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Research Article

Comparative Analysis of Combination Therapy Regimens in Patients with Paranoid Schizophrenia with Non-Suicidal Auto aggression and Identified Signs of Resistance to Ongoing Neuroleptic Monotherapy

Kravchenko I.V [1*], Lvov N.N [2], Chizhikov I.I [2]

[1] Interdistrict Center for Medical Rehabilitation at Polyclinic N38, St. Petersburg, Russia.

[2] FKU "St. Petersburg Psychiatric Hospital of a Specialized Type with Intensive.

***Corresponding Author:** Kravchenko I.V., Interdistrict Center for Medical Rehabilitation at Polyclinic N38, St. Petersburg, Russia.

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Abstract

A comparative analysis of combination therapy regimens was carried out in patients with paranoid schizophrenia with NSAA and identified signs of resistance to ongoing neuroleptic monotherapy. In total, in the period from 2015 to 2022, 155 patients with paranoid schizophrenia with NSAA were studied as part of a multicenter randomized longitudinal study. It has been established that the first-line therapy regimen in this group of patients is a combined regimen of clozapine with haloperidol.

Introduction. The increase in the number of therapeutically resistant patients with paranoid schizophrenia with auto aggression remains one of the most pressing problems in psychiatry remains as the most common nosological unit [1,2,3]. At the same time, a large amount of research material has been accumulated on the factors and conditions that affect the formation of the state of resistance in such patients [4,5,6,7]. First of all, these include: a debut at an early age, an "erased" beginning, a continuous course, the dominance of negative symptoms in the structure of the pathological process, and the fading of the affective component. A special place among the clinical predictors of therapeutic resistance is occupied by psychopathic disorders with auto aggressive tendencies, traditionally considered within the framework of heboid states. At the same time, until recently, the main drug from the group of neuroleptics used to overcome resistance was clozapine [8,9,10,11,12,13]. In practice, up to 30% of patients remain intact to its action, which dictates the need for combination therapy [14,15,16]. This predetermines the search for new schemes for the use of medicinal drugs to solve this problem.

Key words: giant intracranial aneurysm; bypass; trapping; pediatric neurosurgery

Introduction

A total of 155 patients with paranoid schizophrenia with NSAA were studied in the period from 2015 to 2022 as part of a multicenter randomized longitudinal study. All patients were under inpatient treatment at the St. Petersburg Psychiatric Hospital of a specialized type with intensive observation, and the multidisciplinary medical center "Profimed" in St. Petersburg. Consent to participate in the study was confirmed either by the subjects themselves or by their legal representatives in writing. Consent obtained from the ethical committees of both institutions where the studies took place. All subjects were men and women aged 25 to 45 years. The average age of the subjects was 33.3±2.1 years. The average duration of a procedural disease was 17.5 ± 1.6 years. The type of flow of the schizophrenic process is continuous-progressive. Inclusion criteria are:

1) compliance of the diagnosis of paranoid schizophrenia with the criteria of the ICD-10 revision (F20.0);

2) the state of drug remission of schizophrenia itself, with signs of an increasing procedural personality defect;

3) the frequency of non-suicidal self-harm at least 5 times a month for three months prior to inclusion in the study;

4) the ineffectiveness of monotherapy with antipsychotics of different pharmacological groups, prescribed in an amount of at least two, with a duration of admission of three months each.

This condition was regarded as a manifestation of resistance to ongoing therapy. Non-inclusion criteria were:

1) the psychotic level of disorders before the moment of inclusion in the study;

2) auto-aggressive actions in the form of self-suffocation as a means of obtaining sexual satisfaction (asphyxiophilia); The article uses the terminology inherent in the domestic (Russian) school of psychiatry.

The definition of "non-suicidal auto-aggressive actions or "NSAA" 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 the intention to commit suicide. The main research method was clinical observation, the results of which were formulated in accordance with the national recommendations adopted in the Russian Federation and the criteria set out in the 10th revision of the International Classification of Diseases.

All patients were randomly distributed into 5 groups (Table1). The choice of preparations corresponded to the principle of their greatest distribution in practical work.

Distribution of subjects by comparison groups (number of patients). Table 1

International non-proprietary name of the medicinal product	Quantity sick
Clozapine	30
Haloperidol	30
Olanzapine	29
Clozapine + haloperiodol	35
Olanzapine + haloperiodol	31

The choice of dosages of drugs in the examined persons was carried out taking into account the severity of clinical and psychopathological experiences (Table 2)

Distribution of subjects by comparison groups (average daily doses, mg.) Table

International non-proprietary name of the medicinal product	Average daily doses (mg)
Clozapine	465±1,8
Haloperidol	6,7±0,8
Olanzapine	8,0±2,5
Clozapine + haloperiodol	425±2,8 г+ 5,4±1,0
Olanzapine + haloperiodol	8,6 ±0,6+ 5,4±1,0

Also, all subjects received 2 mg of clonazepam per day for a month. Additionally, 1000 mg per day of valproic acid was taken for a period of three months. The assessment of the mental state of the survey was carried out by clinical assessment at the time of inclusion in the study (week 1), at 12 and 24 weeks of the study. The clinical efficacy of therapy was determined by a comparative analysis of the frequency of 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, a brief psychiatric assessment scale and a scale for assessing social functioning were used. For statistical evaluation, Fisher's test and ANOVA analysis of variance were used. Clinical and psychopathological characteristics of the subjects were the following data. Heredity was psycho pathologically burdened in 98% of the subjects. Early development was distinguished by a tendency to excitable, hysteron form manifestations. The premorbid background was formed by hysteroid, emotionally unstable, excitable features at the level of accentuations. The period of initial manifestations fell on the age of 10-12 years, with the growth of protest forms of behavior, opposition. In the future, the clinical picture lost the features inherent in the pubertal crisis, supplemented by rudeness, unmotivated aggression against others, slovenliness, untidiness, in the absence of the possibility of any behavior correction. A distinctive feature of the subjects was a tendency to sexual deviations, the perverse nature of which was directed at close relatives. Outbursts of aggression were transformed into demonstratively blackmailing auto-aggressive behavior. If at first the patients showed

suicidal tendencies at the verbal level, then the nature of self-harm took on the form of complete non-suicidal self-harm (there were no tendencies associated with the desire to take one's own life; the choice of the method of application and localization of self-harm was of the most sparing nature). Patients sought to spend more time in asocial companies, massively became alcoholic, consumed drugs, and committed delinquent acts. The combination of emotional coldness, cruelty, disturbance of desires, episodes of massive consumption of surfactants contributed to the diagnosis of "heboid syndrome", "heboidophrenia", "protracted atypical pubertal crisis", "mixed disorder of behavior and emotions", psychopathic syndrome of residual organic origin, "organic personality disorder." In the prodromal period, anxiety, insomnia, suspicion, transient perceptual delusions, fragmentary delusions of persecution, and relationships increased, which coincided with the opinion of Russian studies on the stage-by-stage formation of paranoid schizophrenia with a psychopathic onset [17]. Clinical pathomorphosis consisted in slowing down the growth of deficient changes after 2-3 years from the moment of the steady nature of the course of the disease, consisting of stages of exacerbation of psychotic symptoms with reduced manifestations of the Kandinsky-Clerambault syndrome, followed by periods of unstable remission. The structure of the latter was dominated by persistent behavioral disorders with aggressive, auto-aggressive tendencies. At the same time, the patients were distinguished by unilateral activity, not revealing pronounced apato-abulic disorders under the usual conditions. Such changes met the criteria for procedural changes in the personality level or a psychopathic form of the defect [17]. The NSAA itself had a distinctly demonstratively blackmailing pattern, they were distinguished by careful planning, repetition and lack of criticism of their behavior, reflecting the pseudo-adaptation of the individual. In some patients, non-suicidal self-harm was of an autochthonous nature. In this case, NSAA was accompanied by short-term changes in the mental state, in which asthenia, apathy, disorganization of thinking, irritability, conflict, sleep disturbances increased for a period of two to three weeks, and protopathic anxiety appeared.

In this case, NSAA were applied without prior preparation, impulsively, once, without criticism of their behavior. The following could serve as the outcome of such states:

1) return to the initial state;

2) an increase in psychopathic manifestations that serve as a “facade” of an extended psychotic episode;

3) subacute course with a wave-like increase in psychopathic forms of response, fragmentary delusional ideas, transient perceptual deceptions, lasting up to 2-3 months. Thus, the consideration of NSAA took place in an integral connection with the leading psychopathological manifestations in this group of patients.

Research Results and Discussion

It was established that all neuroleptics declared in the study had a positive effect on the general mental state (Table N3). It was established that changes in the mental state, at the level of trends, according to the scale of the same name at the level of trends, occurred at the 12th week of the study in all comparison groups. and clozapine. Among the latest changes in the general mental state were statistically significant by the end of the study (24-week study)

Comparative analysis of the effectiveness of therapy according to the short assessment psychiatric scale (in points) Table 3

International non-proprietary name of the medicinal product	Stages of therapy evaluation		
	1- week	12- week	24- week
Clozapine	72,0	60,2 ***(F*** 1.2)	49,0 ***(F*** 1.47)
Haloperidol	69,1	63,0 (***F*** 1.1)	51.4 ***F*** 1.34
Olanzapine	72.7	64.1(F ***F*** 1.13)	51.4 ***F*** 1.41
Clozapine + haloperiodol	73.9	59.4 (***F***1.24)	46.1(***F*** 1.6) *
Olanzapine + haloperiodol	72,3	60.1 (***F***1.2)	48.4 (***F***1.49)

* p≤0,05

It was established that all antipsychotics declared in the study showed a positive effect on the level of social functioning (Table N 4). It was established that changes in the level of social functioning, at the level of trends, according to the scale of the same name at the level of trends, occurred at the 12th week of the study in all comparison groups. These positive changes in the level of social functioning remained at the level of trends until the end of the study in all subjects, except for the group receiving combined therapy with haloperidol and clozapine.

Comparative analysis of the effectiveness of therapy according to the social functioning assessment scale (in points). Table 4

International non-proprietary name of the medicinal product	Stages of therapy evaluation		
	1- week	12- week	24- week
Clozapine	24,5	32.3 (*F* 0.76)	40.1 (*F* 0.61)
Haloperidol	23,3	30.1 (*F* 0.77)	37.8 (*F* 0.62)
Olanzapine	24,1	31,2 (F 0.77)	36,4 (*F* 0.66)

Clozapine + haloperiodol	24.2	33,2 (*F* 1.25)	41.4 (*F* 1.71) *
Olanzapine + haloperiodol	24,8	*33.7 (F* 0.74)	39.2 (*F* 0.63)

* p≤0,05

Comparative analysis of effectiveness in relation to the frequency of NSAA Table 5

International non-proprietary name of the medicinal product	Stages of therapy evaluation (Frequency of NSAA per subject)	
	24 weeks - until the time of the study	24 weeks - after the moment of the study
Clozapine	6,6	3,6 *(F* 1.83) *
Haloperidol	6,8	3,9(*F*1.74) *
Olanzapine	5,8	*4,1 (F*1.41)
Clozapine + haloperiodol	6,7	2,1 **(***F*3.19) **
Olanzapine + haloperiodol	6,3	3,2 (*F* .97) *

* p≤0,05*, **p≤0,01

A positive correlation was found between changes in the Brief Psychiatric Rating Scale and the frequency of NSAA in the control groups at the end of the study. In patients taking clozapine, the f-ratio value is 5.9751. Thep-value is 0.025031. In patients treated with haloperidol, the f-ratio value is 992.41037.

Discussion

As part of a comparative analysis, all the claimed therapy regimens have confirmed their effectiveness. At the same time, differences in the effectiveness of therapy for different elements of the clinical picture of the studied individuals were revealed. It was found that the drugs of all comparison groups contributed to a decrease in the overall score on the Brief Psychiatric Evaluation Scale, the effectiveness of which decreased in the following order: “clozapine + haloperidol” < “olanzapine + haloperidol” < “clozapine < haloperidol>

1). The identified behavioral disorders are more related to the rank of positive disorders, emphasizing negative (deficit) disorders, forming a separate syndrome complex;

2). Positive disorders are most often associated with an increased level of dopamine, which is also involved in the motivational component of behavioral disorders, reinforcing the existing behavior pattern - in this case, non-suicidal auto-aggressive behavior;

3) the combined use of clozapine with haloperidol has the maximum synergy in relation to the normalization of dopamine levels in the examined patients, contributing to the effect of overcoming resistance.

Conclusions

The first-line therapy regimen in patients with paranoid schizophrenia with NSAA and identified signs of resistance to ongoing neuroleptic monotherapy is a combined regimen of clozapine with haloperidol.

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