5,3	8	4,7	2,7	0,7	8,7	3,3	33,3	-	1,4	1,4	2,7	10,8	14,8	2,7	33,8
Total																
abs.	18	37	34	22	9	21	9	150	2	12	12	11	19	16	2	74
%	12	24,7	22,7	14,6	6	14	6	100	2,7	16,2	16,2	14,9	25,7	21,6	2,7	100

***Table 1**: Dynamics of the frequency of EPR symptoms during course therapy with antipsychotics of different generations in the 1st and 2nd groups of patients.*

Among the subtypes of antipsychotic EPR during course therapy, akathisia, tremors, hypo- and hyperkinesia, muscle rigidity and muscle dystonia were observed. A tendency was revealed toward a higher frequency of clinically more severe signs of ESR in the 2nd group of observations - akathisia - 31.1% (p = 0.05), muscular dystonia - 12.2%. But the therapeutic dynamics of the symptoms of akathisia and muscular dystonia in the 2nd group of patients was more favourable, than in the 1st one. In the 2nd group of patients the frequency of the symptom of akathisia among other signs of ESR during the treatment of THF and PA from the 1st to the 21st day of course therapy decreased from 50 to 25% and by the 28th day of treatment was already not present. In the 1st group, the frequency of akathisia, although initially it was less pronounced than in the 2nd group, from the 1st to the 28th day of treatment steadily increased from 16.7 to 33.4%. Besides in patients of the 2nd group the symptom of muscular dystonia was most pronounced among all the signs of ESR on the 3rd day of the course of treatment (41.7%), but by the 7th and 10th days of therapy it significantly reduced to 33, 3 and 9.1%, respectively and on the 14th - 28th days it was no longer registered at all. In the 1st group the symptom of muscular dystonia among other signs of EPR on the 1st day of treatment had an insignificant frequency of 5.6%, although on next days of the assessment its frequency increased to 11.1% and remained at that level up to the 28th day of therapy.

In the 2nd group of subjects the severity of side-effects in overall, determined by the UKU scale, was also higher than in the 1st group: the average severity score of one EPR sign was 1.5 and 1.2 points, respectively. At the same time it should be taken into account, that 46% of patients of the 2nd group were on monotherapy with TN, which are prone to a greater degree than ATN to develop neurological side effects. From all the number of ESR symptoms in the 1st group, 46.7% developed when taking ATN, which was almost twice more often than in patients of the 2nd group (20.3%) and during the treatment with TN ESR signs in the 1st group were observed 2.3 times less than in group 2 (20% versus 45.9%, respectively; p < 0.01). In addition, the previously established dependence of the ESR severity indices on the dynamics of the daily dose of antipsychotics in the prescribed course of treatment was revealed (Figure 2).

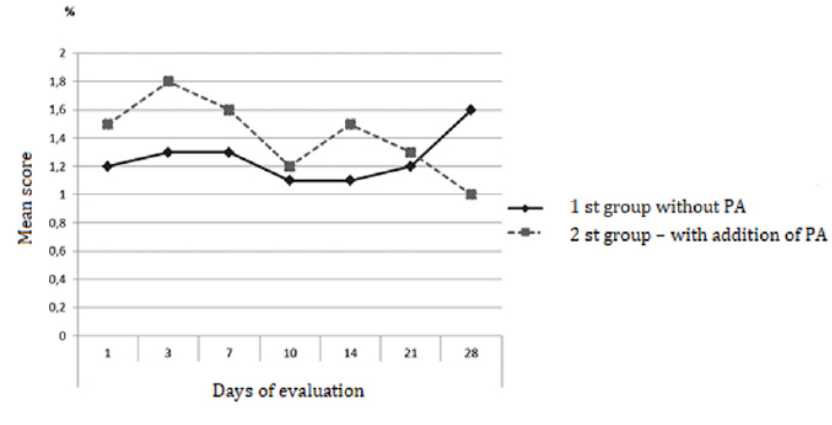

Figure 2: *The dynamics of ESR severity during neuroleptic therapy in patients of the 1st and 2nd groups (according to the mean UKU score).*

There were differences in the number of patients, who did not develop ESR during the treatment with different generations of antipsychotics: in group 1, ESR was absent in 28.6% of patients who received ATN and in 5.6% when treated with TH + ATN. In group 2, among patients treated with ATN and TH + ATN, ESR were not observed equally often, respectively in 41.2 and 45.5%. In addition, only in the 2nd group the patients did not have EPR 16.7% during the treatment with TN. It is noteworthy that among the patients of the 1st group treated

with TN all of them developed ESR (p = 0.01 only for ATN). Thus, only in the 2nd group of patients the prophylactic effect of THF in combination with PA in respect of ESR more often manifested itself in conditions of prescribing TN, which, as is known, had a more pronounced development of side effects, than ATN.

As can be seen from the table 1, depending on the type of antipsychotic therapy received, differences in the dynamics of the frequency of ESR signs were revealed. Despite the fact that patients of the 1st group in the overwhelming majority of cases received ATN both as monotherapy and in combination with TN, the frequency of EPR symptoms was higher than in the 2nd group, where TN were prescribed more often both in the form of monotherapy and in combination with ATN (daily differences from the 3rd to the 14th are highly significant, p = 0.05; 0.01; 0.001).

These data show that PA, introduced into the treatment regimen, enhances the corrective properties of THF, especially when exposed to more severe ESRs, characteristic of TN (Figure 3). The indices of the average duration of one sign of ESR from its occurrence to complete relief in both groups practically coincided and amounted to 2.01 and 2.05 days in the 1st and 2nd groups, respectively, however, the range of the number of days necessary for stopping ESR, in the 1st group varied from 1.5 to 3.6 and in the 2nd group - from 1 to 3, i.e. EPR correction was achieved faster.

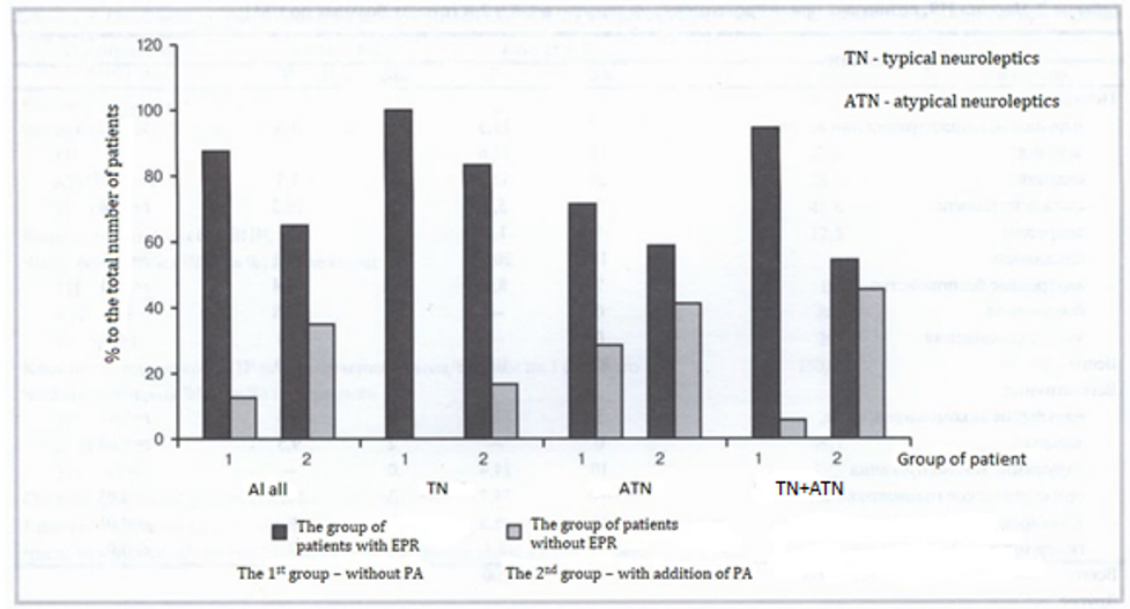

Figure 3: *The frequency of EPR in the 1st and 2nd groups of patients during the treatment with different generations of antipsychotics.*

At all the stages of treatment, in the 1st group, higher average daily doses of THF than in the 2nd group were used to stop EPR: their range of values was 4.7 - 6.9 and 4 - 6.2 mg respectively on different days of therapy. The ESR-stopping effect of THF in combination with PA in the 2nd group on each day of the assessment was achieved in whole with a lower increase than in the 1st group in the average daily dose of THF, at which the ESR initially developed both as on each day of therapy and in their total expression during the entire period of treatment. In the 1st group of observations, the stopping dose of THF as compared with the initial dose during the development of ESR increased by

89.3% and in the 2nd group it was lower by 77.4%. In the second group for EPR-stopping it was required not only less than in the 1st group of days (2.1 days versus 2.2 days, respectively), but also a smaller increase in the dose of THF ($p = 0.001$). The proportion of the initial total dose of THF, at which ESR developed, in respect of stopping ESR total dose in the 1st group was smaller than in the 2nd one and amounted to 52.6% versus 56.1%. For the correction of antipsychotic EPR in the 1st group, the average daily dose of THF for one patient was 4.9 mg; in the 2nd group receiving THF in combination with PA it was 4 mg, i.e. 1.2 times less. Based on these data, it was established, that the total amount of THF, consumed during the entire course of treatment in patients with ESR in the 1st group was greater than in the 2nd group (4786 mg versus 2942 mg). On average, for one patient of the 1st group, 136.7 mg of THF (68.4 tablets of 2 mg) were required for a 28-day course of complex treatment, in the 2nd group it was 113.2 mg (56.6 tablets of 0.002 mg).

In both groups, during the course of treatment with antipsychotics, AEs were observed, other than neurological, characterizing the generally tolerability of antipsychotic therapy. They occurred in 27 (in 67.5%) patients of the 1st group and in 16 (40%) patients of the 2nd group. According to the UKU scale, in the 1st and 2nd groups, a total of 131 and 50 symptoms of AE were respectively registered and on the average, 4.9 and 3.1 AE were recorded per patient, i.e. more than 1.5 times less AE developed with the combined use of THF with PA in patients of the 2nd group. As for frequency in different spheres of AE, no statistical differences were found between the groups, although in the 1st group psychic AEs prevailed (66.4% versus 58%) and other AEs (2.3% versus 0%) and vegetative AEs were more represented in the 2nd group (42% against 31.3%). According to the set of signs in the spheres of mental and vegetative AEs, the 1st and 2nd groups also did not differ much, but their frequency was not the same.

In general in the 1st group as to the frequency and duration of symptoms, asthenia and sedation dominated. In the 2nd group among AEs such symptoms as insomnia and internal anxiety prevailed. Only in patients of the 1st group, single other AEs were found, that is skin rash, itching (1 point of severity), weight gain in a patient with obesity (2 points), observed respectively on the 3rd, 7th and 21st days assessment (Table 2).

The dynamics of AE development in both groups had a tendency towards their highest frequency by the 3rd day of the course treatment (up to 44.3 and 34% of symptoms in the 1st and 2nd groups, respectively), but their further reduction from the 10th day of therapy more intensively occurred in the 1st group: by the 28th day in the 1st group, the frequency of AE became minimal. In the 2nd group, despite the initially lower frequency of AE, their reduction after the 7th day of the assessment was generally not so intense and the frequency of AE remained relatively constant and greater level, than in the 1st group, up to the 28th day. The severity of AEs in both groups was assessed primarily as mild by UKU - from 1 to 1.4 points. In this range AEs in the 2nd group as a whole were heavier than in the 1st, at all stages of the course treatment with antipsychotics, psychic AEs prevailed among them in severity (at a level of 1.4-1.7 points), which can also be associated with the prevalence of typical antipsychotics in the course of treatment of patients of the 2nd group.

Thus, the conducted study made it possible to establish, that the introduction of 0.9 mg of PA into the corrective treatment regimen of THF of neurological side effects of antipsychotic therapy in comparison to THF monotherapy allowed a 1.5-fold reduction in the rate of development of antipsychotic EPR in patients with acute schizophrenic psychoses is 3 times more likely to completely avoid their development and, on the whole, significantly improve the overall tolerability of antipsychotics (Table 3). With the introduction of PA into the treatment regimen, the total number of EPR symptoms, developing over the entire period of the course treatment with antipsychotics reduced 2 times and the average number of EPR symptoms in one patient in one day decreased more than 1.5 times. It was also established, that in patients, receiving in addition to THF PA from the first day of course therapy, the development of EPR was recorded for the first time at a later terms of course treatment with antipsychotics and only after increasing the daily dose of antipsychotics from a minimum of 1- day of treatment to optimally higher therapeutic doses in the next 3-7 days of therapy, while during monotherapy THF EPR were detected not only more often on fixed days of assessment, but also developed from the 1st day of treatment with minimal daily doses of neuroleptics. Also, with a decrease in daily doses of antipsychotics by the end of course therapy (days 21 - 28 of the assessment) in the 2nd group of

Signs of NO	1st group		2nd group		Credibility
	abc.	%	abc.	%	
Mental					
Impaired Concentration	17	19,5	1	3,5	t = 0,77
Asthenia	11	12,6	0	-	-
Sedation	28	32,2	1	3,5	p = 0,001
Memory Decline	5	5,7	3	10,3	t = 0,74
Depression	1	1,2	-	-	-
Drowsiness	18	20,7	7	24,1	t = 0,37
Inner Concern	7	8,1	12	41,4	p<0,01
Insomnia	0	-	4	13,8	-
Frequent Dreams	0	-	1	3,4	-
Total	87	100	29	100	-
Vegetative					
Disturbance of Accommodation	5	12,2	1	4,8	t = 1,07
Constipation	0	-	2	9,5	t = 1,60
Impaired Urination	10	24,4	0	-	-
Orthostatic Dizziness	14	34,2	3	14,3	p = 0,05
Tachycardia	11	26,8	8	38,1	p = 0,01
Hyperhidrosis	1	2,4	7	33,3	p = 0,01
Total	41	100	21	100	-
Other					
Skin Rash	1	33,4	0	-	-
Itchy Skin	1	33,3	0	-	-
Body Weight Gain	1	33,3	0	-	-
Total	3	100	0	-	-
Total	131	100	50	100	

Table 2: *The frequency of AEs arising from antipsychotic therapy in the 1st and 2nd groups of patients according to UKU.*

patients, receiving THF in combination with PA, the development of EPR was not observed as early as the 25th day of treatment and on THF monotherapy in the 1st group of patients, despite the decrease in daily doses of antipsychotics, EPRs were detected up to the 28th day of treatment and with a greater frequency than on the 1st day of antipsychotic administration.

PA introduced into the corrective treatment regimen, allowed to significantly improve the overall tolerance to antipsychotic therapy in terms of the frequency of other than neurological AE. According to the UKU score on monotherapy with THF, AEs were observed 1.7 times more often than in patients, receiving THF in combination with PA. During monotherapy of THF in patients, a total of 131 symptoms of AE were registered and on THF using PA, it was more than 2.5 times less. In addition, although the frequency and "set" of symptoms psychic and autonomous AEs in both groups of patients were presented approximately the same, however, in the 1st group of patients treated with

Indicator	1st group	2nd group
The number of patients with ESR, %	87,5	65
The number of patients with ESR (in%) during treatment		
TN	22,8	38,5
ATN	28,6	38,5
TN + ATN	48,6	23
The number of patients without ESR, %	12,5	35
The number of patients without ESR (in%) during treatment		
TN	0	14,3
ATN	80	50
TN + ATN	20	35,7
The number of signs of ESR per treatment course: amount/average for 1 patient	150/4,3	74/2,8
The number of patients without ESR (in%) during treatment		
TN	20	45,9
ATN	46,7	20,3
TN + ATN	33,3	33,8
The average duration of stopping EPR, days	2,1	1,9
The number of patients with other AEs, %	67,5	40
The number of signs of other AEs per course of treatment: amount /average per patient	131/4,9	5/3,1

Table 3: *Features of the formation of antipsychotic EPR in the corrective treatment of patients of the 1st and 2nd groups during the treatment with TN and ATN.*

THF monotherapy, symptoms of AE such as asthenia, sedation, autonomic disorders were detected significantly more frequently and in the 2nd group of patients, with the combination of THF with PA, significantly more frequent and more permanent were the symptoms of internal anxiety and insomnia.

The established priority corrective properties of PA with combined use of THF were detected more than twice more often in patients, taking typical antipsychotics, which, as is known, are more likely than ATN to develop neurological side effects, including the most pronounced ones. It is reasonable to assume that, for this reason, the indices of the severity of EPR symptoms during course therapy with antipsychotics in the group of patients, receiving THF in combination with PA were 1.3 times higher than the indices severity of ESR in patients, receiving "pure" THF. Patients, receiving PA, were also more likely to experience more severe clinical manifestations of ESR, such as akathisia and muscular dystonia. However, it should be noted, that 50% of patients without ESR, who received PA, were treated with TN as monotherapy, or in combination with ATN, whereas in the group of patients treated with THF alone, during monotherapy with typical neuroleptics, no cases without ESR were noticed.

During the treatment of predominantly TN in the group of patients, receiving PA, the value of the initial daily dose of THF, at which the EPR were first developed, was higher than with THF monotherapy (3.1 and 2.8 mg, respectively). But in their duration, the episodes of EPR from the beginning of their appearance to the day of their relief in patients, receiving PA, were almost 1.5 times shorter in absolute terms as compared to those, who received only THF. Although on average ESR-stopping dose of trihexyphenidyl in both groups of patients did not differ much (5.3 and 5.5 mg), in patients receiving PA, the stopping EPR effect was achieved with a quantitatively smaller increase

in the stopping dose of THF. In whole, when PA was introduced into the corrective treatment regimen for stopping ESR, a 1.2 times smaller amount of THF was required, which ensured the economic effect of the approved method of ESR correction.

Conclusion

The foregoing allows us to make a conclusion, that PA, administered daily in a dose of 0.9 mg in addition to THF during the corrective treatment of neuroleptic side neurological effects, that occur during the treatment of acute endogenous psychotic conditions, contributes to better tolerance to antipsychotic general therapy. When combined with THF, PA has a greater effect than THF on antipsychotic EPR, reduces their frequency and duration and reduces the daily need for a traditional corrector. PA has a greater neuroprotective effect on side ESR, promoting prevention and prophylaxis of the development of their symptoms, including the most severe ones, associated with the use of TN. The data obtained allow us to consider PA as an effective remedy for the neurological side effects of antipsychotic therapy, which has a pronounced neuroprotective effect on their formation and clinical manifestations and can be recommended as the drug of choice on the way to optimizing and improving methods for correction and prevention of side effects of antipsychotics, contributing to their better tolerance during course treatment and improving the quality of life of patients.

Conflict of Interest

There is no conflict of interest.

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