Medical University
City of Pleven
Department of Psychiatry and Medical Psychology

Assoc. Prof. Dr. Georgi Panov Panov, Ph.D.

Comparative clinical-neurophysiological and a psychological evaluation of patients with resistant schizophrenia

Abstract

On a dissertation for obtaining a scientific degree
" Doctor of Science"

The scientific specialty
03.01.20 Psychiatry

Field of higher education
7. Health and sports

Professional direction
7.1 Medicine

Pleven, 2021

The dissertation is written on 489 pages and is illustrated with 137 tables and 74 figures, and ten appendices. Eight hundred forty-six literature sources are cited.

The dissertation is approved and aimed at defending the extended departmental council of the Department of Psychiatry and Medical Psychology at the Medical University, Pleven.

The public defence of the dissertation before the scientific jury will take place on 16.05.2022 year in the Auditorium of the Medical University, Pleven, 1 Kliment Ohridski Str., Pleven

The materials on the defence are available at the Scientific Department of the Medical University of Pleven, 1 Kliment Ohridski Str. And on the website of the Medical University of Pleven. **http://www.mu-pleven.bg**

Contents

Abbreviations used:

AM absolute power

BMI body mass index

BPRS short psychiatric rating scale

CPZ chlorpromazine

FFT fast Fourier transform

PANSS scale for assessment of positive and negative symptoms

AM absolute power

APM antipsychotic medications

DLR dissociative personality disorder

DOX dimensional obsessive-compulsive scale

DR dissociative disorder

DR dissociative disorders

DS depressive symptoms

CPQ short psychological questionnaire

CR clinical remission

FA main activity

OCD obsessive-compulsive disorder

ACS obsessive-compulsive symptoms

PAM is the first antipsychotic drug

RS Resistant schizophrenia

MD mixed dominance

AP anxiety symptoms

SCH Schizophrenia

SD schizophrenic disorder

SPS short psychopathology scale

Introduction

Schizophrenia is a severe mental disorder that affects how a person thinks, feels, perceives the world around them and reacts with a change in behaviour that corresponds to these perceptions. These are fundamental and combined disorders of thinking and perception associated with the effect that is either inappropriate or dull. Clarity of consciousness and intellectual ability are usually preserved, and cognitive gradient changes may be observed in some patients over time. These changes affect the essential functions that give a healthy person a sense of individuality and independence. That is why patients with schizophrenia look like they have lost touch with reality. These changes lead to significant distress for themselves, their families and relatives / ICD, 10 /.

Like any disease, psychiatry uses different therapeutic strategies to normalise deviations in the thought process, the perceptual sphere and affect. In medicine in general, we can say that there is no disease whose treatment can be carried out efficiently and without problems. In medical science, the categorical model is used to classify diseases by certain features into groups in specific nosological units. Despite the "generalising" nature of the diagnostic process according to these specific criteria and symptoms related to a certain prognosis, the individuality of "his majesty" the patient remains in the essence of the treatment. It is characterised by a unique genome that has undergone the transformation of epigenetic influences in its life cycle and is "chained" in various social relationships with concomitant successes and failures in life, modelling its individuality.

The unified nature of the diagnostic process is the basis of the unified approach in therapy with the use of drugs following a specific conceptual model / in the case - of the dopamine hypothesis /. When we talk about the treatment of schizophrenia, we can talk about the treatment in general, but when we take it to the individual patient, there is a different degree of effectiveness, not the same therapeutic response, different dose ranges of drugs used derivable from all this. Different prognosis of the disease The patient's first symptoms cannot consistently recognise the prognosis of the schizophrenic process. In treatment, patients are usually observed with an excellent response to symptoms with those with no effect of therapy and progressive worsening of symptoms over time. In general, we can apply the principle of continuum in this case: from patients with a perfect and

rapid effect of treatment to patients with the development of refractoriness, disease progression and the formation of severe social deficits. What are the differences and traits that make the patient resistant to therapy with the progressive development of deficits in different areas of social functioning?

The present study aims to establish the differences between patients with the achieved effect of treatment and those with registered resistance to it. When looking for differences, we have tried to look at them in different directions and look comprehensively at the problem of resistance. We have attempted to derive the factors associated with the highest probability of refractoriness by ranking them in importance, time of manifestation and interdependence with statistical methods. Recognition and evaluation are the basis for seeking timely and comprehensive interventions to prevent disease progression by forming a gradient of social and intellectual deficits over time.

CHAPTER ONE: OVERVIEW. The analysis of all sections of the literature review gives us grounds for the following conclusions

1. No data were found in the available literature to compare the anthropometric data/weight of patients, BMI / with the achieved effect of the antipsychotic therapy and those with resistance to it.

2. The conclusions of the conducted studies analysing the habit of patients with schizophrenia are inconsistent. In general, they show a prevalence of patients with an asthenic habit, especially those with early onset of the disease. There are no comparative observations between patients with resistance to treatment and those with a good effect on schizophrenic symptoms and resocialization.

3. The onset of the schizophrenia process can begin in different ways (acute, under acute, gradient, and with a long prodromal period) and different age groups. The period during which changes in behaviour and perception were registered but no treatment was started turned out to be important in prognosis. No study has been performed that indicates a relationship between the duration of symptoms of the disorder before treatment and the effectiveness of therapy.

4. No comparative study has been performed on the age of onset psychosis and the relationship with resistance to treatment.

5. The assessment of depressive symptoms in patients with schizophrenia showed that these symptoms are common, and there is no consensus on their relationship with the prognosis and effectiveness of treatment. Data from the literature are contradictory, citing bipolar views: from a relationship with a better prognosis to one with treatment resistance. There is no comparative analysis of their presence in resistant schizophrenia and remission patients.

6. Anxiety is an essential clinical phenomenon, and we have not found a study comparing its severity in patients with refractory symptoms and those with recovery from treatment.

7. From the review it is clear that dissociative phenomena have emerged as an evolution of psychological and corresponding neuronal and biochemical mechanisms in order to build adaptive behaviour. Dissociative phenomena are a clinical reality and are highly found in patients with schizophrenia. The literature review suggests that the overlap of symptoms in dissociative disorders and schizophrenia is often the basis for misdiagnosis and treatment. From the assessment

we found that a comparative study of the severity of dissociative phenomena in patients with resistant schizophrenia and those with treatment effect.

8. According to the literature, some patients with schizophrenia have used or are using alcohol, cannabis and other psychoactive substances. In the available literature, no correlation has been made between symptom resistance and associated behaviour with psychoactive substances.

9. In patients with schizophrenia, changes in circadian rhythms are observed. These changes affect both the duration and latency of sleep and its architecture. Changes in the duration and manifestation of the individual phases of sleep in its structure have been registered. Currently, there are no studies to indicate the relationship between the identified changes in sleep performance as latency and duration and as features of architecture and hypnogram in patients with resistance and those in remission.

10. Many studies have conflicting results related to the lateralisation of brain processes in patients with schizophrenia. Most point to the predominance of left-handed people and those with mixed dominance in patients with schizophrenia. No study has been conducted on the relationship between lateralisation of brain processes and the effect of treatment using regulated criteria for assessing resistance in patients with schizophrenia.

11. The analysis of the results of studies on the relationship between psychotic symptoms and blood cortisol levels is mixed. Various studies have been performed on patients with schizophrenia with no consistent results. Studies have been performed to compare patients with high-risk schizophrenia and healthy controls, with no comparative analysis of cortisol levels and daily dynamics in patients with resistant schizophrenia and those with clinical remission.

12. Gender identity research shows that schizophrenia is associated with gender identity disorders and reduces male-related traits among men and women. There was no analysis of the difference in gender identity assessment in patients with resistant schizophrenia compared to those who achieved treatment outcomes.

13. Patients with schizophrenia have high comorbidity with obsessive-compulsive symptoms. They were conducted with various observations related to the analysis of this co-conditionality. The results are contradictory and mixed. However, they do not provide information on the relationship between obsessive-compulsive symptoms, the likelihood of resistance, and the presence of resistance.

14. No analysis was made of the therapeutic interventions used to evaluate the effectiveness of the first antipsychotic drug used in patients with schizophrenia and the relationship between this effectiveness at the start of treatment with resistance.

15. No analysis was made of the period of the first two weeks of therapy on the future development of the schizophrenic process.

16. Changes in routine EEG in patients with schizophrenia are inhomogeneous. There are correlations between the characteristics of EEG changes and the presence of a psychotic process. No lasting EEG patterns have been found to suggest possible resistance to the psychotic process. No isolated and accurate analyses of the individual structuring of the EEG components have been performed. Diffuse changes, focal changes and their lateralisation are not compared separately with the prognosis of the disease, i.e. resistant or remitting form of schizophrenia associated with these changes.

17. The registration of paroxysmal activity in the EEG is not unique to patients with epilepsy. It is a characteristic of patients with brain dysfunction associated with neurophysiological abnormalities based on a specific biochemical imbalance. No analysis has been performed for epileptiform paroxysmal episodes in patients with psychosis, and no association has been established with the effectiveness of therapy.

18. Many studies and quantitative analyses/absolute and relative capacities / have been conducted on the bioelectrical signals registered by EEG examination. These studies do not compare patients with schizophrenia who have the effect of treatment and those with established resistance to it. Some analyses compare patients with the first episode of schizophrenia and those with chronic schizophrenia. Chronic schizophrenia can be relapsing, and between attacks, patients may be in remission, in which case they would not meet the definition of resistance.

19. No studies have been performed on the average peak frequencies for the individual frequency spectra in the EEG in patients with resistant symptoms. We did not find a study to show the relationship between split alpha frequency as a factor of clinical significance in patients with schizophrenia.

These conclusions give us reason to conduct a comprehensive comparative assessment of patients with resistance to treatment and those with remission and to identify the factors determining the differences between them.

The expected effect of our study is to build an algorithm and conceptual model for the early detection of resistant patients, which would justify the search for optimal. In some cases, we will allow ourselves to use the term "aggressive" therapy to achieve remission and prevention of early disability in them.

CHAPTER TWO: PURPOSE AND TASKS

OBJECTIVE: 1. To identify the differences in the course of schizophrenic disorders in patients with symptoms resistant to therapy and those with clinical remission, deriving the factors and their significance associated with resistance.

2. To build a conceptual model of the patient with resistant schizophrenia

To achieve these goals, we set ourselves the following **tasks:**

1. To diagnose patients with resistant schizophrenic symptoms and those with established clinical remission after conducting complex clinical, psychological and neurophysiological studies.

2. The clinical trial shall establish:
- Age of onset of schizophrenia
- Anthropometric characteristics / gender, height, BMI, weight /
- Level of education / primary, secondary, higher, doctor /
- The duration of untreated symptoms
- The duration of the schizophrenic process
- Assessment of clinical scales: positive, negative and disorganised symptoms.

- Measurement of cortisol / in the morning and at 4 pm /
- Assessment of habits / alcohol, tobacco, cannabis, psychostimulants /
- Anxiety assessment
- Assessment of concomitant affective symptoms
- Differences in the scale for dissociative symptoms
- Assessment of active attention
- Memory and its characteristics / fixation, retention and reproduction and memory curve /
- Accompanying obsessive-compulsive symptoms

3. Analysis of sleep and its phases
- sleep latency
- the presence of nightmares
- Duration of sleep
- Number of awakenings at night
- Duration of SWS

- Duration of the REM phase
- Characteristics of the hypnogram
4. Analysis of the lateralisation of brain processes
5. Assessment of the acceptance of gender identity / role / with the Bem scale.
6. Conducting neurophysiological tests - Standard EEG / electroencephalography / with analysis of diffuse changes, focal and paroxysmal
7. To make a quantitative assessment with spectral analysis of the dynamics of the electroencephalographic finding.
5.1 Estimation of the absolute power of the individual frequency spectra
5.2 Estimation of the relative power of the individual frequency spectra
5.3 Analysis of the average peak spectral frequencies for the individual ranges

8. To conduct neuroimaging tests / traffic police, MRI /
9. To develop an algorithm for the differences in patients with resistance to treatment and those in clinical remission.
10. Assessment of the degree of social functioning respectively / social dysfunction /.

CHAPTER THREE: MATERIAL AND METHODS

A / CLINICAL CONTINGENT

The clinical contingent includes 105 patients with schizophrenia, of which 60 achieved clinical remission and 45 with established resistance to therapy. Patients were prospectively studied and observed from October 2016 to July 2021. In connection with the specifics of the present study/analysis of patients with resistance to therapy / an in-depth study was conducted in retrospect of the drug regimens used in previous outpatient or clinical observations. Additional anamnesis data from the relatives of the patients regarding both adherence to therapy and to describe the characteristic patterns of behaviour in patients associated with the treatment plan were used.

The selection of patients included in the study took into account the possibility of good communication and accurate description of their own experiences, feelings, emotions, and dynamics over time.

The clinical diagnosis is based on detailed anamnesis of patients, their relatives, accompanying documentation, clinical examination / most of which was conducted under active observation in a hospital setting /, the results of neurophysiological and neuroimaging methods, as well as psychological tests.

Place for conducting the research - Psychiatric Clinic of UMHAT-AD, "Prof. Dr Stoyan Kirkovich". Mainly patients from Stara Zagora were covered, but some patients from other areas were also followed.

Criteria for inclusion of patients with resistant schizophrenia / RS /

1. Diagnosed with schizophrenia in patients who meet the diagnostic criteria of ICD 10 and DSM5 / following the future requirements of ICD 11 /
2. Despite the use of different therapeutic strategies when using more than two-drug regimens with antipsychotics in the required dose (600 mg chlorpromazine equivalents), and in some cases when using clozapine in the maximum tolerated and tolerable dose regimen.
3. Monitoring period of at least three months/consensus requirement for resistance verification is at least 12 weeks, i.e. three months / during which, despite changes in medication regimens, both mono and polytherapy with various antipsychotics and combinations, no resolution of schizophrenic symptoms have been achieved / we use the term schizophrenic since the term "psychotic" usually refers to a narrower range of positive symptoms.
4. Patients during the observation and for the period outside it in family and social environment have pronounced social dysfunction and impaired social adaptation/requirement both in the diagnostic assessment tool / DSM5 / and in the consensus for resistance in patients with schizophrenia.
5. Regular clinical and paraclinical observations of the patient's condition for the observed period were performed.
6. Normal values of MMSI
7. The condition of the patients allows their assistance in conducting neurophysiological tests / there is the necessary assistance and attention for a complete examination /.
8. Age between 20 and 60 years.

Criteria for inclusion of patients with schizophrenic disorder in clinical remission.

1. Diagnosed with schizophrenia in patients who meet the diagnostic criteria of ICD 10 and DSM5 / following the future requirements of ICD 11 /.
2. Achieved full resolution of schizophrenic symptoms in patients with schizophrenia using antipsychotic drugs tailored to the individual characteristics of patients.
3. Period of observation of at least six months during which the patient has a regular intake of therapy and during which no relapse of psychotic experiences has been established.
4. Preserved social activity and behavioural plasticity allowing leading a socially active lifestyle comparable to the premorbid level of functionality.
5. Regular clinical and paraclinical observations of the patient's condition for the observed period were performed.
6. Normal MMSI values
7. Patients have the necessary level of assistance in conducting neurophysiological tests / there is the necessary assistance and attention for a complete examination /.
8. Age between 20 and 60 years.

Excluding criteria for both groups of patients:

1. Oligophrenia / mental retardation /
2. Presence of severe somatic disease.
3. Invalidating and progressive diseases of the CNS
4. Severe traumatic CNS injuries
5. Pronounced personality change, dominating the clinical picture
6. Established data on alcohol abuse
7. Abuse and or dependence on psychoactive substances
8. Education lower than 8th grade
9. Insufficient knowledge of the Bulgarian language
10. First psychotic episode / except in the absence of resistance /

The first psychotic episode is associated with a relatively low rate of development of resistant psychotic symptoms (about 10%). Most of these patients would develop resistance in subsequent psychotic attacks, so we decided to exclude them since it is difficult to judge after this first episode which of them will develop future resistance and which will not.

B / METHODS

1. Clinical methods

History, somatic, neurological and mental status.

1.1 History of the patient and his relatives about the onset of psychotic symptoms, age, mode of occurrence, provoking factors, dynamics, changes in behaviour, the presence of premorbid features, the effect of previous treatment, the impact of symptoms on social behaviour and communication.
1.2 The generally accepted physical examination by systems
1.3 Neurological status
1.4 Detailed assessment of the mental status / a structured interview was conducted according to the diagnostic tools of ICD 10 and DSM 5 /.

2. Neurophysiological methods

2.1 Standard survey. Electroencephalography was performed with a 24-channel EEG recording from Neurosoft. In the process of recording the records, the electrodes are placed following the requirements of the system 10-20 and are connected to longitudinal, transverse and combined programs/installations/. Standard tests for activation with eye-opening and closing, photo-stimulation and hyperventilation were performed. EEG recordings were assessed visually according to generally accepted criteria, and the individual indicators: essential activity, diffuse changes, focal and paroxysmal were introduced into a standardised diagnostic map.
2.2 Quantitative methods of analysis. An analysis of the absolute power, registered with Neurosoft software package with analyses of the spectra and cartograms of the patient for the individual frequency spectra /FFT/. An analysis of the relative/percentage power / for the individual frequency spectra, individually and in groups. Quantitative analysis methods were performed on encephalographic

recording epochs lasting 2 to 20 seconds. The epochs are pre-selected to ignore the artefacts, comparing similar epochs from the functional.

3. Neuroimaging methods

Native CATs were performed in all patients, and, if necessary, a contrast-enhanced study was performed. MRI was also used in many patients with clinical suspicions to detect discrete brain lesions and hippocampal changes.

4. Laboratory methods

All patients underwent clinical laboratory compliance following drug therapy, including haemoglobin, hematocrit, erythrocytes, leukocytes, DCC, platelets, glucose, haemoglobin, AST, ALT, GGT, alkaline phosphatase, electrolyte, electrolyte, creatinine possibly also measuring some medications in the blood serum. In connection with the task set in the present study, cortisol was also tested in patients /at seven in the morning and 16.00 in the afternoon /.

5. Sleep research

In order to assess the structure of sleep and its phases, it is used by the recently established and significantly simplified method of photoplethysmography. Patients in the period to reach a relative clinical plateau were analysed, which would allow their comparison concerning the leading indicators in the sleep phases: SWS, REM and characteristics of the hypnogram. The percentages of the individual phases were estimated, and an analysis of their distribution during the night was made.

6. Psychological methods

Research methodology:

The psychological set used in the present study includes scales related to the assessment of positive, negative and disorganised symptoms, cognitive functions, depression, anxiety, dissociation, lateralisation of brain functions and assessment of gender identification.

1. PANSS

The Positive and Negative Syndrome Scale (PANSS) is a medical scale used to measure the severity of symptoms in patients with schizophrenia. It was published in 1987 by Stanley Kay, Louis Opler and Abraham Fishbein. It is widely used in the study of antipsychotic therapy. The scale is known as the "gold

standard" that all assessments of psychotic behavioural disorders must follow. (Opler LA, Mark GA et al 2017)

2. Dissociative Experience Rating Scale (DES II)

Dissociation is the lack of standard integration of thoughts, feelings and experiences in the flow of consciousness and memory. Dissociation occurs to some extent in normal individuals and is thought to be more common in people with severe mental illness. The Dissociative Experience Scale (DES) has been developed to offer a tool for the reliable measurement of dissociation in normal and clinical populations. The scale elements were developed with the help of clinical data and interviews, scales involving memory loss, and consultations with dissociation experts. A pilot test was conducted to refine the formulation and shape of the scale. The scale is a 28-point self-report questionnaire. The average value of all results from items varies from 0 to 100 and is called the DES result.

3. Hamilton Depression Rating Scale

The Hamilton Depression Rating Scale (HRSD), also known as the Hamilton Depression Rating Scale (HDRS), abbreviated HAM-D, is a multi-item questionnaire used to indicate depression and as a guide to assessing recovery. (Hedlund JL, Viewig BW 1979) Max Hamilton first published the rock in 1960 (Hamilton M, 1960) and reworked it in 1966 (Hamilton M, 1966) 1967 (Hamilton M, 1967). 1969, (Hamilton M, 1969) and 1980 (Hamilton, M, 1980). The questionnaire is designed for adults and assesses the severity of their depression by probing mood, guilt, suicidal thoughts, insomnia, agitation or lagging, anxiety, weight loss and somatic symptoms.

The original 1960 version contained 17 elements (HDRS-17), but four other questions that were not added to the overall result were used to provide additional clinical information. Each element of the questionnaire is evaluated on a scale of 3 or 5 points, depending on the element, and the overall result is compared with the corresponding descriptor.

4. Hamilton Anxiety Rating Scale

HAM-A was one of the first rating scales developed to measure the severity of anxiety symptoms and is still widely used in clinical and research settings. The scale consists of 14 elements, each defined by a series of symptoms, and measures mental anxiety (anxiety and psychological distress) and somatic

anxiety (physical complaints related to anxiety). Although HAM-A is widely used as a measure of measurement in clinical trials and clinical practice, it has been criticised for its difficulty distinguishing between anxiolytic and antidepressant effects and somatic anxiety versus somatic side effects. However, reported levels of reliability among scale assessors to be acceptable in practice (Maier W et al., 1988; Borkovec T, Costello E 1993; Hamilton M. 1959;).

5. Test for assessment of cognitive impairment

Test with ten words / according to Luria /. The methodology includes stimulus material, which is usually developed by the experimenter himself and is a set of 10 words that should be popular, and short (1-2 syllables and should not be close in meaning). The three main memory processes are studied: a / memorisation (fixation), b / reproduction (reproduction) and c / retention (retention).

An assessment of the memory curve was made, giving information about the state of active attention.

6. Sandra Bem Gender Role Rating Scale

The theory of gender was officially introduced by Sandra Bem in 1981 as a cognitive theory to explain how individuals determine their gender in society and how related characteristics are maintained and passed on to other members of culture (Bem, S. L. 1981). Gender-related information is transmitted primarily through society through specific frameworks, schemes, or information networks that allow it to be more easily assimilated than others. Bem argues that there are individual differences in the way people perceive and "play" these gender patterns. These differences are manifested by how individuals are typed by gender.

The most enduring contribution in the field is the attempt to quantify the Bem Sex-Role scale. Originally developed as a tool for identifying gender-typed individuals, many researchers have used the measure to address other components of gender, including the endorsement of gender stereotypes, and as a measure of masculinity/femininity (Hoffman, R. M., & Borders, L. D. A. 2001).

Bem herself admitted that she was ill-prepared to develop the Bem Sex-Role scale inventory and never expected it to be as widely used today (Bem, S. L. 2001).

Bem herself admitted that she was ill-prepared to develop the Bem Sex-Role scale inventory and never expected it to be as widely used today (Bem, S. L. 2001).

We used the short version of the Bem scale of 30 questions in the study with five possible answers.

7. Scale for measuring the lateralisation of brain processes

The Edinburgh Dominance Rating Scale (left, right or mixed) is used to assess the dominance of a person's right or left hand in daily activities, sometimes called lateralisation. The inventory can be used by an observer assessing the person or in a self-assessment. The latter method tends to be less reliable due to excessive attribution of tasks to the dominant hand.

The Edinburgh Inventory of Dominance was published in 1971 by Richard Charles Oldfield (Oldfield, RC, 1971) and used in various scientific studies (Verdino, M; Dingman, S, 1998; Knecht, S; et al., 2000). As well as in popular literature (Wolman, David, 2006).

There are also questions concerning the use of the foot and assessment of the dominant eye (if only one eye needs to be used).

We decided to consider this problem in connection with the characteristics of the observed patients / it is not always possible to make an accurate registration when evaluating individual activities due to patient uncertainty / in a simpler version, namely: right-handed, left-handed and mixed lateralisation.

8. Scale for assessment of obsessive-compulsive symptoms

The Obsessive-Compulsive Scale (DOCS-Dimensional Obsessive-Compulsive Scale) is a 20-element self-assessment tool that assesses the severity of obsessive-compulsive disorder (OCD) symptoms in four empirically supported dimensions based on:

(a) pollution,
(b) liability for damage and errors,
(c) incompleteness / symmetry and
(d) unacceptable (taboo) thoughts. (Abramowitz, Jonathan S .; 2010)

The scale was developed in 2010 by a team of OQR experts led by Dr Jonathan Abramovich to improve existing OQR measures and improve the evaluation and

understanding of OQR. DOX contains four sub-scales (corresponding to the four dimensions of symptoms) that have been shown to have good reliability, validity, diagnostic sensitivity and sensitivity to the effects of treatment in different intercultural and multilingual settings (Kim, Hae Won; et al., 2013). ; Melli, Gabriele; Chiorri, et al. 2014; López-Solà, Clara; et al. 2014; flafsson, Ragnar P .; et al. 2013). As such, DOCS meets the needs of clinicians and researchers who want to measure current OCD symptoms or assess changes in symptoms over time (e.g., during treatment) (Overduin, Mathilde K .; et al. 2012).

9. Short psychopathological questionnaire (CPV)

MMPI is a test developed and used for decades in clinical practice. Despite the opportunities it provides with a more detailed assessment of the personal profile of the person/patient/, it has one significant drawback, and it is related on the one hand to its volume and, on the other hand, to the time required for its preparation. The comprehension of the 566 statements of the test and the realisation of an alternative answer place very high demands on the subjects, especially when it comes to psychiatric patients. Therefore, from the creation of the test until today, the efforts to create reduced test forms remain, preserving its diagnostic scope and validity.

The test is an abbreviated version of the Minnesota Test (MMRI). "Short Psychopathological Questionnaire (CPV) (adaptation - Mechkov, 1976). It consists of 11 scales: 3 scales for validity - false (L), credibility (F), corrective (K)) and eight clinical scales (hypochondria, depression, hysteria, psychopathy, paranoia, psychoresponsia, schizophrenia and hypomania).
The CPV test technique is similar to that of MMPI.

10. Statistical methods

All data from the above methods are plotted in a developed map and a database for computer analysis.
The obtained results are processed with the IBM SPSS version 26 (2019) statistical software package. The following statistical analyses were used:

1. Non-parametric methods of analysis - X2 test to test hypotheses.
2. Correlation analysis by measuring the correlation coefficients of Pierson and Cramer.
3. Student's T-criteria for comparing averages.
4. Student's T-criteria for comparing% in small samples.

5. Analysis of variance to study the influence of certain factors on the indicators related to the study.

6. Discriminant analysis was used to determine the most critical factors related to the resistance of the symptoms (influencing the differences between the two groups of patients studied).

7. Comparison of proportions (percentages). When comparing two proportions in the frequency distribution tables, the Student's T-test is used, and for less than 0.25, the Yates correction for continuity is used (Statistica textbook, 1995).

Graphical analysis was also used to compare and illustrate statistical information.

CHAPTER FOUR: PERSONAL STUDIES AND RESULTS

The term resistant schizophrenia refers to that part of patients with schizophrenia who remain with psychotic symptoms despite the implementation of modern drug regimens as both mono- and polytherapy to be effectively affected by treatment. Thus, using the term resistance, the patient population is divided into two groups: a) patients in remission without psychotic symptoms with preserved and restored social functioning and b) patients with persistent psychotic symptoms who, despite the use of different therapeutic strategies, remission and remain with a functional deficit leading to impaired social adaptation.

Naturally, the question arises whether we have used all available opportunities to try to update the persistent psychotic production in our patients.

To achieve this goal, we have used all possible antipsychotics available in our country in the maximum allowable and tolerable dose range relative (according to the requirements of the consensus on the issue of resistance to schizophrenia) to chlorpromazine equivalents over 600 mg. We used equivalent doses of over 800 mg per day in our study. In all patients, the follow-up period was more than 12 weeks, most of whom were followed up in a hospital to monitor their condition and ensure adherence to therapy. The information on the condition of the patients in the home environment was controlled both as a therapy and as a social commitment and the possibility of fulfilling sure public and individual commitments to assess the possibilities for building autonomy/requirement such as resistance assessment /.

All patients with resistant psychotic symptoms meet the requirements set by various authors and the requirements of the consensus opinion on the issue of resistance to schizophrenia in 2017.

This section presents the results of a comprehensive clinical, psychological and neurophysiological assessment of the differences between patients with resistant psychotic symptoms and those in clinical remission.

Of the 105 patients observed, meeting the included inclusion and exclusion criteria, it was found that 45 / 47.25% / of the patients have resistant psychotic symptoms, and 60 / 52.75% / are in remission.

Demographics

1. Gender

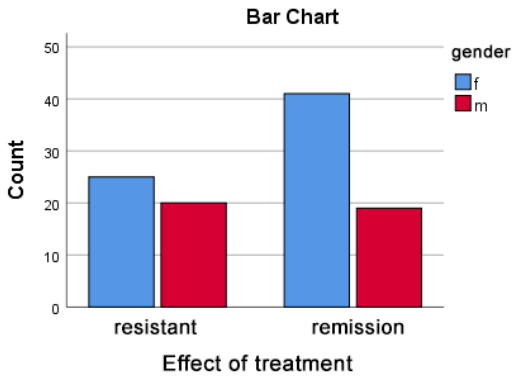
Of the observed contingent 66/69% / persons are female and 38 / 31.7% / are male. We observe a predominance of female patients. This fact can be viewed from the inclusion and exclusion criteria about the requirements related to education, level of intelligence, lack of progressive CNS diseases and the need for lack of pronounced personality change that has begun to dominate in the clinical picture of patients. These features are observed predominantly in males, which would not allow their inclusion and conduct a comparative study on the established criteria.

In patients with resistant schizophrenia it was found that the distribution by sex is as follows: 20 / 44.4% / of the patients are male and the remaining 25 / 55.6% / are female.

In the patients in remission the distribution by sex is: 41 / 68.3% / are female and 19 / 31.7 / are male.

In patients with resistant psychotic symptoms, there was a small (to insignificant) difference between the sexes in the sample, while in those in remission, we registered more than two differences in favour of females. Figure 1

FIG. 1 Comparative analysis of the distribution by sex and the effectiveness of therapy



Conclusion: Males are more likely to be resistant to treatment in patients with schizophrenia.

2. Education

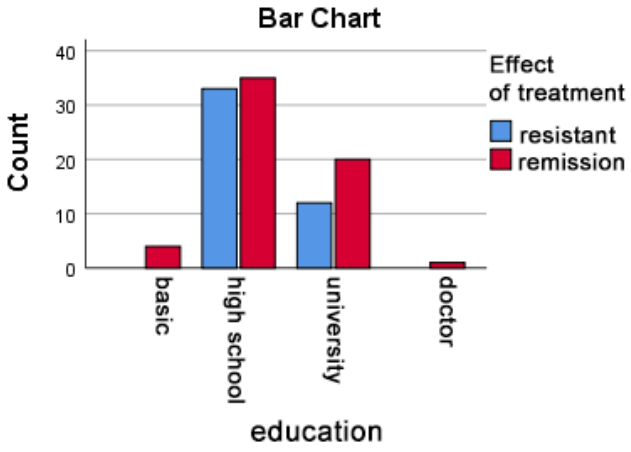
The assessment of the distribution of the educational level shows that out of all 105 patients, 4 have primary education, 68 have secondary education, 32 have higher education / in this group, we have included the persons with achieved bachelor's and master's degrees / and one patient with a doctor's degree.

Of the patients with RS, it was found that 33 / 73.3% / persons have secondary education and 12 / 26.7% / have higher education.

Of the patients in the CR - 4 / 6.7% / patients with primary, 36 / 58.3% / patients with secondary, 20 / 33.3% / patients with higher education and one patient / 1.7% / with education "Doctor."

It is noteworthy that patients with primary education and a doctorate are from the group of patients in the CR. Figure 2

Fig. 2. Influence of educational degree on the effect of treatment



Conclusion: The results show that the factor "education" cannot be deduced as influencing the probability of refractoriness.

Anthropometric data

3. Growth

The average height of the patients in the study was 168.55 cm, with a minimum height of 155 cm and a maximum of 191 cm.

The average height of females is 164.62, while the average height of males is 175.21 cm. These results are comparable to the results obtained from a survey in 2014 analysing the growth of individuals in Bulgaria. This analysis shows that the average height of females is 164.8, and that of males is 178.2. The result shows that in the patients we studied, no differences were observed compared to the data characteristic of the main population (NCD Risk Factor Collaboration (NCD-RisC, 2016).

In patients with RS, it was found that the average height was 170.11 cm with a standard deviation of 8,896, while in patients in remission, the average height was 167.38 cm and less standard deviation - 7,190 cm. Figure 3

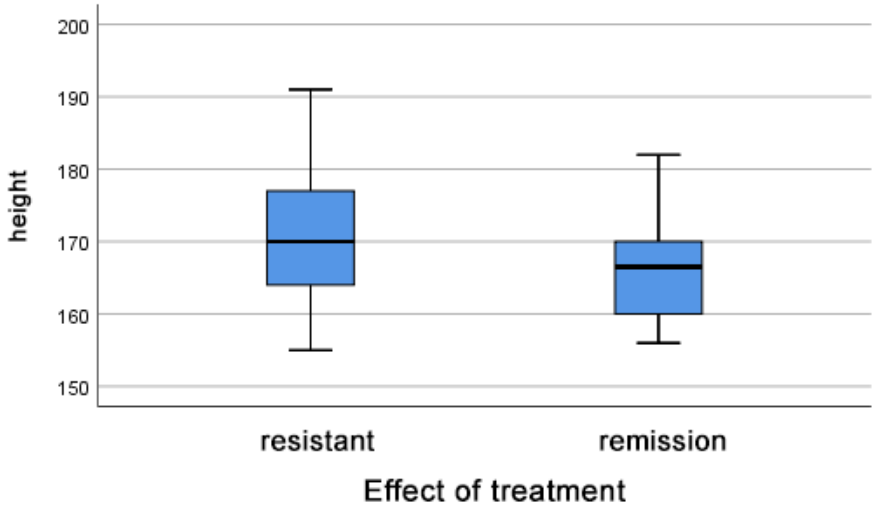


Fig. 3 Influence of growth on the effectiveness of treatment

Conclusion: There was no statistically significant difference in the growth of patients from the two groups.

4. Weight

The mean weight measured in all patients with schizophrenia was 76.10 kg. Their weight varies from the lowest 48 kg to the highest 124 kg. In the group of patients with resistant schizophrenia, the average weight was 76.09, and in the group of patients in remission, it was 76.12.

While in the group with resistance, the standard deviation is 14,998, in those with remission, it is 17,289. On the other hand, the minimum and maximum weight in patients with RS varies in a narrower range between 50 and 105 kg, while in those in remission, it is in a broader range - 48 and 124 kg, respectively.

The fact remains related to the weak trend for dynamics in body weight in resistant patients. An explanation for this phenomenon can be found in the accumulated data that weight gain is usually associated with treatment and is particularly pronounced in the first psychotic episode (Kinon BJ et al., 2005; Kahn RS et al. 2008; Citrome L et at., 2011). On the other hand, there is less adherence to treatment in resistant patients and the associated lower weight gain.

Conclusion: There is no difference in the average weight of patients between the two groups.

5. BMI / Body Mass Index / in both groups of patients

The analysis of the BMI in both groups of patients showed that in the group of those with resistant symptoms, the average BMI was 26.60, and in the group with remission , it was 27.22. On the other hand, most probably by analogy with the data related to the body weight of patients with BMI, more significant variability is observed in the group of patients with remission.
The lowest BMI in the group with RS is 18.37, and the highest is 38.06.
The lowest BMI in the CoR group was 18.34, and the highest was 44.14.

Conclusion: There is no difference between patients in the two groups regarding BMI.

6. Habitus

From the observation it is clear that 42 patients / 40% / have an asthenic habit, 40 / 38.1% / have a normosthenic habit and 23 / 21.9% / have a picnic habit. There is an emphasis on patients with asthenic habits.

The analysis of the habitus in patients with refractoriness and those without refractoriness shows that there are differences in the distribution of patients by the criterion of habitus in the two groups:

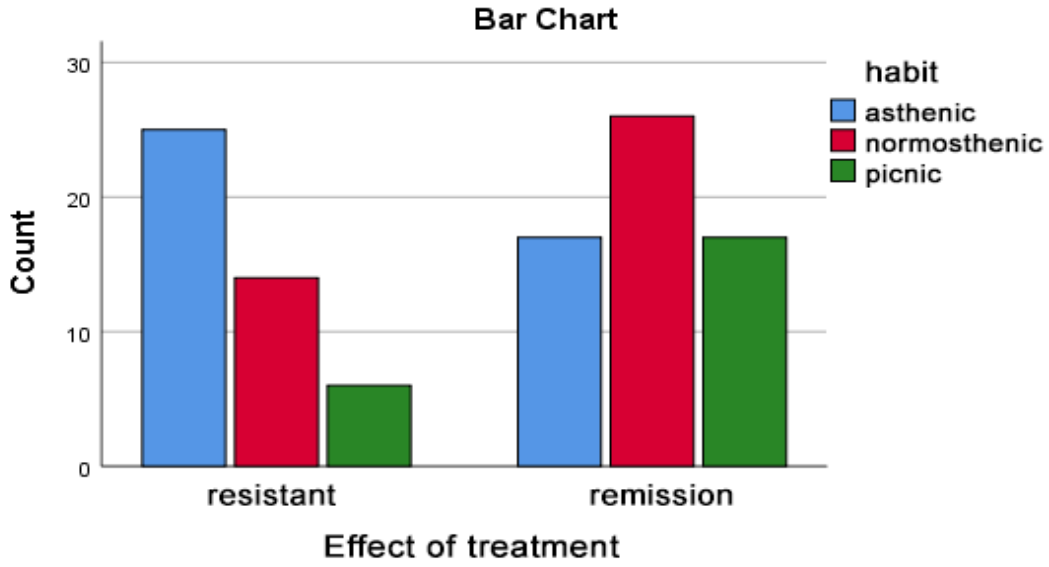
In patients with RS 25 / 55.6% / have an asthenic habit. For those with normosthenic - 14 / 31.1% / and for those with picnic - 6 / 13.3% /.

In patients with CR -17 patients / 28.3% / have asthenic habit, 26 / 43.3% / have normosthenic and 17 / 28.3% / have picnic.

Approximately two **times** higher rates of patients with asthenic habits are observed in patients with resistance than those in clinical remission. Figure 4

There is a statistically significant difference of p <0.01 (**)

Fig. 4 Relationship between habit and resistance to therapy



These results support the data of other authors who point out that linearity in bodybuilding is associated with a higher incidence of schizophrenic disorders and associated with forms of schizophrenia with a more severe and progressive course. (Kornetov NA, Gubernik V. 1980, Sivkov S, Akabaliev V. 1999; Sivkov S, Akabaliev V, 1998; Sivkov S et al 2005).

Conclusion: The analysis of anthropometric indicators shows that asthmatic habit is predominantly observed in patients with resistant schizophrenia, and it is associated with slightly higher height and lower variation in body weight compared to patients in the CR.

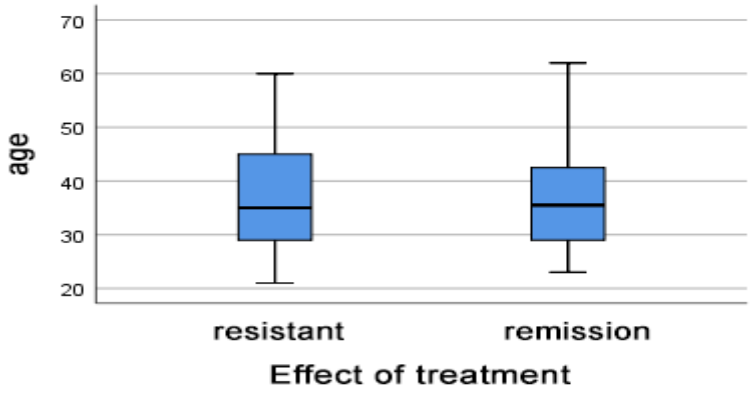
Evaluation of age-related features in both groups of patients

7. Age

The mean age of patients in the RS group was 36.98 years. The minimum age is 21 years, and the maximum is 60 years.

The mean age of CR patients was 37.25 years. The minimum is 23 years, and the maximum is 63 years. Figure 5

Fig. 5 Distribution of age in the two groups of patients



Conclusion: We do not observe a difference in the mean age of patients in the two experimental groups.

8. Age of onset of psychotic symptoms

There are age-related differences in the onset of psychosis in male and female patients.

Male patients' mean age of onset of psychotic episodes was 21.38 years.

The mean age of onset of psychotic episodes in female patients was 27.97 years.

The onset of psychosis in resistant patients is, on average, 23.04 years, and in those in remission, 27.37 years. The data show an earlier onset of psychotic symptoms in patients with RS than in the CR.

The age distribution in the two groups shows that the lowest age of onset of psychosis in the group with RS is 13 years of age and in those with remission at 17 years of age. The latest age of onset of psychosis in patients with resistant schizophrenia is 47 years, and in those in the CR at 50 years.

In males, approximately 6.45 years earlier incidence of psychosis was observed compared to females. This difference in the onset of psychosis in men and women and the predominance of males in the group with RS necessitated further differentiation of the age of onset of psychosis in persons from females only.

In females with resistant symptoms, the onset of psychosis averaged 26 years of age. Among female patients in the CR, the average age of onset was 29.17 years. We found more than three years difference in the onset of psychosis in females in the two experimental groups of patients. The conclusion is that the earlier onset of psychosis in patients with RS is due to the predominance of males in them and the earlier onset of psychosis in women in the resistance group. We found a statistically significant difference with $p < 0.01$(**).

These results support the data of other authors on the relationship between the early onset of psychosis and the refractoriness of symptoms in schizophrenia (Meltzer HY., Et al. 1997; Lieberman JA., Et al. 1994; Juola, P., Miettunen, J. Et al. 2013).

Conclusion: Patients with resistant schizophrenia have an earlier onset of the disease than those in clinical remission. Males have an earlier onset of the disease than females. The analysis of only females also showed a significant difference in the onset of psychosis, with earlier onset in the resistance group.

9. Duration of schizophrenia in both groups of patients

In the analysis of the duration of the schizophrenic process, we found that the average duration in patients with resistant schizophrenia is 14.31 years, SD is 11,548, and the minimum and maximum are 2 and 45 years, respectively.
In patients in remission, we found an average duration of schizophrenia of 9.87 years, SD -8.4 years, minimum and maximum are 2 and 42 years, respectively. Figure 6

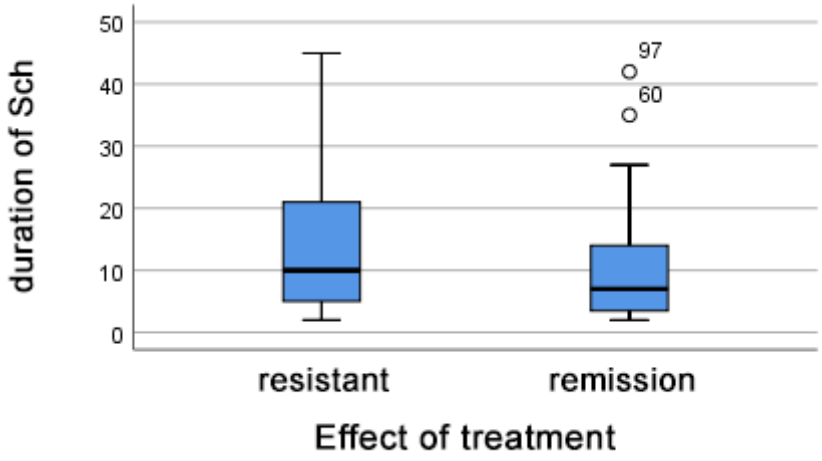


Fig. 6 Relationship between resistance to treatment and the duration of the schizophrenic process

Conclusion: Patients with resistance to therapy have a longer duration of the schizophrenic process.

10. Duration of untreated psychotic symptoms

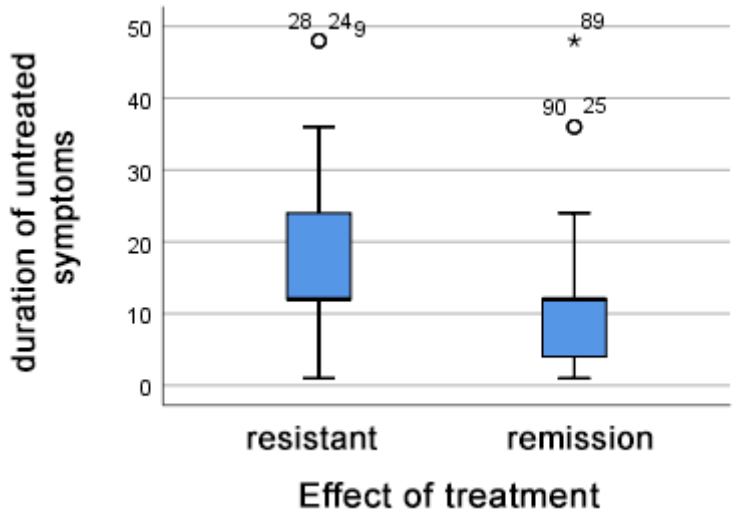
To estimate the duration of untreated symptoms, we considered it appropriate to present this period measured in "months" firstly because a retrospective assessment can always lead to a misinterpretation of the time
interval, and secondly, because there were significant differences in the duration and use of "years" is a long interval for benchmarking.

The mean duration of untreated symptoms in the group of patients with resistance was 14.31 months.

The mean duration of untreated symptoms in the remission group was 9.87 months.

Patients with RS had an average of 1.5 times longer duration of untreated symptoms than those with CR. There is a statistically significant difference with $p < 0.001$ (***). Figure 7

FIG. 7 Association between the duration of untreated symptoms and the effect of therapy



With these results, we support the observation of other authors about the importance of the duration of untreated symptoms on the prognosis of psychosis (Lieberman JA., Et al. 1992; Edwards J., Maude D., et al. 1998: Robinson DG., et al. 1999; Bartko G. et al., 1990; Bailer J. et al. 1996).

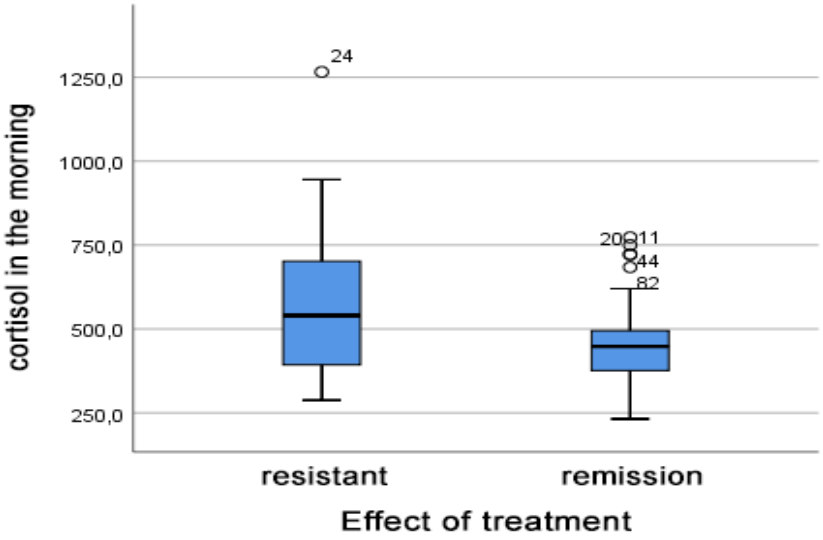
Conclusion: From the studies conducted on the factors "time of onset" and "period of untreated symptoms", we can conclude that in patients with resistance to therapy, there is an earlier onset of the disease and a longer duration of untreated symptoms and - long duration of the schizophrenic process.

11. Assessment of cortisol levels in patients with RS and those in the CR

We conducted a study of cortisol secretion, and the studies were conducted in a clinical setting. In all patients, blood was taken in the morning at seven and in the afternoon at 16 hours.

In the group of patients with resistance, there is a higher level of cortisol in the morning than in patients in the group in remission. The mean value of cortisol in resistant patients was 509,150, and in the group of patients in clinical remission, it was 456,035. Figure 8

Fig. 8. Distribution of the level of morning cortisol secretion in both groups of patients



The assessment of the average cortisol level at 16.00 hours showed that in the resistant group, it was 253,678, and in the remission group, it was 228,737. There are no significant differences in the distribution of cortisol within the group - there are no significant differences in the minimum and maximum values in the two groups of patients.

We found a difference in the cortisol level in the morning between the two groups of patients with elevated cortisol levels in the group of patients with resistant psychotic symptoms. $p < 0.05$ (*). No difference in the level of cortisol in the afternoon was found. These results support other authors' data on elevated cortisol levels in patients with schizophrenia (Newcomer et al., 1991; Tandon et al., 1991; Lammers et al., 1995; Meltzer et al., 2001).

Conclusion: The cortisol level in the morning in patients with resistance is higher than in those in remission. No difference in cortisol levels was found in the afternoon.

12. Relationship of resistance with the lateralisation of brain processes

When conducting a study with the Edinburgh test to assess the lateralisation of brain processes, we used a trimodal classification: mixed / cross-dominance /, right-handed, left-handed.

When analysing the relationship between the lateralisation of brain functions and the sex of the studied data, we found the following data:

In female patients - a total of 65.27 / 41.53% / are cross-dominant, 35 / 53.84% / are right-handed and 3 / 4.62% / are left-handed.

In male patients - 40, 17 / 42.5% / have mixed dominance, 21 / 52.5% / are right-handed and 2/5% / are left-handed.

From the comparison, we can say that the distribution of the lateralisation of brain processes is represented equally in both sexes.

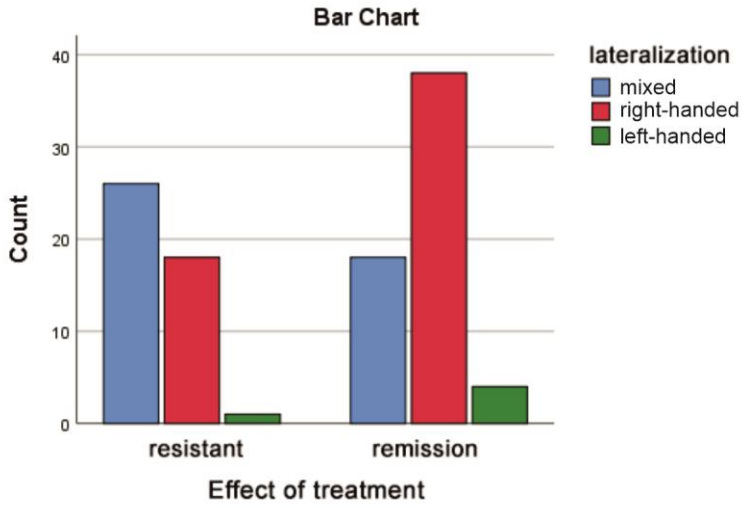
Of the 105 patients studied, 44/41, 89% / have mixed lateralisation / cross-dominance /, 56 / 53.34% / are right-handed and 5 / 4.76% / of the patients are left-handed. These results do not support the data of other authors on the predominance of leftists in patients with schizophrenia (Dragovic & Hammond, 2005; Webb J.R. et al., 2013). We find a high percentage of patients with mixed lateralisation / i.e. cross-use of hand, foot or eye. Most likely, some studies did not look at cross-lateralisation but only left-handed or right-handed dominance and did not use a trimodal classification but a bimodal one. If we have to use the bimodal classification and look at the lateralisation in hand dominance, we found that 14 patients have a dominant left hand. That accounted for 13.3% of all patients enrolled in the study. The range of reported results of left-handedness in patients with schizophrenia varies from 7% to 31%.

The distribution of lateralisation of dominance in patients with resistance to symptoms shows that 26 / 57.78% / are cross-dominant, 18/40% / are right-handed and 1 / 2.22% / are left-handed. We found that more than half of patients with RS have mixed (cross-dominance), and a small percentage are pure leftists.

The distribution of the dominance of the lateralisation of brain processes in patients in clinical remission shows that 18/30% / of the patients have mixed dominance, 38 / 63.33% / are right-handed, and 4 / 6.66% / are left-handed.

The results unequivocally show that cross-dominance is more common in patients with resistant schizophrenia than in remission. $P < 0.05$ (*) Figure 9

Fig. 9 Distribution of functional lateralisation in patients with resistance and those in remission



These data unequivocally confirm the results of other studies, which indicate that mixed or cross-dominance is three times more common in patients with schizophrenia (Cannon, M. et al., 1995). It is not in vain that some authors view cross-dominance as a biological marker of schizophrenia (Satz P & Green MF. 1999). Our analysis shows two times more patients with cross-dominance in patients with resistance than those in remission. These data support the view that cross-dominance is associated with a more intense course of schizophrenia, as recorded by other groups (Browne et al., 2000; Hayden, Kern, Burdick, & Green, 1997).

Conclusion: Cross-dominance is associated with two times higher probability of symptom resistance in patients with schizophrenia.

13. Gender identity in patients with schizophrenia

The analysis of patients with resistant psychosis and those in remission using the Sandra Bem questionnaire to assess gender identity found the following results:

Of all patients with schizophrenia, 80 / 76.19% / show a more extensive scale when measuring identification with the female role, 17 / 16.19% / make an association with the male, and in 8 / 7.61% / of patients, the same results are found in identifying with gender roles, i.e. with both the male and female roles.

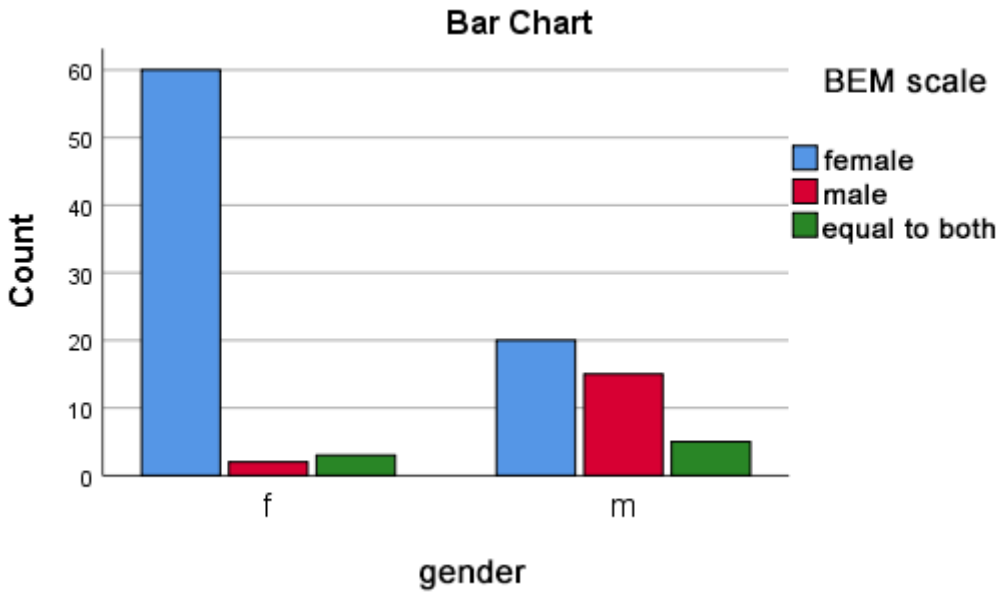
In a comparative study comparing the actual sex of the patients studied with the results of using the Bem scale, the following data were observed:

Among females - 65 it was found that 60 / 92.31% / identify with the female gender role, 2 / 3.07% / with the male gender role and 3 / 4.62% / perceive both gender roles equally.

Among males - 40 it is found that 20/50% / identify more with the female gender role, 15 / 37.5% / identify with the male and 5 / 12.5% / perceive both roles equally.

These data show that the registered predominance of female gender identification is at the expense of males, half of whom identify with the female gender. Figure 10

Fig. 10 Distribution of gender-specific identification in males and females



In patients with RS-45, 34 / 75.56% / identify more with the female gender role, 6 / 13.33 / perceive the male as active and in 5 / 11.11% / the identification is equal with both the male and female roles.

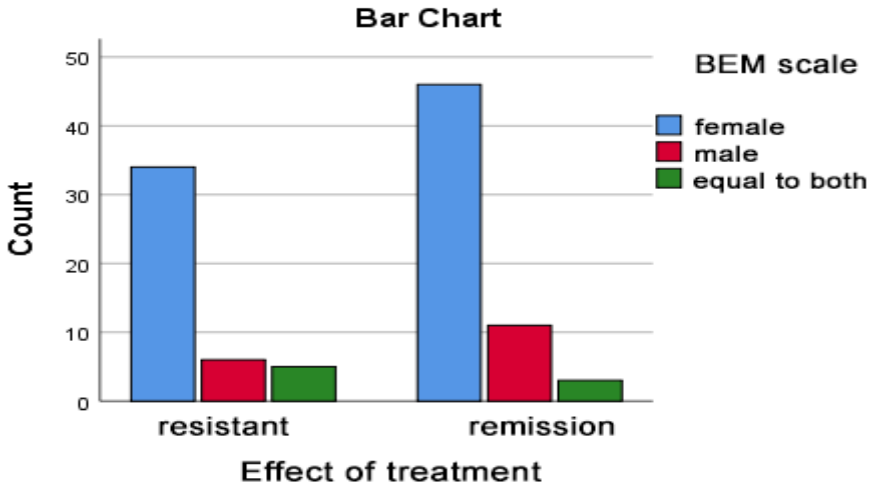
In the patients in the CR - 60, 46 / 76.67% / accept the female role as active, 11 / 18.33 / identify with the male and in three / 5% / both roles are accepted equally.

Count

		Scale of BEM			
		woman	man	equel to both	Total
Effect of therapy	Resistant remission	34	6	5	45
		46	11	3	60
Total		80	17	8	105

Even when comparing percentages, there is no statistically significant relationship in the assessment and identification of gender roles in the two groups of patients. P> 0.05 Figure 11

Fig. 11 Distribution of gender-specific identification in patients with resistance and those in remission



With this observation in patients with schizophrenia, we found that it is easier to identify and perceive the female gender role. These data confirm the

observations of other authors that there is a change in gender identification in patients with schizophrenia (Rajkumar RP. 2014; M. Sajatovic et al., 2005).
Conclusion: We find greater identification with the female gender role in evaluating all observed patients. This feature is characteristic of patients with schizophrenia in general, and no significant differences are observed between resistant patients and those in clinical remission.

Psychometric indicators

14. Assessment of patients with the PANSS scale

The use of clinical evaluation scales allows for quantitative comparison of the condition of patients and their follow-up in dynamics. The study of patients on clinical scales was performed when clinical remission was achieved and when the reduction of PANSS points was achieved within more than 12 weeks without reaching a complete resolution of psychotic symptoms in patients with resistant schizophrenia.

The average value of PANSS in the group of patients with resistance was 82.51 with SD 12,356, while in patients in remission, PANSS was 48.32 with SD - 5,395.

These results show that the total score on PANSS in the group of patients with resistant schizophrenia is almost twice as high as in clinical remission.
Even the standard deviations point to a "unification" of symptoms in patients in remission.

A clear statistical dependence is established between the two groups. P <0.001

Examining the differences in the sub-scale for only positive symptoms also shows differences. In patients with RS, the average value of PANSS positive was 19.39 with SD - 4.163, while in patients with CR, this result was 10.83 and SD 1.924. These data show that we observe almost twice the difference in favour of the resistance group between the two groups. This difference is also found in the standard deviations for this sub-scale, also p <0.001.

The PANSS negative symptom sub-scale shows a value of 21.91 with SD 6.324 for the RS group and 13.23 SD 2.770 for those in clinical remission. There is a statistically significant difference, but there is a tendency for greater standard deviation variability within the group than in the sub-scale for positive symptoms. P <0.001 (***)

The analysis of the disorganised sub-scale recorded the following values and differences between the two observed patient populations: In the group of those with RS - 41.16 SD 7.907 and the group in the CR 24.50 SD 3.903.

The analysis shows that the denounce is most pronounced in the general PANSS scale, followed by the sub-scale for positive and negative disorganised symptoms.

Conclusion: When using the PANSS scale, we find approximately twice as high values in the group of patients with resistant symptoms.

15. Analysis of the results using the BPRS scale

After using the BPRS scale, we found the following dependence in the analysed groups of patients when analysing the results.

The mean BPRS in patients with resistant schizophrenia was 57.80. The registered standard deviation / SD / in this group is 9,671.

The mean BPRS in CR patients was 35.62 with a standard deviation of 5.099.

The analysis result of BPRS values is similar to the results observed when used on the PANSS scale. Here, too, the differences are almost two times both in terms of the average values and the standard deviations found in the statistical processing. $p < 0.001$ (***)

Conclusion: When using the BPRS scale, we find approximately twice as high values in the group of patients with resistant symptoms.

16. Results of the Hamilton Depression Rating Scale

The analysis of depression in all patients observed by us showed that the average value of depressive symptoms is 11.81, SD 5.105, and the registered values of minimum and maximum are 2 and 32, respectively.

The mean value of depressive symptoms assessed in the RS group was 13.80, with a standard deviation of 5.911.

The group of patients in the CR is 10.77, with a standard deviation of 4.159. There are corresponding results with a slightly higher value in the group of patients with resistance.

Both patient groups fall into the evaluation column on the scale in the range of mild depression, and those with RS are at the upper limit.

We observe up to 30% higher depression in patients with resistant schizophrenia.

Studies have shown that the onset of depressive symptoms during the development of schizophrenia is observed in about 25-30% of patients with clinically significant symptoms that require medical interventions (Siris, SG, Bench, C. 2003; Buckley PF et al., 2009;). These are usually patients with a more severe course of the disease (Siris, SG, Bench, C. 2003). That indicates that increased depression is completely deducible from the course of the psychotic disorder, especially in those patients with resistant schizophrenia. $p < 0.05$ (*)

Conclusion: The assessment of depressive symptoms in the studied patients shows that the value is in the range of mild depression. The differences between the two groups are related to the fact that in the resistant ones, the value is in the upper range, and in those in remission, it is in the lower range of the scale.

17. Results of the Hamilton scale for anxiety assessment

Anxiety assessment is an essential component in the overall assessment of patients with schizophrenia, especially in cases of resistant psychotic symptoms. On the one hand, psychosis is associated with an ego-syntonic characteristic underlying the lack of cooperation. On the other hand, anxiety as an ego-dystonic phenomenon is an essential factor based on which the patient's adherence to the therapeutic model is sought.

When analysing anxiety with the Hamilton scale in the patients we observed, we obtained the following results:

The mean value of anxiety in all patients was 10.74, SD 5.588, and the minimum and maximum values were 2 and 27, respectively.

When using the Hamilton scale in patients with RS, we recorded an average of 12.91 with a standard deviation of 6.619.

In CR patients, we found that the mean anxiety on the scale was 9.12, and the standard deviation was 4.013.

In the group of patients with resistant psychotic symptoms, approximately 30% higher anxiety was observed compared to patients in clinical remission. We found a statistically significant difference between the two groups of patients p <0.001 (***).

The Hamilton scale analysis shows that both recorded values for inpatients are mild anxiety (up to 17).

An association was made between anxiety and cortisol levels in the morning, and a correlation was found between them.

Conclusion: Patients with refractory psychotic symptoms have a higher level of anxiety than patients in remission. The increased anxiety scale in patients with resistance corresponds to the established higher cortisol levels in the morning.

18. Dissociative symptoms recorded with the Carlson and Putnam scales

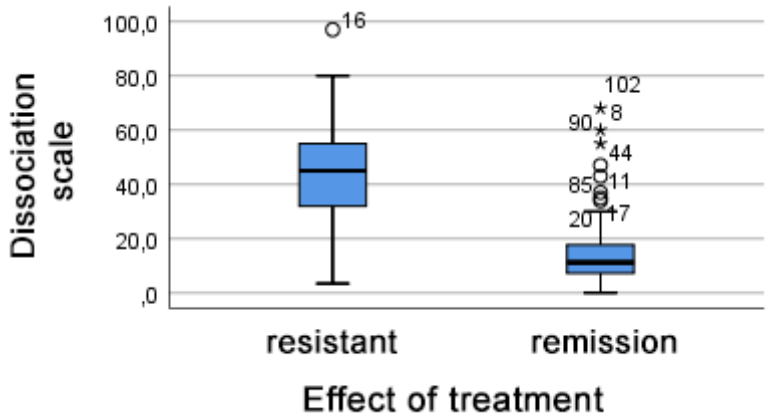
The mean value of the dissociative symptoms scale found in all patients with schizophrenia was 29.1356, SD was 22.3898, and the lowest and highest values were 0 and 97, respectively.

The mean value of the measured points with the Carlson and Putnam scale in patients with RS is 42.578, and the standard deviation is 20.8977.

For patients with CR, the mean was 15,907, and the standard deviation was 14,530.

Up to a 3-fold higher dissociation incidence values were observed in patients with resistance than in remission. p <0.001 (***) Figure 12

Fig. 12 Distribution of the degree of dissociation in the two groups of patients



Observation is confirmed by the data of other authors on the existence of a connection and correlation between psychotic symptoms and dissociative ones. They find the most significant connection in delusions and hallucinations and with the scale of positive symptoms and not so much in those with negative symptoms (Spitzer C, Haug HJ, Freyberger HJ 1997; Pec O, Bob P, Raboch J. 2014). Our analysis found an association between both positive and negative and disorganised symptoms.

Studies show that outcomes in patients with schizophrenia typically range from 11.9 to 44.24 (Schäfer I et al., 2006; Goff DC et al., 1991). As per our results, if the mean values are positioned in the same range, we observed a group of symptoms with a statistically significant difference between resistance and remission.

Many authors have found an overlap of symptoms in patients with schizophrenia and those with dissociative disorders (First MB, 2005; Kaplan B et al., 2006). Some studies do not show co-occurrence of schizophrenic and dissociative disorders (Tschoeke S et al., 2014). Others find that between 9% and 50% of patients with schizophrenia also meet the diagnostic criteria for dissociative disorder. (Haugen MC, Castillo RJ, 1999; Moise J, Leichner P, 1996; Ross CA, Keyes B. 2004).

Conclusion: In patients with resistant psychotic symptoms, there is a high degree of dissociation, which exceeds the rating scale three times that found in the group of patients in remission.

19. Obsessive-compulsive symptoms in patients with schizophrenia

The assessment of obsessive-compulsive symptoms with the ACS rating scale in all observed patients showed an average value of 18.02, SD 10.087, and the minimum and maximum values are 2 and 46.

The mean value on the OCD scale in the group of patients with RS was 20.76, and the standard deviation was 10.232.

In patients with CR, it was 15.97, and the standard deviation was 9.554.

We found a higher result of OCD values in the group of patients with resistant symptoms. Figure 13 There is a statistically significant difference of p <0.05 (*)

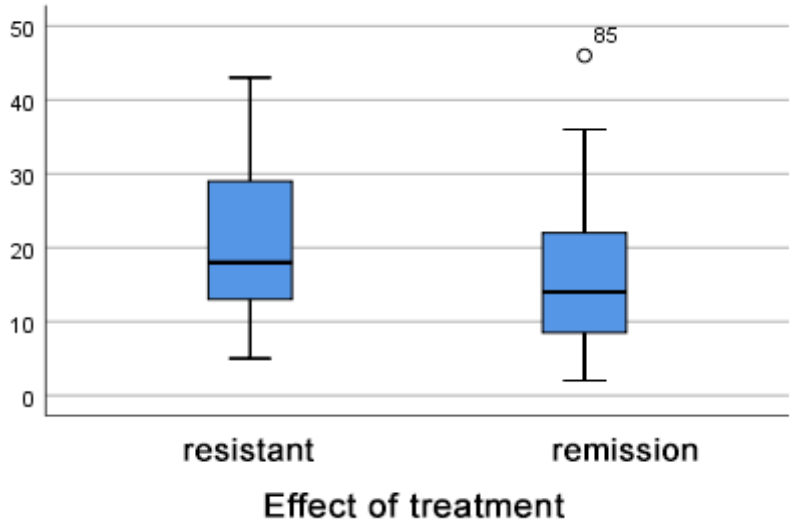


Fig. 13 Distribution of obsessive-compulsive symptoms in both groups of patients

From the analysis of the literature, it is clear that patients with clinically present symptoms of OCD are a total of about 12.5% of the population, and those with OCD symptoms reach 30.3% of cases (Swets M et al., 2014; Hagen K Hansen B et al., 2013). Our data indicate that of all patients, 34.2% have more than 18 points on the DOCS scale. The remaining studies have not been conducted using this toolkit.

Our observations do not confirm the data obtained from other authors who indicate no difference in the prognosis of patients with schizophrenia who have OC symptoms and those without severe ones (Tonna M et al., 2016). It supports other studies that show a higher incidence of patients with OC symptoms in patients with schizophrenia with a more severe course of the disease (Baytunca B et al., 2017).

Conclusion: We observe an increased frequency of symptoms of the obsessive-compulsive spectrum in patients with schizophrenia who have resistance to treatment compared to those in remission.

STUDY OF COGNITIVE FUNCTIONS

In studying cognitive functions, we have used the 10-word test described in Chapter Two. Examination of auditory-speech memory. Test of learning ten words according to Alexander Luria (ZDDL).

This test has been widely used and verified in many countries (Lezak MD.1995; Caitlin L et al., 1995; Chaves ML, Izquierdo I, 1992).

20. Evaluation of fixation

The average fixation assessment in all patients we observed was 75.07, SD 15.561, and the minimum and maximum values are 45 and 100%, respectively.

When assessing fixation in patients with resistant symptoms, we found that the average value of fixation in them was 65.18%. The standard deviation is 11,161, and the minimum and maximum values are 45 and 100. From these results in patients with RS, it is evident that fixation disorders in them as a mean can be described as moderate / although in the upper range of the assessment moderate /.

We found an average fixation value of 82.48% when assessing fixation in CR patients. The standard deviation is 14,263, and the minimum and maximum values are 45 and 100, respectively (the same values as those with resistance to treatment). The data show that the found average value / 82.48 / is at the upper end of minor violations/close to the lower end of the norm /.

In both groups, there is an intra-group variance of the values, and in the group, in the CR, the variance is higher. Figure 14

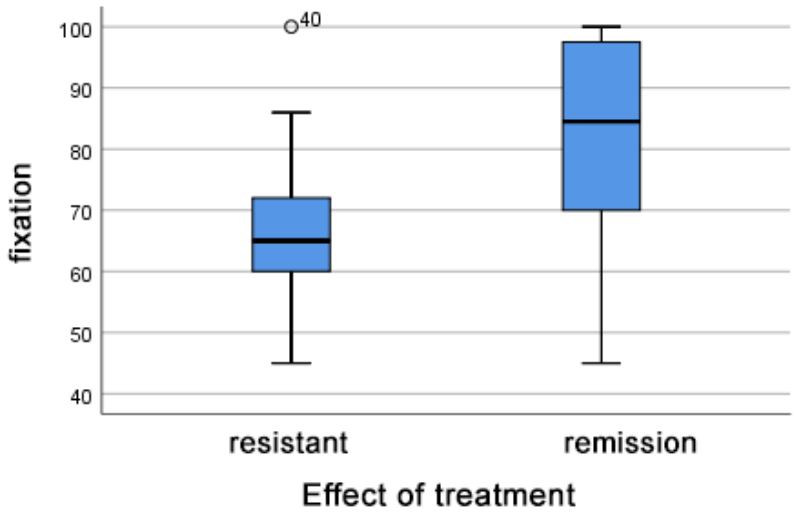


Fig. 14 Comparative representation of fixation in the two groups of patients

Conclusion: In patients with resistant schizophrenia, there is a significant violation of fixation, and in those in remission, fixation is within the upper end of mild disorders/close to the lower end of the norm /.

21. Evaluation of reproduction

The mean reproduction value in all patients was 86.63, SD was 17.219, and the minimum and maximum values were 45 and 100%, respectively.

In patients with RS, the average reproduction value was 77.07%, and the standard deviation was 16,708, with a minimum value of 45 and a maximum of 100.

In the group of patients with CR, the average value for reproduction was 93.80%, and the standard deviation was 13.872. The minimum value is 50, and the maximum is 100.

We observe less impairment of reproduction than fixation involvement in both groups of patients. P <0.01

Conclusion: In patients with resistant schizophrenia, there is a more pronounced impact on reproduction than in patients in remission, which show values in the normal range of the scale.

22. Evaluation of retention

Concerning this indicator and the peculiarities related to its calculation, we have grouped the patients into a group - normal, slightly impaired and moderate. As seen below, this indicator is less affected in the studied patients. Table 2

Table 2 Comparative analysis of retention disorders in patients with resistance and those in remission.

		Normal	Renewal slight violation	moderate	Total
Effect of the therapy	resistant remission	37	6	2	45
		54	5	1	60
Total		91	11	3	105

From the above table it is clear that in the group of patients with RS 37 / 82.2% / have normal values of retention. 6 / 13.3% / have mild disorders and 2 / 4.4% / have moderate disorders.

In the group of patients in the CR - 54/90% have no disorders /, 5 / 8.3% / have mild and 1 / 1.67% / have moderate disorders.

These values indicate that retention disorders in patients with resistant psychotic symptoms are more pronounced, but no significant statistical difference is observed for the indicator. $p > 0.05$

Conclusion: No significant difference was found in retention values in the experimental groups of patients.

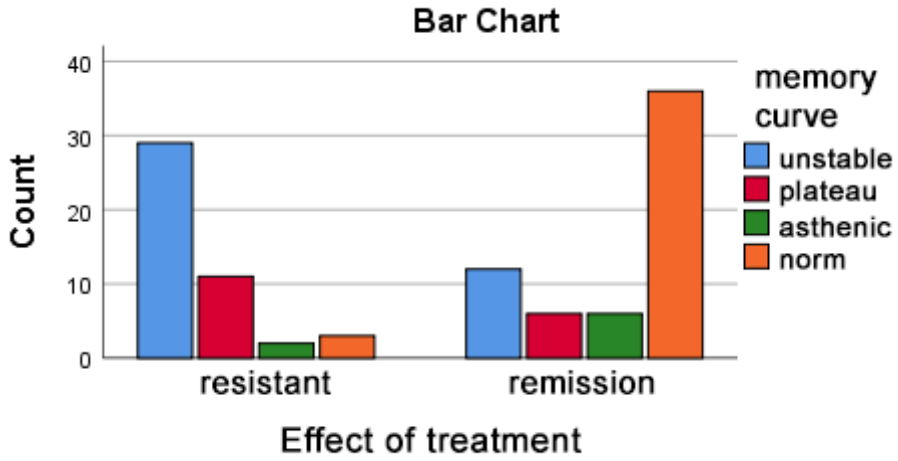
23. Estimation of the memory curve in both groups of patients

The analysis of the memory curve in patients with schizophrenia shows that 41 / 39.04% / patients have an unstable / zigzag / type memory curve, 17 / 16.19% / have a plateau type, 8 / 7.61% / with asthenic type and 39 / 37.14% / have normal characteristics. These data give us information that almost 60% of people with schizophrenia have a problem with attention.

In patients with resistance it was found that 29 / 64.4% / have an unstable / zigzag type / memory curve, 11 / 24.4% / have a plateau type curve, 2 / 4.4% / have an asthenic and 3 / 6.7% / have a normally presented one.

In patients in remission, the distribution is as follows: 12/20% / have an unstable memory curve, 6/10% / have a plateau type, 6/10% have an asthenic one, and 36/60% / of patients have a standard memory curve. We find a statistically significant difference with p <001 (***) Figure 15

Fig. 15 Estimation of the type of memory curve in patients with refractory symptoms and those in remission



The described distribution shows that in the group of patients, there is more than three times higher percentage of patients with "unstable" memory curve type and two times more with plateau memory curve compared to patients in remission.

On the other hand, more than half of patients in remission have a standard memory curve compared to almost ten times fewer patients with a standard memory curve in those with resistant symptoms.

Zigzag and plateau-type memory curve is observed in patients with organic disorders (Mechkov, 1995). A link can be made with the data on the possible

presence of a neurodegenerative process in a certain subgroup of patients with schizophrenia, which is also associated with the formation of progressive cognitive deficits observed in them (Swapnil Gupta, Parmanand Kulhara, 2010).

Conclusion: There was a difference in the type of memory curve in patients with RS and those in the CR. The results show a more than three times higher percentage of patients with an "unstable" type memory curve in the group of patients with resistance and two times more with plateau memory curve than patients in remission.

24. Assessment of the personality profile of patients with RS and those in the CR when using BPQ

After making the necessary adjustments, the high scale assessment questionnaire allowed us to compare the results using only the most extensive scale comparison. Table 3

Table 3 Distribution of BPQ scales in both groups of patients.

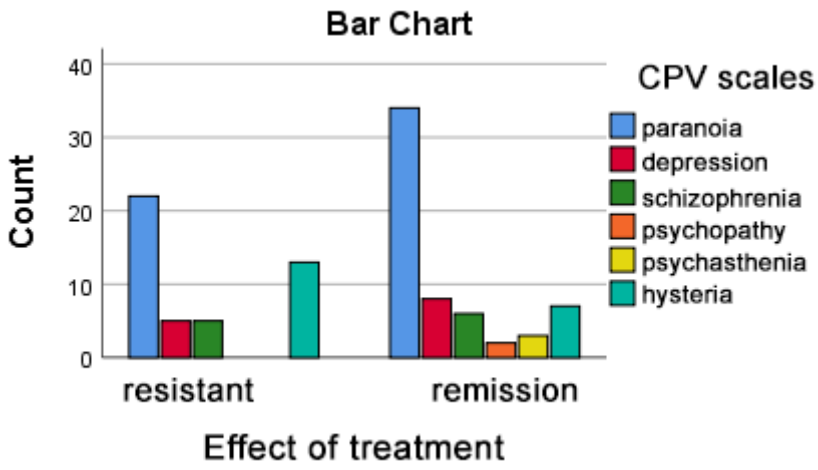
Count

		Scale BPQ						
		par-a-noia	de-pres-sion	schiz ophr enia	psy-chop-athy	psy-chasth enia	hys-teria	To tal
Effect of the ther-apy	Re-sistan t re-mis-sion	22	5	5	0	0	13	45
		34	8	6	2	3	7	60
Total		56	13	11	2	3	20	10 5

The above table shows that in patients with resistant schizophrenia, the most significant number of patients have the highest scale of paranoia - 22 / 48.9% /, 5 / 11.1% / patients with the most significant scale of depression, 5 / 11.1% / patients are represented with the most significant scale of schizophrenia and 13 / 28.9% / patients - of hysteria. In the group with resistance to symptoms, we found that the scales of paranoia and hysteria were the highest.

In patients in remission with respect to the highest scales of BPQ we found the following distribution: 34 / 58.7% / are paranoid, 8 / 13.3% / are depressed, 6/10% / are schizoid, 2 / 3.3% / have psychopathy, 3/5% / have psychasthenia and 7 / 11.7% / have hysteria. We find the highest percentage of patients with paranoia scale in this group, while there is no significant difference on other scales. Figure 16

Fig. 16 Distribution of BPQ scales in the two groups of patients



There is no statistically significant difference between the groups when conducting a statistical analysis. p> 0.05

Upon closer examination of the study results, it was found that in terms of the scale of hysteria in the group of patients with resistance to symptoms, almost three times higher result was registered.

What is the explanation of this indicator, which as a sub-scale in the BPQ, is interpreted as "the presence of clarity on personal issues and increased vulnerability" (Kukov K, MMPI-MULT-R, 2019)? In the analysis of patients from both groups using the Carlson and Putnam Dissociative Experience Scale, we found a

statistically significant difference between patients with RH and those in the CR. Interestingly, the assessment of dissociative symptoms also shows three times the higher degree of dissociation in resistant patients. That is most likely the reason for the increased values of the hysteria sub-scale in BPQ in refractory patients.

Conclusion: The analysis of the features of the scales in patients with RS and those with CR showed a significant difference in the scale of hysteria. The hysteria scale in patients with resistance to symptoms shows almost three times higher results than those in clinical remission.

Evaluation of therapeutic interventions

25. The effect of the first antipsychotic drug

The efficacy of the first antipsychotic drug, which is selected individually for the individual patient, is consistent with the profile of symptoms and previous history of one or another antipsychotic effect. The following were taken into account: the profile of side effects, the tolerance to the dose ranges and the presence of concomitant somatic diseases requiring the reception of a particular therapy for them. We found that in total, in the studied contingent of patients with schizophrenia with both resistant symptoms and those in remission, we find the following distribution: Table 4

Table 4 Effect of the application of the first APM in both groups of patients.

Count

		Answer to 1 APM		
		Without effect	With effect	Total
Effect of the therapy	Resistant remission	36	9	45
		20	40	60
Total		56	49	105

After applying one antipsychotic drug in 49 / 46.67% / of the patients, we find an answer, while the lack of effect in the remaining 56 / 53.13% /. From this distribution, it is clear that the probability of achieving effectiveness with the first antipsychotic drug is almost like the game of "ezi" "tour", i.e. 50/50.

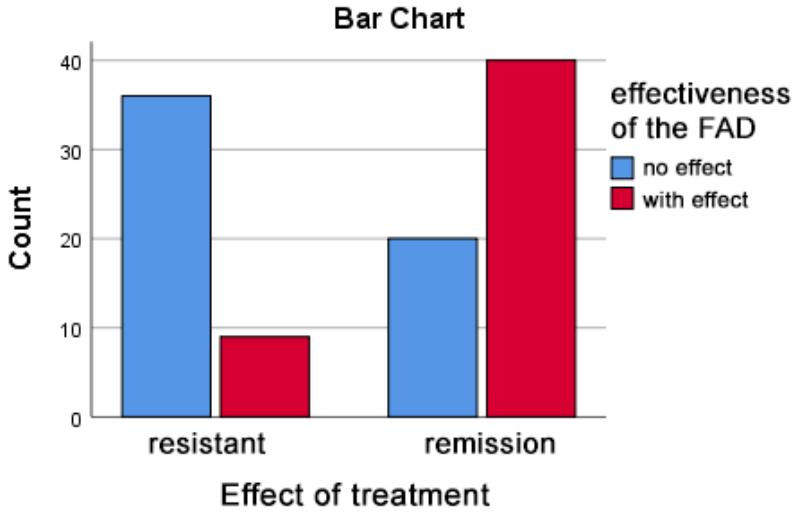
Of interest is that if we start from the idea of biological antagonism in patients with epilepsy, a study found that the probability of achieving control of epileptic seizures with the first anti-epileptic drug is 47% (Kwan P, Brodie MJ. 2000). Our result of 46.67%. We find corresponding results in the two nosological units, which can be considered as expected / from another point of view and surprising / having in mind the similarities and, on the other hand, opposite pathogenetic constructs.

The distribution of patients according to the response to the first antipsychotic in the resistance group shows that no effect was observed in 36/80% / of patients, and in the remaining 9/20% / such an effect was registered.

In the group of patients in remission, it was found that in 20 / 33.33% / patients, no effect was observed when using the first neuroleptic, and in the remaining 40 / 66.57% /, it was found.

These results show that patients with RH are 2.5 times more likely to have no effect after the first antipsychotic drug than patients in remission. There was a statistically significant difference between the two groups of patients with p <0.001 (***). Figure 17

Fig. 17 Relationship between the effectiveness of the first antipsychotic drug and resistance to therapy



Conclusion: The effect on the first antipsychotic drug is a significant predictor of resistance. We find 2.5 times more likely to be resistant in the absence of effect from the use of the first neuroleptic.

26. Presence of efficacy from the first two weeks of treatment

We analysed the effectiveness of the treatment during the first two weeks. Many authors present this indicator as an essential and significant indicator for developing future resistance.

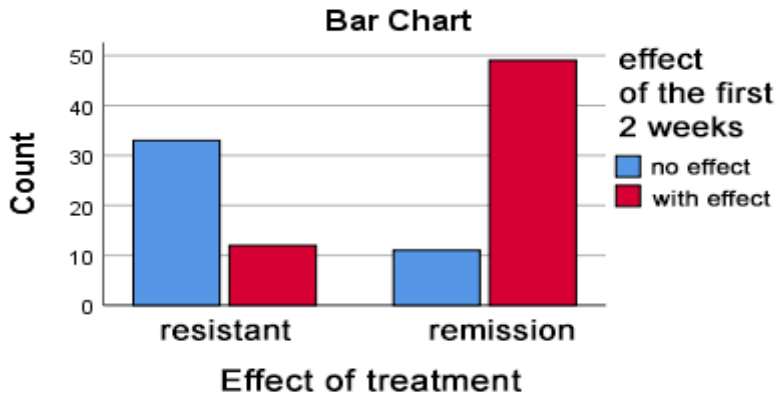
The data showed the following results. The assessment of all patients found that 44 / 40.90% / had no registered effect during the first two weeks of therapy, and the remaining 61 / 60.10% / had an observed effect of therapy.

In patients with resistance, it was found that 33 / 73.33% / had no effect observed during the first two weeks of treatment, and in 12 / 26.67% / such a change was observed.

In patients in remission, it was found that 11 / 18.33% / patients, no effect was observed, and in the remaining 49 / 82.67% / such an effect was found.

These results show that patients with resistance are four times more likely to have no effect from the first two weeks of treatment than the group of patients in clinical remission. p <0.001 (***) Figure 18.

Fig. 18 The effect during the first two weeks of treatment in the experimental groups of patients.



This relationship is attractive because, for the first four weeks of treatment, the most significant change in PANSS is reported in the first week - about 13.8% and in the rest, it is about 3-5% (Agid et al., 2003). If no evidence of the onset of effects is observed, an early change may be made before waiting two weeks.

Of the patients who responded to treatment with the first antipsychotic drug (49), 4 (8.16%) had no effect during the first two weeks of treatment, and the remaining 45 (91.84%) had a clinically significant effect.

Of the patients without effect from using the first antipsychotic drug (56), without effect from the first two weeks are 40 / 76.42% /, and the remaining 16 / 23.58% / are with registered effectiveness. Figure 19

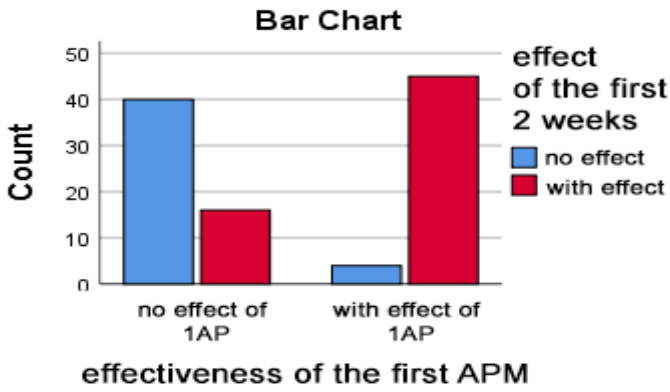


Fig. 19 Relationship between the effectiveness of therapy with the first APM and the effectiveness during the first two weeks of treatment

Conclusion: Evaluation of efficacy in the first two weeks is a reliable resistance marker. Patients with resistant schizophrenia were four times more likely to have no effect than the first two weeks of treatment compared to the group of patients in clinical remission.

27. Estimation of the number of administered antipsychotic drugs in both groups of patients

An analysis of the use of antipsychotic drugs over time has been made, and this number does not include drug interventions to potentiate the effect, correct side effects, and the use of thymostabilizers in the presence of effective fluctuations.

The distribution in all patients is shown in Table 5

Table 5 Comparison between the total number of APMs taken and the resistance to treatment

Count

		Number of medications taken							
		1	2	3	4	5	6	7	Total
Effect of the therapy	Resistant remission	0	0	0	4	14	11	16	45
		5	14	10	12	10	7	2	60
Total		5	14	10	16	24	18	18	105

The distribution in patients with resistance showed that 4 / 8.9% / patients were treated with 4 AP, 14 / 31.1% / patients with 5 neuroleptics, 11 / 24.4% / patients with 6 and 16/35, 6% / patient with seven AP.

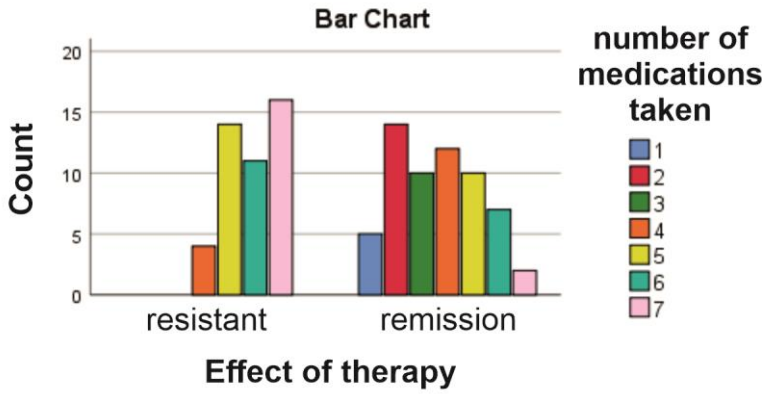
The distribution in patients in remission is: 5 / 8.3% / patients were treated with 1 AP, 14 / 23.3% / took two AP, in 10 / 16.7% / were discharged 3, in 12/20 % / with 4 AP, 10 / 16.7% / took 5, 7 / 11.7% / used 6 and 2 / 3.3% / were treated with 7 drugs.

We observe that in patients with resistance, more drugs are used to find the right therapeutic strategy to deal with psychotic symptoms. In patients in remission, we also see patients using a more significant number of antipsychotic

drugs, which is deducible from the course of the schizophrenic disorder and the lack of adequate adherence to therapy, requiring a frequent restart of treatment and use of other drugs in search of a balance between effectiveness and side effects.

The analysis performed to estimate the average number of antipsychotic drugs showed that the average number of APM in the resistance group was 5.87, while in the group in clinical remission, it was 3.62. P <0.001 (***) Figure 20

Fig. 20 Comparative analysis between the total number of APMs taken and the resistance to treatment



Analysis of the relationship between the duration of schizophrenia and the total number of antipsychotics taken showed the following relationship:

Patients taking only one AP drug had an average duration of schizophrenia of 4 years / SD 2,828 /, those taking 2 drugs had an average duration of 5.43 years / SD 3,694 /, those with 3 AP - 8.5 years / SD 6,786 /, in 4 antipsychotics - 11.5 years / SD 11,349 /, in 5 neuroleptics - 12 years / SD 8,993 /, 6 drugs are associated with a duration of 11.7 years / SD 6,939 /, and 7 neuroleptics respectively 21.22 years / SD 12,754 /.

From the above dependence, it is clear that in the course of time and the development of the disease and, of course, the patient's circumstances are associated with using a more significant number of drugs. On the one hand, this dependence may be related to the weak adherence to therapy observed in patients with schizophrenia or, on the other hand, to the progression of the disease and the search for more "aggressive" therapeutic interventions to be effective in psychotic symptoms. figure 21

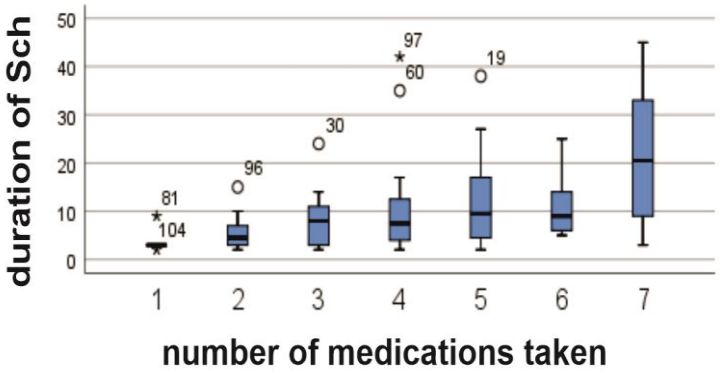


Fig. 21 Relationship between the duration of the schizophrenic process and the total number of medications taken.

Conclusion: In patients with resistant schizophrenia, a more significant number of antipsychotics have been used in a different number (almost twice), which is correlated with the longer duration of the schizophrenic process in them.

Abuse and intake of psychoactive substances

Regarding the intake of psychoactive substances, we have grouped them into four categories: cigarette smoking/nicotine/, marijuana, alcohol and psychostimulants/amphetamines, pico and cocaine /. Given the relatively small number of patients who used different surfactants (such as cocaine) from the group of psychostimulants, we decided to look at the whole group together.

28. Smoking nicotine

Of the total observed patients, we found that 49 / 46.7% / regularly smoke cigarettes / bought from a store or with a typewriter / and 56 / 53.3% / do not smoke. If we compare it with the data published for Bulgaria by the WHO, we can say that there is an increased use of cigarettes in the patients we observe whom data show that 43.3% of men and 26.9% of women in Bulgaria regularly smoke cigarettes (European health interview survey, EHIS wave 2 - 2014).

Our contingent's analysis of smokers distributed by sex showed slightly different data.

Among males, 16/41% / percent are smokers and 23/59% / are non-smokers.

A different distribution was found among females: 33/50% / are smokers and 33/50% / are non-smokers.

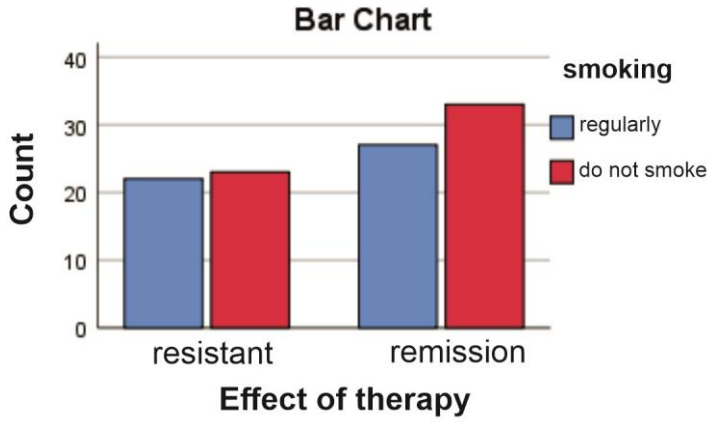
We find that the increased percentage of smokers in patients with schizophrenia compared to the general population in Bulgaria is mainly related to the increased percentage of **females.**

The analysis of the differences in the two compared groups of patients showed the following distribution:

In patients with resistance, 22 / 48.9% / are regular cigarette users and 23 / 51.1% / do not smoke.

In patients in remission 27 / 45.0% / regularly use and 33/55% / do not use. Figure 22

Fig. 22 Relationship of tabakism with the effectiveness of treatment



The results show no statistically significant difference between the two groups, despite our initial expectation that the percentage of smokers will be higher in the group of patients with resistant symptoms.

Conclusion: We found approximately twice as high a percentage of smokers in females with schizophrenia than non-smokers (according to WHO data for Bulgaria). We did not find differences in the percentage of smokers in the two groups of patients we observed.

29. Alcohol use

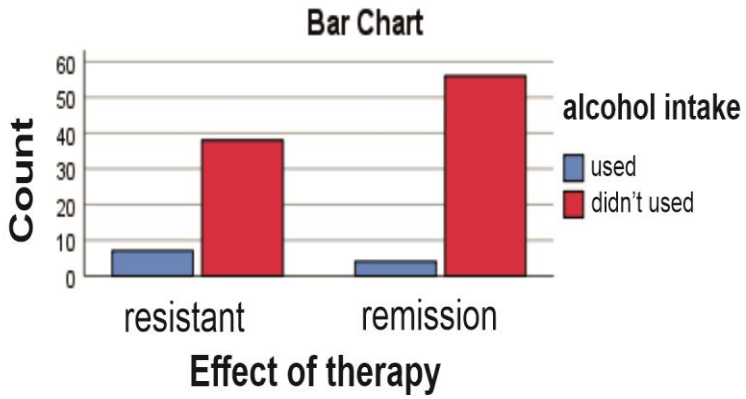
We use the term alcohol use in this case since patients with alcohol abuse and those with addiction are not included in the study. They are included in the exclusion criteria.

Of all observed patients, we found that 11 / 10.5% / had periods of alcohol use, and the remaining 94 / 89.5% / had no data on such.

In patients with resistance 7 / 15.6% / used alcohol, and 38 / 84.4% / did not use.

In patients in remission - 4 / 6.7% / have used and 94 / 93.3% / have not.

Figure 23 Association between alcohol intake and resistance in patients with schizophrenia



The analysis showed no statistically significant dependence. However, it is noteworthy that there is (if we compare percentages) more than two times higher percentage of those who have consumed alcohol in patients with resistance.

Conclusion: Patients with RS have a higher percentage of patients who consumed alcohol than those in the CR.

30. Marijuana use

These data are not consistent with data from other authors, who show that after the onset of psychosis, between 1/3 and 2/3 of patients begin to use marijuana regularly (Hahn B., 2018). This discrepancy is most likely since, for our study, we excluded patients with active marijuana use since, despite the reduction of psychotic symptoms, they would not respond using the SOFAS and Sheehan

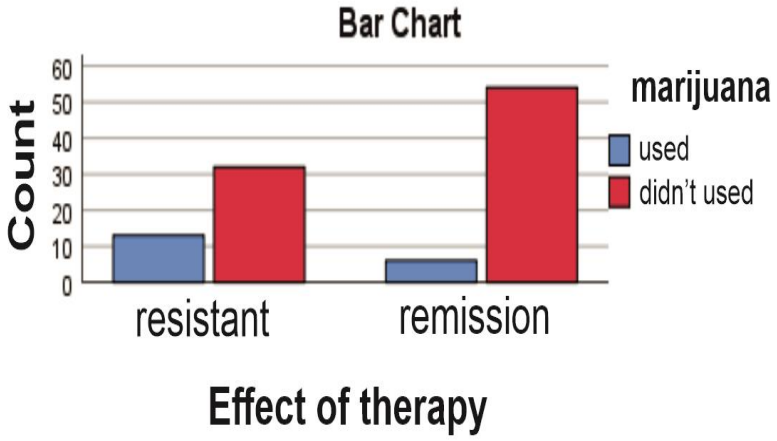
scales, which could not be included in either of the two groups. On the other hand, after de-hospitalization and some during it, many of them continue to use, which makes it impossible to achieve effective remission and raises the question of pseudo-resistance of psychotic production.

Of the entire contingent of monitored patients, we found marijuana use in 19 / 18.1% /, and in the remaining 86 / 81.9% / of patients, we did not find data on such use.

The analysis of the use of marijuana in the group of patients with resistance showed data 13 / 28.9% /, and for the remaining 32 / 71.1% /, no such data was not found.

Such admission was documented in patients in clinical remission in 6/10% /, and the remaining 54/90% / admission data were not established. Figure 24

Fig. 24 Relationship between cannabinoid intake and treatment resistance



We found a statistically significant difference with $p < 0.05$ as the analysis of the percentages showed a three times higher percentage of patients who used marijuana in the group of patients with RS than those in the CR.

At this stage, it is difficult to precisely determine the relationship between cannabis use and the presence of a schizophrenic process. On the one hand, some studies highlight the vital role of cannabis as a trigger for the development of psychotic states (Pearson NT, Berry JH 2019; Pearson NT, Berry JH; Singh S, Balhara YPS.). On the other hand, there is evidence that cannabidiol (CBD), an essential component of cannabis, could have a therapeutic effect, and some patients tend to take cannabis for this purpose (Gage SH, Jones HJ, et al., 2017). On the other hand, we must not forget that the very desire to use cannabis is related to the need to resolve pre-existing mental discomfort.

Conclusion: Patients with resistance to therapy have a higher percentage of patients (3 times) using cannabis than patients in the CR.

31. Use of psychostimulants

Psychostimulants have the potential to provoke psychotic experiences and, if present, to support and play a role in their evolution. That necessitated the admission of patients who have accidentally used these substances, and there is no evidence of chronic use.

In the contingent we observed, we found that 13 / 12.4% / of patients had taken substances from the group of psychostimulants, and the remaining 92 / 87.6% / had not used them.

The distribution in patients with resistance is as follows: 9/20% / have taken psychostimulants, and the remaining 36/80% / have not had such experience.

In patients in remission: 4 / 6.7% / took and 56 / 93.3% / did not use. When comparing the percentages between patients who used psychostimulants, there was a three times higher percentage of patients in the group than those in the CR.

Conclusion: Comparing the percentage of psychostimulants used in the two groups of patients, a three times higher percentage of patients in the group was found than in the CR.

Assessment of sleep and its characteristics

32. Sleep latency

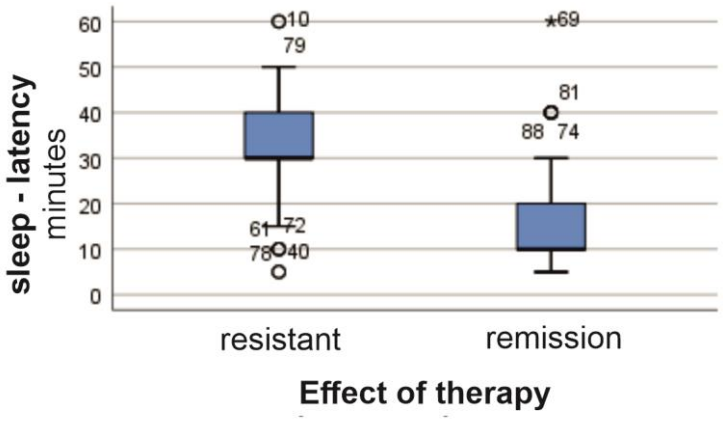
In patients with resistant psychotic symptoms, we found that the mean-time to sleep was 32.89 minutes, the standard deviation was 13,420 with a minimum of 5 minutes and a maximum of 60 minutes.

In patients in clinical remission, the mean sleep time was 16.08 minutes, with a standard deviation of 12.076. The minimum time is five, and the maximum is 60 minutes.

Literature data show that the average time to sleep is usually 10-20 minutes (Jung DW, Hwang SH, et al., 2013). Our data show that in the group of patients with remission, the average sleep time is within these limits - 16.08 minutes / between 10 and 20 minutes /.

The main difference is in patients with resistance, as there is two times greater sleep latency in the group of patients with resistance to psychotic symptoms. Figure 25, p <0.001 (***)

Fig. 25 Relationship between sleep latency and treatment resistance



Conclusion: Patients with resistant schizophrenia have approximately twice as much sleep latency as patients with clinical remission and those in the general population.

33. Duration of sleep in both groups of patients

The duration of sleep in patients from both groups showed the following distribution.

In patients with RS, the average duration of sleep is 550.80 minutes. The standard deviation is 70,102 minutes, and the minimum and maximum are 425 and 690 minutes, respectively.

In patients with CR, the average duration of sleep was 511.73 minutes. The standard deviation is 60,718, and the minimum and maximum are 401 and 640 minutes, respectively. p> 0.05

Conclusion: Our study did not find differences in sleep duration between patients with RS and those in the CR.

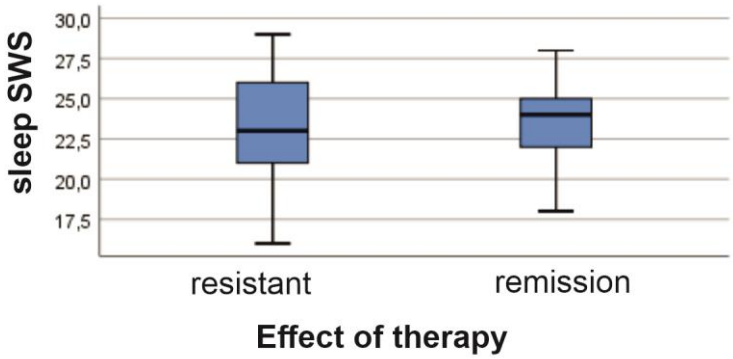
34. Duration of SWS /Slow Wave Sleep - Phase 3 /

We found the following distribution when estimating the duration of slow-wave / SWS / sleep in both groups of patients.

In patients with RS, the mean duration of SWS was 22.93, SD was 3,230, with minimum and maximum values of 16 and 29 per cent, respectively.

Among CR patients, the mean duration was 23.63%, the standard deviation was 2.447, and the minimum and maximum values were 18 and 28 per cent, respectively. Figure 26, p> 0.05

Fig. 26 There was no significant difference between the duration of SWS and the effectiveness of treatment



We found a slightly lower percentage of SWS in patients with resistant seizures and found no clinically significant difference. From the above figure, we can conclude that the distribution of patients with different duration of SWS has much greater variability than those in the group with remission of symptoms. Some authors point out that a reduction in SWS is observed mainly in negative

symptoms or inverse dependence with disorders of the thought process (Yetkin S, Aydın H, et al. 2011; Chan MS et al. 2017). this indicator is very variable in patients with schizophrenia (Forest G et al. 2007; Tandon R et al. 1992).

Conclusion: We do not find a difference in the duration of the slow-wave / SWS, phase 3 / in patients from the two experimental groups.

35. Duration of REM phase / paradoxical sleep - R phase /

The analysis of the duration of REM sleep in the two groups of patients showed the following differences and distribution:

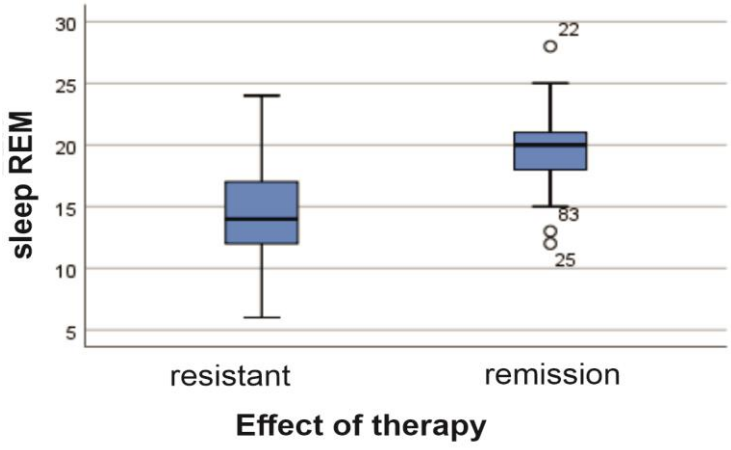
In patients with resistant psychotic symptoms, the mean value of REM sleep was 14.53%, the standard deviation was 4,019, and the minimum and maximum values were 6 and 24 per cent, respectively.

In patients in clinical remission, an average value of 19.57% was found, the standard deviation was 3,109, and the minimum and maximum values were 12 and 28 per cent, respectively.

Intragroup analysis showed that in patients with resistant schizophrenia, the percentage of REM sleep was generally below 20% - in the range of 10 to 20%.

In patients in clinical remission, the prevailing rate is over 20%. Figure 27, p <0.001 (***)

Fig. 27 Comparative analysis of the duration of REM sleep in the observed groups of patients



Our data show a significant difference between patients who are resistant to treatment and those who respond well to it. Observations by other authors (conducted meta-analysis) confirm the thesis that in patients with schizophrenia, a reduction in REM sleep is registered (Chan MS et al., 2017; Yetkin S, Aydın H, et al., 2011; Chouinard S et al., 2004). All authors point out that since there is no uniform population of patients with schizophrenia, but it is a heterogeneous disease, different data represent different variables. In all of them, however, it is emphasised that the reduction of REM sleep is a relatively stable indicator, probably related to the fact that patients with schizophrenia have cognitive impairments manifested as early as the onset of psychosis and with a tendency, albeit variable. To a deterioration over time (Andreasen NC, Moser DJ, et al., 2005; Brewer WJ, Francey SM et al., 2005)

Conclusion: In patients with resistance to treatment, there is a more significant reduction in REM sleep compared to patients in clinical remission.

36. Characteristics of the hypnogram

The hyptogram is a characteristic model that represents the sequence of the individual phases of sleep for the period of its duration. In analysing the hypnograms in the contingent we observed, we divided the hypnograms into two groups according to the time of occurrence of the individual phases of sleep and their number and duration. We included those with normal phase distribution in one group, such as duration and distribution during sleep, and in the other group, those with uncharacteristic manifestations, variable duration and general fragmentation of the hypnogram.

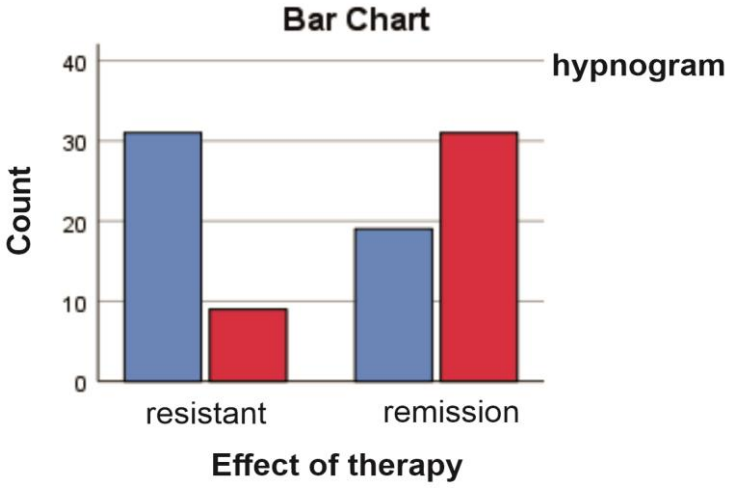
In the analysis of all patients we observed with follow-up of the hypnograms, we found 50 / 55.56% / fragmented form of the hypnogram and the remaining 40 / 44.44% / normal configuration of the hypnogram.

When comparing the hypnograms of patients with RS and those in clinical remission, we obtained the following data:

In patients with resistant symptoms, we found out of 40 analyzed patients in 31 / 77.5% / presence of fragmentation in the hypnogram and 9 / 22.5% / normal distribution of sleep phases. These data show that approximately four times more patients from the refractory group with a fragmented hypnogram were found than the normal distribution in the others.

In patients in remission it was registered at 19/38% / fragmentation, and in the remaining 31/62% / no deviations were found. Figure 28, $p < 0.001$ (***)

Fig. 28 Relationship between hypnogram fragmentation and resistance to therapy



Conclusion: We found that in the group of patients with refractoriness, there was a two times higher frequency of patients with hypnogram fragmentation than patients in clinical remission.

37. Number of awakenings at night in patients with schizophrenia

In the contingent we observed, the following data were found the average number of awakenings at night is 1,375.

In patients with resistant symptoms, an average of 1.83 awakenings were found. The standard deviation was 1,378, with a minimum and a maximum number of 9 and 5 awakenings, respectively.

In patients in remission, the average number of awakenings was 0.92, the standard deviation was 1.111, and the minimum and maximum number were 0 and 4 awakenings, respectively. P <0.001 (***) Figure 29

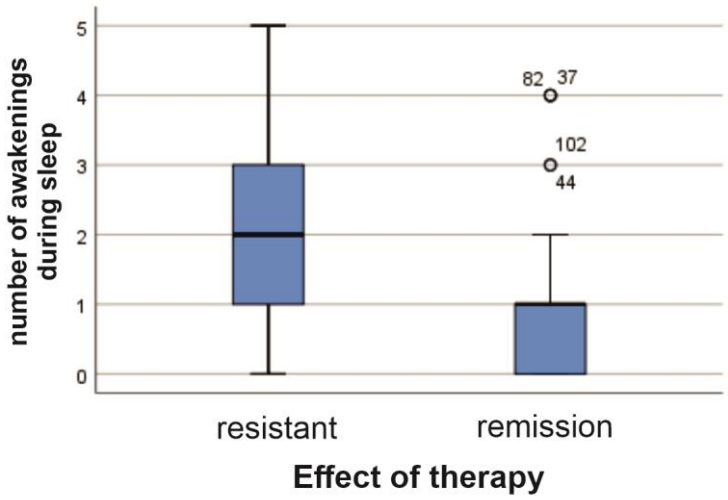


Fig. 29 Distribution of the number of awakenings at night in the observed patients from both groups

From the above data, it is clear that patients with resistant schizophrenia are two times more likely to wake up at night than patients in remission. On the other hand, the tables and data show that there is a much more significant variance in the number of awakenings at night compared to those in the group with control over psychotic symptoms in the resistance group.

Conclusion: We found two times more frequent waking up at night in patients with resistant symptoms than those who achieved remission.

38. Nightmares in patients with schizophrenia

The evaluation of the experiences of the patients we studied showed that some people have terrible, painful and often recurring dreams. They were experienced as negatively burdened experienced by patients that e defined as nightmares. Moreover, given the strictly subjective nature, it is not easy to objectify them with a particular methodology.

In total, in our patients, we found 25 / 23.8% / presence of nightmare experiences and in the remaining 80 / 73.2% / such were not shared.

In patients with resistance to therapy, 19/42% / registered the presence of nightmares and the remaining 26 / 57.8% / did not share the presence of such.

In patients in remission in 6/10% / we found nightmare experiences, and in the remaining 54/90% / we did not find such. Figure 30 p <0.001 (***)

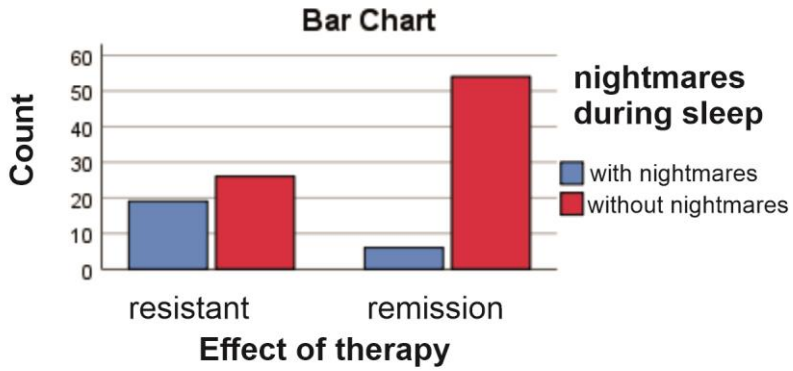


Fig. 30 Relationship of nightmarish experiences with the effectiveness of treatment

From the above results, we can conclude that there is a four times higher percentage of patients with nightmarish experiences than patients in remission in patients with resistance to treatment. Data from the literature analysis show that up to 5% of the population have nightmares with weekly occurrence (Hartmann E. 1984). In 50% of patients with borderline personality disorder, nightmare experiences are reported (Semiz UB, Basoglu C et al. 2008). In schizophrenia, this percentage is estimated to be above 10% (Li S, Lam J, et al. 2015; Sheaves B, Onwumere J, et al. 2015).

It was found that there is a positive correlation between the experience of nightmares and the presence of dissociative experiences. (Levin R, Fireman G. 2002). Given that in our studies, we found a higher level of dissociation in patients with resistant symptoms, we decided to look for another correlation. We sought a link between the results of a study with the Carson and Putnam Dissociative Experience Scale and the presence of nightmares in the contingent we observed.

In patients with established nightmare experiences, we found an average dissociation value of 40,880 / very high /, the standard deviation is 20,388, the minimum value is 4.5 / one patient / and the maximum value is 80.

In those without nightmares, a different distribution is observed. The mean value of the dissociation is 23.105, the standard deviation is 20.5854, and the minimum and maximum values are 0 and 97, respectively.

The result shows that the dissociation in patients with nightmarish experiences is approximately two times higher than in those without them.

Regarding the results obtained about the fragmentation of the hypnogram, waking during sleep and nightmarish experiences, we can draw the following conclusions. On the one hand, we find increased fragmentation of the hypnogram in patients with resistant psychotic symptoms. We find more frequent episodes of

awakening / twice as often as in remission / and approximately four times more frequent experiences of nightmares during sleep. The more frequent awakenings and the nightmares experienced intensively during the REM sleep phase are also directly related to the fragmentation of the hypnogram we observed. A large team of authors confirmed our conclusions by analysing the so-called/lucid dream/living dreaming, concluding that it is associated with fragmentation of the hypnogram, which has been proven in 4 other studies (Jarrod Gott, Michael Rak, et al., 2020).

Conclusion: We found that in patients with resistance to treatment, there is a four times higher percentage of patients with nightmares during sleep compared to the group of patients in remission.

Neurophysiological studies in patients with schizophrenia

39. Assessment of background activity and diffuse EEG changes

When assessing the main activity in all patients observed by us, we found the following dependence. In 32/36% / no deviation in the background activity was found, 23 / 25.8% / have mild ones, 24/27% / have moderate ones and 10 / 11.2% / have severe diffuse changes. Table 79

The distribution of patients in the resistance group showed that patients with a typical finding of basically EEG activity were 4 / 10.3% / those with mild changes were 8 / 20.5% /, on average, we have 19/48, 7% / and severe diffuse changes were observed in 8 / 20.5% / patients.

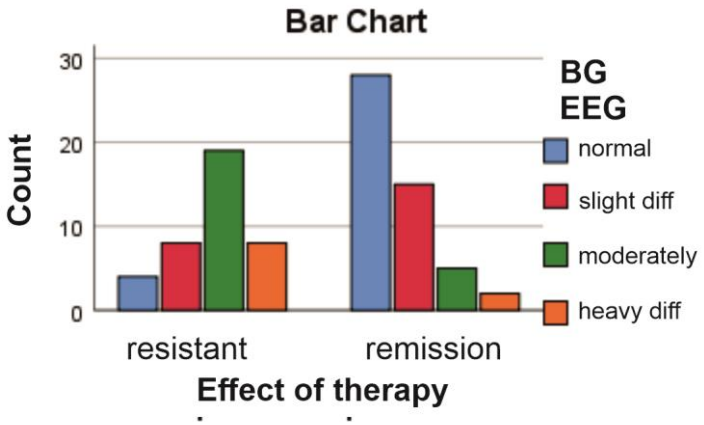
In patients in clinical remission 28/56% / have no deviation in FA, 15/30% / have slight changes, 5/10% / have moderate changes and in 2/4% / severe changes in the basal activity are found. p <0.001, (***) Table 6, Figure 31

Table 6. Distribution of changes in the main activity in patients with resistance and those in clinical remission

Count

		Background activity of EEG				
		nor-mal	Slight diff changes	Moder-ately pro-nounced	Heavy diff changes	Total
Effect of ther-apy	Resistant Remis-sion	4	8	19	8	39
		28	15	5	2	50
Total		32	23	24	10	89

FIG. 31 Distribution of changes in the main activity of patients from both groups



Of all the patients, we found changes in the main activity in 42.2%, and in the literature, the reported percentage of patients with EEG abnormalities ranged between 20 and 60% (Hughes, J.R. and John, E.R. 1999; Torrey, E.F. 2002; Itil, T. M. 1977). There is no consensus on the therapeutic significance of these EEG changes. On the one hand, some authors find that in abnormal manifestations in the EEG, an excellent response to treatment can be expected (Kirkpatrick, B. and Galderisi, S. 2008; Galderisi, S. et al., 2008; Galderisi, S. and Maj, M. 2009). On the other hand, abnormal manifestations in the background activity are associated with an increase in slow-wave activity in general and a slowdown in alpha rhythm.

Other author groups have found that alpha-slowing is mainly associated with poor prognosis (Mucci, A. et al., 2006).

Conclusion: When comparing the percentages of changes between the two groups of patients, it is found five times higher frequency of moderate diffuse changes in the main activity of EEG in the group of patients with resistance and again five times higher frequency of severe diffuse changes in the group of patients with resistant psychotic symptoms.

40. Estimation of alpha rhythm variations

We evaluated the variations in the frequency of the alpha rhythm in both groups of patients. The presence of dysrhythmia / more than 1 Hz difference / was found in 41 / 45.1% / of the patients, and in the remaining 50 / 54.9% / we did not find such. Our data do not differ from those recorded in the general population of healthy individuals (about 1,500 people studied), which shows that split alpha is found in approximately 44% of them (Chiang AK, Rennie CJ, et al. 2011).

The distribution in patients with resistant schizophrenia showed that 25 / 62.5% / have dysrhythmia, and in the remaining 15 / 37.5% / no such is registered.

In patients in clinical remission 16 / 31.4% / have dysrhythmia and the remaining 35 / 68.6% / have no such. Table 7, Figure 32, $p < 0.01$ (**)

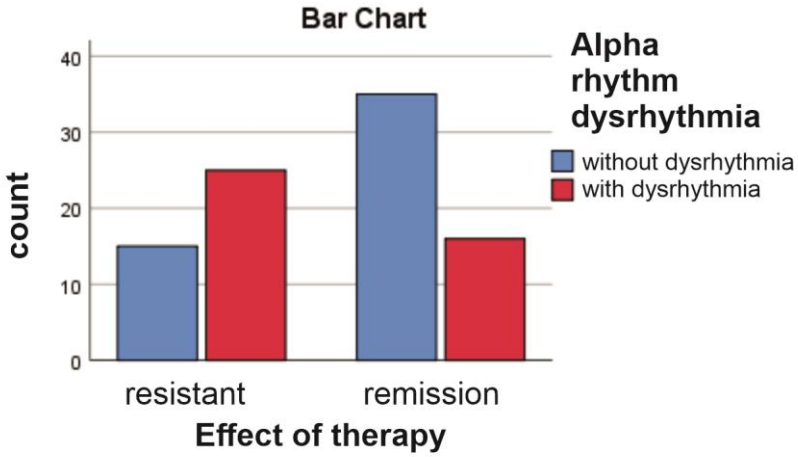
Table 7 Peculiarities of alpha rhythm in both groups of patients

Count

		Alpha rhythm dysrhythmia		
		Without dysrhythmia	With dysrhythmia	Total
Effect of the therapy	Resistant	15	25	40
	Remission			

	35	**16**	**51**
Total	**50**	**41**	**91**

Fig. 32. Relationship of alpha activity dysrhythmia with treatment efficacy



From the analysis, it is clear that in the group of patients with resistant schizoprenia, there is a two times higher incidence of registered alpha rhythm dysrhythmia in the EEG compared to patients in clinical remission. Studies show that the harp frequency usually varies within 1 Hz. More significant variations in alpha frequency are considered to be a pathology that reflects different generators of activity in the brain. Our observations confirm this fact by finding a higher percentage of patients with dysrhythmia in the alpha frequency range than patients with resistance to treatment.

Conclusion: Patients with resistance to treatment have approximately twice as many patients with split alpha rhythm compared to patients in remission.

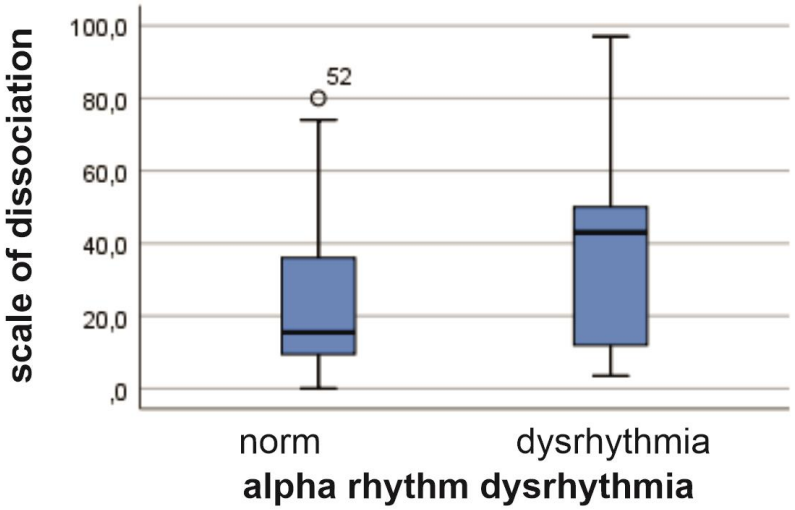
41. Correlation between the presence of dysrhythmia and the degree of dissociation in the observed patients.

In the analysis of the relationship between the registered dysrhythmia and the degree of dissociation, we obtained the following results:

The mean Carlson and Putnam scale dissociation in patients with dysrhythmia was 37.366, SD was 23.6981, and the minimum and maximum values were 3.5 and 97.

The mean value in patients with one peak of the alpha rhythm is 23.688, SD is 20.2069, and the minimum and maximum values are 0.1 and 80.0, respectively. ($p < 0.05$, *), Figure 33

Fig. 33 Relationship between dysrhythmia and the degree of dissociation in patients with schizophrenia



Conclusion: We found a correlation between the split frequency of the alpha rhythm and the level of dissociation. Patients with split alpha rhythm have almost twice the level of dissociation (concerning the median and more than twice) compared with those with one peak of alpha activity.

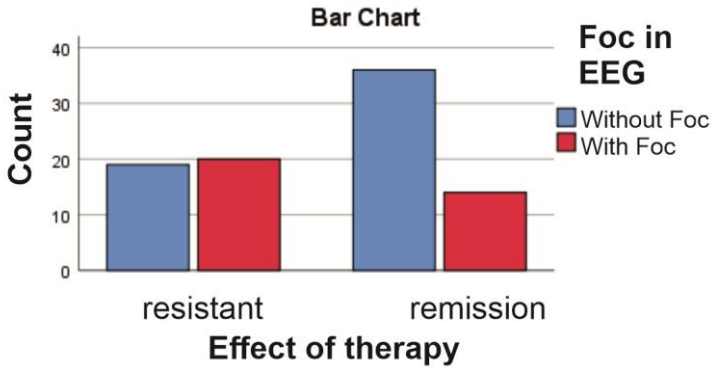
42. Focal activity in EEG in patients with schizophrenia

Analysis of the focal activity from both epileptiform and slow-wave changes showed that in 34 / 38.2% / of the patients with schizophrenia, focal manifestations were registered, and in the remaining 55 / 61.8% / such ones were not detected.

In patients with resistant psychotic symptoms, we found focal activity in 20/51% / of the patients, while in the remaining 19 / 48.7% / no such activity was registered.

In patients in remission in 14/28% /, we found focal activity, and in the remaining 36/76% /, we did not find such. p <0.05, (*) Figure 34

Fig. 34 Relationship between the presence of focal activity in the EEG and the effect of treatment.



Our results show that more than 1.5 times more patients with focal activity in the EEG are observed in patients with resistance than those who achieved clinical remission during treatment. These results correspond to the findings of other authors that in patients with schizophrenia, abnormal manifestations in the EEG are associated with worse course of the disease at a 2-year follow-up (Manchanda R, Norman R, et al., 2005).

Conclusion: We found a higher rate of focal EEG changes in patients with resistant schizophrenia than patients in clinical remission.

43. Lateralisation of focal changes in EEG in both groups

The analysis of the lateralisation of focal activity found that in 61 / 68.5% / of patients, no deviations related to the lateralisation of EEG changes are observed / there may be deviations, but they are not of a focal nature /. In 24/27% /

there are changes in the left hemisphere, and in 4 / 4.5% / of patients, changes were found in the right hemisphere.

Analysing the results in both groups, we found that in the group of patients with RS, 24 / 61.5% / have no lateralisation, 11 / 28.2%/ have abnormalities in the EEG in the left hemisphere, and 4 / 10.3%/ deviations are in the right hemisphere. Despite the differences, no statistically significant difference was found.

When assessing the lateralisation of focal activity in interictal EEG recordings, those with elf-sided lateralisation predominate-65% of studies (Loddonkemper T, Burgess RC et al., 2007). Despite the smaller number of patients, our data correspond to the results of the above authors, and we also found a higher percentage of patients with focal activity in the left hemisphere.

Conclusion: Lateralised focal changes in the EEG predominate in the left hemisphere. In patients with resistance, a higher percentage of patients with lateralisation of the changes is observed than those in the CoR.

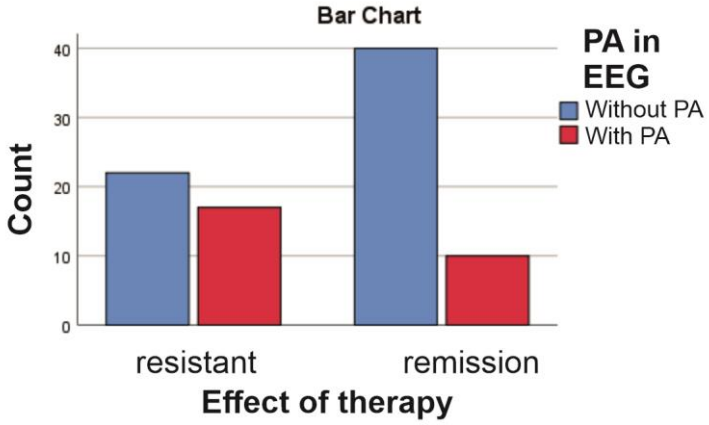
44. Paroxysmal EEG activity in patients with schizophrenia

In the patients with schizophrenia, we observed epileptiform paroxysmal episodes found in 27 / 30.3% / and in the remaining 62 / 69.7% / patients, no such changes were found.

In patients with resistant symptoms, we found 17 / 43.6% / presence of epileptiform discharges, while the remaining 22 / 56.4% / paroxysmal changes were not observed.

In patients in clinical remission, we found 10/20% / paroxysmal activity, while in the remaining 40/80% /, we did not register such. $p < 0.05$ (*), Figure 35

Fig. 35 Relationship between paroxysmal EEG activity and treatment effect



Conclusion: The results show a more than two times higher incidence of paroxysmal epileptiform discharges in patients with resistance than in patients who reach clinical remission.

Evaluation of quantitative parameters and frequencies in EEG in both groups of patients with schizophrenia

45. Estimation of the absolute power of the delta frequency range

When estimating the absolute power of the delta spectrum in the two experimental groups of patients, we found the following results:

In the group of patients with resistant psychotic symptoms, the mean value of absolute power was 18.0541, the median was 14.9000, and the standard deviation was 14.9000. The minimum and maximum values are 4.15 and 79.00, respectively.

In the group of patients in remission, the mean was 12.7780, the median was 7.8000, and the standard deviation was 14.19201. The minimum and maximum values are 2.5 and 68.10, respectively. Our research shows a trend, but without reaching a statistically significant difference.

What is impressive from the obtained results is that there is approximately two times higher absolute power of delta activity in the group of patients with resistance to treatment than the median values. Table 8

Table 8 Comparative analysis of delta activity in EEG in the observed groups of patients.

M-Estimators[a]

	Effect of the therapy	Huber's M-Esti-mator[b]	Tukey's Biweight[c]	Hampel's M-Esti-mator[d]	Andrews' Wave[e]
Absol delta	Resistant re-mission	15,1326	14,0456	14,8772	14,0366
		8,1171	7,3471	7,6516	7,3446

Conclusion: In patients with resistance to treatment, approximately two times higher absolute power of delta activity is observed about the median values.

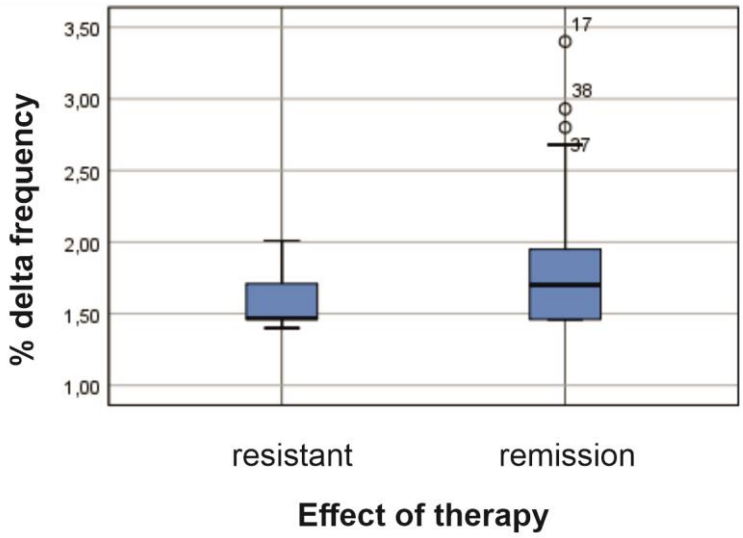
46. Comparative assessment of the mean peak spectral frequency of the delta frequency range in the two groups of patients

The following values were found when estimating the peak frequency in the delta spectrum with FFT in both groups of patients.

In patients with resistant symptoms, the mean frequency in the delta range is 1.5995 Hz, the standard deviation is 0.19479, and the minimum and maximum values are 1.40 and 2.01 Hz, respectively.

In the group of patients with CR, the average value of the frequencies in the delta spectrum is 1.8243 Hz, the standard deviation is 0.45681, and the minimum and maximum frequencies are 1.49 and 3.4, respectively. Figure 36

Fig. 36 Distribution of the peak frequency in the theta frequency range in the two groups of patients



Conclusion: Patients with RS have lower peak delta spectral power than those in CR.

47. Estimation of the absolute power of the theta frequency range

In the analysis of the absolute power of the theta spectrum, we found that in the group with resistance, the average power in the theta frequency range is 10.6987 mkV / 2, the standard deviation is 9.09066, and the minimum and maximum values are 3.36 and 55, respectively. 4 mkV / 2.

In the clinical remission group, the mean power was 6.6904, the standard deviation was 7.44455 mkV / 2, and the minimum and maximum values were 1.6 and 45.0 mkV / 2, respectively.

What is impressive from the results obtained is that there is approximately two times higher absolute power of theta activity than the median values in the group of patients with resistance to treatment. There is a statistically significant difference -p <0.001 (***).

Conclusion: The results show that in the group of patients with resistant psychotic symptoms there is a higher absolute power in the theta frequency range.

48. Comparative assessment of the peak spectral frequency of the theta frequency range in both groups of patients.

The following values were found when estimating the peak frequency in the theta spectrum with FFT in both groups of patients.

In patients with resistant symptoms, the average frequency in the theta frequency range is 5.5477 Hz, the standard deviation is 1.27631, and the minimum and maximum values are 4.01 and 7.32 Hz, respectively.

In the group of patients with CR, the average value of the frequencies in the theta spectrum is 6.7814 Hz, the standard deviation is 0.45681, and the minimum and maximum frequencies are 4.01 and 7.8 Hz, respectively.

Conclusion: Studies have shown a lower mean peak frequency of theta spectrum in patients with resistance without statistically significant difference in outcomes between groups.

49. Estimation of the absolute power of the alpha frequency range

In the analysis of the absolute power of the alpha spectrum, we found that in the group with resistance, the average power in the alpha frequency range is 54.3733 mkV / 2, the standard deviation is 41.24774, and the minimum and maximum values of 5.20 and 150 mkV, respectively / 2.

In the clinical remission group, the mean power was 60.6545, the standard deviation was 50.78137 mkV / 2, and the minimum and maximum values were 3.50 and 185 mkV / 2, respectively.

The analysis of the results shows no statistically significant difference in absolute power in the alpha frequency range between the two experimental groups of patients. In contrast to the consideration of the other powers in the above frequency spectra, in this case, we have increased absolute power in the group of patients in clinical remission. There was a more significant variance in the results between patients in the same group, both in terms of averages and medians. We have higher values for both indicators in the clinical remission of symptoms group.

Conclusion: The absolute spectral power for the alpha frequency range showed that a higher value was observed in the CR group but without statistical significance.

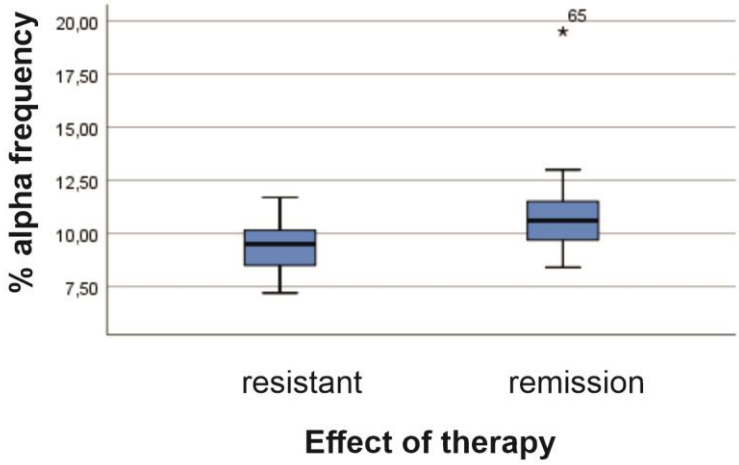
50. Comparative assessment of the peak spectral frequency of the alpha frequency range in both groups of patients.

When estimating the peak frequency in the alpha spectrum with FFT in both groups of patients, the following values were found:

In patients with resistant symptoms, the mean frequency in the alpha frequency range is 9.3538 Hz, the standard deviation is 1.08770, and the minimum and maximum values are 7.2 and 11.70 Hz, respectively.

In the group of patients with CR, the average value of the frequencies in the alpha spectrum is 10.8665 Hz, the standard deviation is 1.68505, and the minimum and maximum frequencies are 8.4 and 12.5 Hz, respectively. Figure 38

Fig. 38 Distribution of the peak spectral power of the alpha frequency range in relation to the effect of the therapy



The above results found that a lower mean spectral peak frequency of the alpha rhythm was observed compared to patients in clinical remission. The difference between the two groups is 1.5 Hz, which indicates that there is a general delay in alpha rhythm in patients with resistant symptoms. These differences outline a trend that does not reach a statistically significant difference of $p > 0.05$.

Studies in patients with schizophrenia have shown that analysis of almost all studies has shown a reduction in peak alpha rate (Karson CN et al., 1988; Ramsay, I.S., Lynn, P.A., et al., 2021). Our study shows that the reduction in alpha peak

frequency is more pronounced in patients with resistant psychotic symptoms. The mean peak alpha rhythm frequency in resistant patients is 9.4 Hz (median 9.5 Hz), with frequency studies showing that a mean frequency below 10.2 Hz is associated with the development of changes in neuroimaging studies in patients with schizophrenia (Carson CN et al., 1988).

Conclusion: We find a lower frequency of alpha rhythm / low mean peak spectral frequency / in patients with resistance than in those who have reached clinical remission.

51. Estimation of the absolute power of the beta frequency range

In the analysis of the absolute power of the alpha spectrum, we found that in the group with resistance, the average power in the alpha frequency range is 4.0869 mkV/ 2, the standard deviation is 3.29040, and the minimum and maximum values are 0.70 and 16, respectively. 50 μV /2.

In the clinical remission group, the mean power was 3.7333, the standard deviation was 2.16567 mkV /2, and the minimum and maximum values were 0.40 and 2.50 mkV / 2, respectively.

Conclusion: There were no differences in the absolute power for the beta frequency range between the two groups of patients

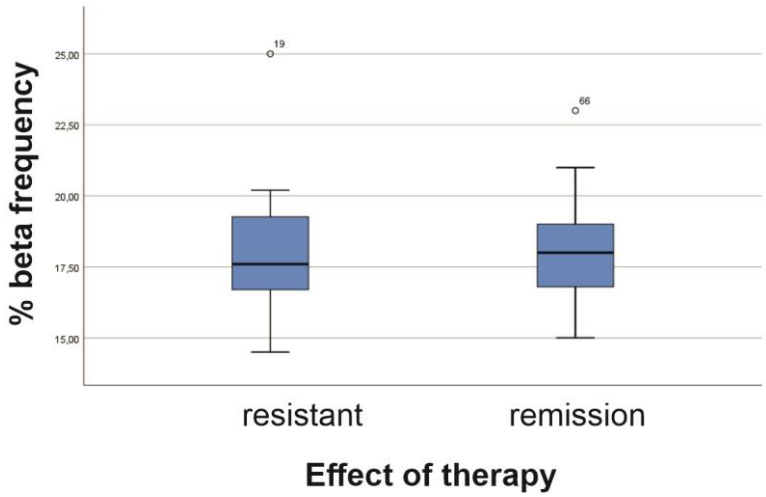
52. Comparative evaluation of the peak spectral frequency of the beta frequency range in both groups of patients.

The following values were found when estimating the peak frequency in the alpha spectrum with FFT in both groups of patients.

In patients with resistant symptoms, the mean frequency in the beta frequency range is 17.9600 Hz, the standard deviation is 1.86955, and the minimum and maximum values are 14.5 and 25.00 Hz, respectively.

In the group of patients with CR, the average value of the frequencies in the beta spectrum is 18.0161 Hz, the standard deviation is 1.55074, and the minimum and maximum frequencies are 15.00 and 23.00 Hz, respectively. Figure 40

Fig. 40 distribution of the peak frequency in the beta spectrum in both groups of patients



Conclusion: There is no difference when comparing the mean peak frequencies of the beta frequency range in the two groups of patients.

53. Estimation of the absolute power of the gamma frequency range

In the analysis of the absolute power of the gamma spectrum, we found that in the group with resistance, the average power in the gamma frequency range is 0.6015 mkV/2, the standard deviation is 0.44723, and the minimum and maximum values are 0.08 and 1, respectively. Nine μV /2.

In the clinical remission group, the mean power was 0.5022 mkV/2, the standard deviation was 0.39573, and the minimum and maximum values were 0.03 and 1.8 mkV/2.

The analysis showed no statistically significant difference between the two groups of patients, noting the higher variance of the results and the higher power in the gamma spectrum in the group with therapeutic resistance.

Conclusion: We do not find a difference in the absolute power for the gamma frequency range in patients with resistant symptoms and those in clinical remission. The higher variance of the results in the gamma spectrum in resistant patients was also reported.

54. Comparative evaluation of the peak spectral frequency of the gamma frequency range in both groups of patients.

The following values were found when estimating the peak frequency in the gamma spectrum with FFT in both groups of patients

In patients with resistant symptoms, the average frequency in the gamma frequency range is 31.2154 Hz, the standard deviation is 1.86955, and the minimum and maximum values are 29.60 and 35.60 Hz, respectively.

In the group of patients with CR, the average value of the frequencies in the gamma spectrum is 31.1129 Hz, the standard deviation is 094999, and the minimum and maximum frequencies are 29.79 and 34.18 Hz, respectively.

The obtained results show that no significant difference was observed between the two groups, as again, a slightly more significant variance of the results was found in the group of patients with refractory treatment.

Conclusion: There was no difference in the mean peak frequency for the gamma frequency range between the two groups.

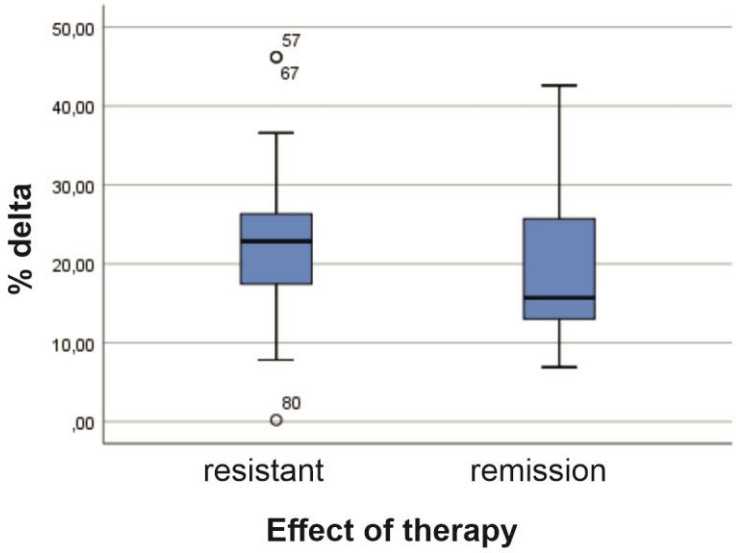
Estimation of the relative / percentage / power of the individual frequency spectra in the two groups of patients

55. Estimation of the relative power of the delta frequency range

When estimating the relative/percentage / power of the delta spectrum in the two experimental groups of patients, we found the following results:
In patients with resistant psychotic symptoms, relative power was found - 23.0900%, the median was 22.8500, and the standard deviation was 9.15235. The minimum and maximum values are 0.20 and 46.20%, respectively.

In the group of patients in remission, the mean was 19.7757%, the median was 15.7000, and the standard deviation was 9.13639. The minimum and maximum values are 6.90 and 46.60%, respectively. Figure 42 $p < 0.05$ (*)

Fig. 42 Comparative analysis of the relative power in the delta range in the two groups of patients.



The described results show that in the group of patients with RH, there is a higher percentage of power in the delta frequency range than in those with clinical remission. This is particularly demonstrative of the medians in both groups. The median of relative power in patients with resistant symptoms is about 50% higher than in patients in remission.

Conclusion: We find that there is a higher percentage of power in the delta frequency range in the group of patients with resistant schizophrenia than in those with clinical remission.

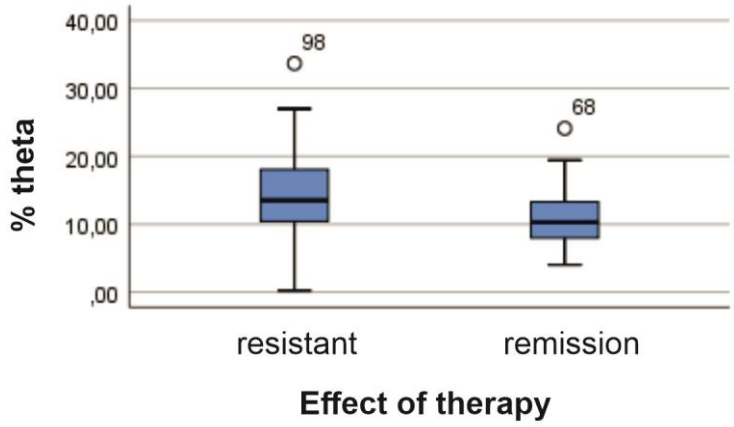
56. Estimation of the relative power of the theta frequency range

When estimating the relative/percentage / power of the theta spectrum in the two experimental groups of patients, we found the following results:

In patients with resistant psychotic symptoms, relative power was found - 14.5851%, the median was 13.5000, and the standard deviation was 6.72990. The minimum and maximum values are 0.24 and 33.67%, respectively.

In the drug remission group patients, the mean was 10.8335%, the median was 10.2900, and the standard deviation was 4.24839. The minimum and maximum values are 4.02 and 24.11%, respectively. P <0.01 (**) Figure 43

Fig. 43 Comparison of the relative power of the theta frequency range according to the effect of the treatment



A comparative analysis revealed a statistically significant relationship between the two groups of patients, with approximately 50% higher relative power values in the group with RH that in the clinical remission group.

Conclusion: In patients with resistance to treatment, we find a higher relative power of the theta spectrum than patients in remission.

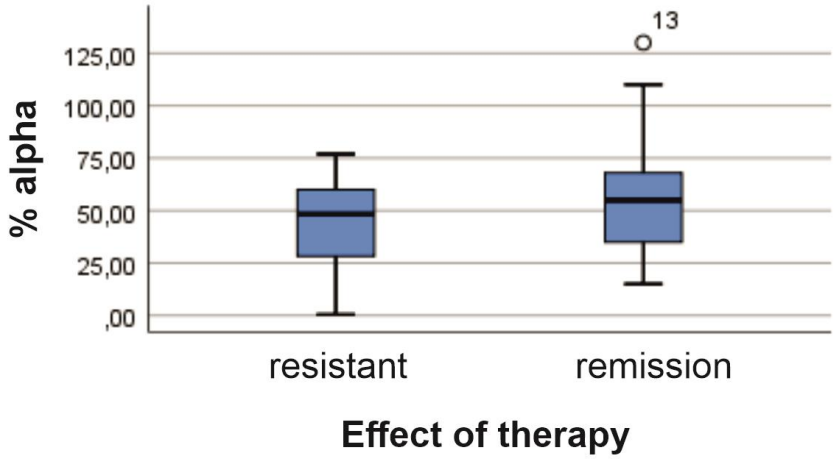
57. Estimation of the relative power of the alpha frequency range

When estimating the relative/percentage / power of the alpha spectrum in the two experimental groups of patients, we found the following results:

In patients with resistant psychotic symptoms, relative power was found - 44.9038%, the median was 48.3400, and the standard deviation was 19.52865. The minimum and maximum values are 0.50 and 77.00%, respectively.

In the drug remission group patients, the mean was 54.5347%, the median was 55,000, and the standard deviation was 23.31727. The minimum and maximum values are 15.00 and 130.00, respectively. $p < 0.05$, (*) Figure 44

Fig. 44 Comparison of the relative power of the alpha range in the two groups of patients



The presented results show that a higher relative power of alpha is observed in the group of patients in remission compared to those with refractory symptoms, finding a statistically significant difference with a relatively low correlation coefficient.

Conclusion: We found a higher relative power for the alpha frequency range in the group of patients in clinical remission compared to those with resistance to therapy.

58. Estimation of the relative power of the beta frequency range

When estimating the relative/percentage / power of the beta spectrum in the two experimental groups of patients, we found the following results:
In patients with resistant psychotic symptoms, the relative power was -6.836346%, the median was 5.0000, and the standard deviation was 4.9906010. The minimum and maximum values are 0.275 and 19.3300%, respectively.

In the drug remission group, the mean was 7.137347%, the median was 6.50000, and the standard deviation was 4.0752688. The minimum and maximum values are 1,400 and 18,300, respectively.

From the presented data, it is clear that there is no significant difference between the two groups in terms of relative power in the beta spectrum.
Conclusion: There were no differences in the relative power in the beta frequency range between the two groups of patients.

59. Estimation of the relative power of the gamma frequency range

When estimating the relative/percentage/power of gamma spectrum in both groups, we found the following results:

In the group of patients with resistant psychotic symptoms, the relative power of 1.0267% was found, the median was 0.6600, and the standard deviation was 0.85692. The minimum and maximum values are 0.00 and 3.10%, respectively.

In the drug remission group patients, the mean was 1.2333%, the median was 0.7500, and the standard deviation was 1.47845. The minimum and maximum values are 0.13 and 9.00%, respectively.

The assessment of the relative power in the gamma spectrum showed no difference between the two groups of patients. An insignificant prevalence of percentage power is observed in patients in clinical remission.

Conclusion: No differences in the relative power in the gamma frequency range between the two groups of patients were found.

60. Comparative assessment of the scale for social functioning in the two groups of patients / SOFAS /

This scale focuses mainly on functioning mainly in social and work aspects. These two aspects are essential for the adaptation and socialisation of patients. Factors that are impaired in various mental disorders are derivable from it. However, even the definition of "mental disorder" emphasises the importance of addressing these two aspects of human behaviour that underlie the building of its autonomy.

In the analysis of the SOFAS scale in both groups, we observed the following distribution:

In the group of patients with RS, the average value of the scale is 41.78, SD 7.699, as the registered minimum and maximum values are 20 and 50 points.

In patients with CR, the mean value of the scale is 83.50, SD is 9.356, and the minimum and maximum values are 70 and 100 points, respectively. $p < 0.001$

The results again demonstrate the requirement to identify the presence of a severe social and occupational disorder in the differentiation of patients, and in resistant cases, the SOFAS score should be below 60 points (Howes, Oliver D et al., 2017).

Conclusion: In the resistant patients we studied, the SOFAS index is below 60 /41.78/, finding approximately twice as low a value as patients in clinical remission.

CHAPTER FIVE: CONCLUSIONS

The analysis of the results showed that we could draw the following conclusions about the differences between the two groups:

1. Males are more likely to be resistant.
2. Asthenic habit is more common in patients with resistant symptoms.
3. Early onset of psychosis, longer duration of schizophrenia, and longer duration of untreated psychosis are more likely to be resistant.
4. More severe forms of schizophrenia are associated with higher morning cortisol levels.
5. Assessment of lateralisation of brain functions shows that cross-dominance is associated with twice the likelihood of symptom resistance
6. More than half of patients with male schizophrenia have a female role identification. We have not found a link between this identification and seizure resistance. There are no differences between the groups regarding identification with a particular gender role.
7. In patients with resistant schizophrenia, PANSS and BPRS are approximately twice as high as in remission.
8. The level of depressive symptoms, anxiety and obsessive-compulsive spectrum symptoms are higher in patients with resistance to symptoms
9. Patients with resistant schizophrenia have three times higher levels of dissociation than patients in remission. That seriously raises the question of the overlap of symptoms between the two nosological constructs (dissociative personality disorder and resistant schizophrenia) and the lack of a clear demarcation line between them.
10. We found more severe impairment of fixation and reproduction in patients with resistant schizophrenia than in those in clinical remission. No difference was found in terms of information retention in the two groups.
11. We found severe differences in the type of memory curves / the way of memorising/reflecting the state of active attention in the two groups. The primary type of memory is "unstable" or "plateau" type memory curves, more characteristic of patients with resistant symptoms.
12. The comparison between the highest represented scales of CPV showed that the scale of hysteria is overrepresented (three times more) in patients with RH. We did not find differences in the performance of the other rocks in the two groups of patients

13. The evaluation of the effectiveness of the first administered antipsychotic shows that the lack of effect is associated with a 2.5 times higher probability of resistance to symptoms, and in the analysis of the effect of therapy in the first two weeks of treatment is registered four times more high probability of resistance.
14. Patients with resistant seizures have taken twice as many different types of antipsychotic drugs as those in clinical remission.
15. We find an overall increased percentage of smokers, drinkers, cannabinoids and psychostimulants in patients with resistant schizophrenia without a statistically significant difference.
16. The analysis of sleep and sleep architectonics found twice as high sleep latency, more significant reduction in REM sleep and twice as much fragmentation of the hypnograms in patients with resistance to treatment.
17. Patients with resistant schizophrenia were twice as likely to wake up at night and four times more likely to have nightmares than those in clinical remission.
18. The assessment of diffuse changes in the background EEG activity showed a significant prevalence (up to 5 times difference) in patients with RS than those in the CR.
19. In the group of patients with resistance to treatment was found a twice as high percentage of patients with a split peak frequency of alpha/dysrhythmia/, up to 1.5 times more frequent registration of focal activity and twice as frequent registration of epileptiform paroxysmal episodes in the EEG compared with those with remission of symptoms.
20. In patients with resistance to treatment, approximately higher absolute power of delta and theta activities and lower peak frequencies were observed for these spectral powers in the group with resistant schizophrenia.
21. The characteristics of the alpha frequency range in the studied patients showed lower values of spectral power/relative and absolute / and a lower peak frequency in patients with resistant schizophrenia.
22. In the resistant patients we studied, the SOFAS index is below 60 /41.78/, finding approximately twice the value compared to patients in clinical remission.

CHAPTER SIX: ALGORITHM OF DIFFERENCES BETWEEN THE TWO GROUPS

ALGORITHM OF THE DIFFERENCES IN THE COURSE OF THE DISEASE IN PATIENTS WITH RESISTANT AND REMITTED FORMS OF SCHIZOPHRENIA

The complex assessment of the peculiarities of the course of schizophrenia: psychological analyses, scales for assessment of individual subdomains, complex clinical observation and neurophysiological studies allowed us to identify the most critical factors determining the differences in the course of the disease.

In patients in clinical remission

1. Later onset of psychosis
2. Normosthenic or picnic habit
3. Early initiation of treatment after the onset of psychosis
4. Normal cortisol levels
5. The patient may be right-handed or left-handed.
6. No severe depressive symptoms
7. Milder or no symptoms of obsessive-compulsive spectrum
8. Low level of dissociative symptoms
9. Slight impairment of cognitive functions
10. There is no connection with a certain scale of the BPQ
11. Effect of the first antipsychotic drug
12. Effect of treatment during the first two weeks of the therapeutic course
13. Taking a smaller total number of antipsychotic medications used
14. Lack of history of alcohol, cannabis and psychostimulants.
15. Normal / preserved / sleep latency
16. Normal duration of REM sleep.
17. Normal structure of the hypnogram
18. No waking during sleep is observed
19. Nightmare experiences are not shared during sleep
20. No diffuse changes in the background activity of the EEG were observed
21. Alpha rhythm has a normal distribution and configuration
22. No focal activity was observed in the EEG
23. No paroxysmal episodes are recorded in the EEG
24. When conducting FFT, there is no increased absolute and relative power for the slow-wave spectra
25. No changes were observed concerning the mean peak frequencies for the delta, theta and alpha spectra.

26. The SOFAS index is in average values corresponding to adequate social potential.

In patients with resistant schizophrenia

1. Early onset of psychosis
2. Asthenic habit
3. Delayed, late start of treatment after the onset of psychosis
4. High levels of cortisol in the morning
5. The patient has cross dominance / mixed dominance /
6. With higher depressive symptoms, but without reaching a syndromic severity.
7. High level of dissociation
8. More pronounced symptoms of the obsessive-compulsive spectrum.
9. Severe impairment of cognitive functions
10. Higher scale of hysteria when conducting BPQ
11. Lack of effect of the first antipsychotic drug
12. Lack of effect of treatment during the first two weeks of the therapeutic course.
13. Taking a more significant total number of antipsychotic medications used
14. There is a history of alcohol, cannabis and psychostimulants.
15. Prolonged sleep latency
16. There is a reduction in REM sleep.
17. Fragmentation of the hypnogram
18. Frequent waking during sleep.
19. Nightmare experiences during sleep are shared.
20. Pronounced diffuse changes in the EEG FA.
21. Alpha rhythm is divided in terms of peak frequency.
22. There is s focal activity in the EEG
23. Registration of paroxysmal activity in EEG
24. When conducting FFT, there is an increased absolute and relative power for the slow-wave spectra
25. Registration of lower mean peak frequencies for delta, theta and alpha spectra.
26. The SOFAS index has low values corresponding to the loss of social skills.

CHAPTER SEVEN: CONCEPTUAL MODEL OF A PATIENT WITH RESISTANT SCHIZOPHRENIA

Based on the unmeasured differences, we can try to describe the patient with resistant schizophrenia.

A male patient with an early onset of psychosis (before 20) did not receive treatment after its onset. The patient is left-handed or of mixed dominance, to be more precise. He does not engage in sports activities, avoiding the pain of sports. And social contacts in general. He has a high degree of dissociation when conducting research and elevated scales for depression and anxiety. There are also obsessive-compulsive symptoms without a syndromic degree of manifestation. Conducting an EEG shows the dissociation of the alpha rhythm, diffuse changes in background activity, and the presence of focal and paroxysmal manifestations. There are difficulties in concentration, attention and working memory. The patient has episodes of alcohol, cannabis and psychostimulants. There are sleep problems, difficulty falling asleep, getting up often and evidence of nightmare sleep experiences. Conducting EEG (with FFT) shows high values for the delta and theta spectrum and slows down the alpha rhythm's frequency. Difficulties in dealing with daily activities and subsequent isolation from the social environment.

Explanation of the described model / logical modelling /

Male sex / is probably because most diseases are more malignant in him /. Earlier age of onset is understandable in increased vulnerability, especially during puberty. On the other hand, it is essential to note that cognitive and behavioural changes begin years before the onset of psychosis.

The changes expected during puberty are also the most vulnerable period during which the third age crisis of identity, sexuality and authority is resolved. On the other hand, susceptibility to situations of stress and vulnerability are also

related to genetic predisposition. It is materialised in the way of lateralisation of brain processes set as the presence of cross-dominance in patients with schizophrenia.

Puberty is the period that, due to its vulnerability, is most susceptible to experiencing stressful situations predisposing to the development of dissociative symptoms. Lack of criticality and non-cooperation associated with psychosis lead to a long period during which no treatment is provided. A period during which there are no opportunities for establishing gender identity and taking a subordinate position. A period in which psychosis transforms the individual's biochemical, neurophysiological, and behavioural. Changes over time / during which no treatment has been carried out / are consolidated as models of organisation in the CNS. The consolidation of the new organisation models makes it difficult to achieve an effect when using the first antipsychotic drug and the difficulties in achieving an effect in the first two weeks of treatment.

Stress and dissociation reactions and changes associated with the duration of untreated psychosis also transform the generators of neuronal activity, represented by the fundamental frequency - alpha frequency cannot reach general synchronisation, and a split alpha rhythm appears. It emphasises the presence of dissociated neuronal substrates looking for common synchronisation mechanisms. Unconscious attempts are often made to restore the described imbalance by testing the effectiveness of external factors such as alcohol, cannabis and psychostimulants. That leads to additional violation (we can also use the term catalysis) of the changes in the internal associative relations with subsequent expression of the described phenomena in the EEG.

There is a change in behaviour and an increase in PANSS and BPRS, a transformation of the personality profile to "hysteria" on the scale of CPV / reflecting the dissociation /again. The search for stability in a new level of organisation also leads to a shift of alpha generators to lower frequencies, which we find in these patients. Driving this vicious circle leads to additional changes in sleep and sleep architectonics with the formation of an unstable type of hypnogram, frequent awakening, and further intensification of aneroid experiences and dissociative phenomena of experiencing stress associated with the disease and increased cortisol levels. Therapeutic interventions have a partial and incomplete effect. The loss of social cohesion is intensifying. Dissociation becomes high and measurable with dissociative personality disorder (DLD). The

treatment of DLR itself with antipsychotics is unsuccessful, and the patient with a similar profile falls into the group of patients with resistant schizophrenia.

That is a modest attempt to logically assemble the factors we have identified related to resistance and their interdependence as influencing the development of the schizophrenic process.

CHAPTER EIGHT: CONCLUDING REMARKS AND CONTRIBUTIONS

The above differences in the factors determining the course of the disease in the two groups of patients give us reason to conclude that the main difference between them is the progression of the disease in the group of patients with resistant schizophrenia.

The progression of the disease in them exceeds the potential of antipsychotic drugs. A natural result is the long duration of the disease, the presence of numerous changes in the scales for assessing anxiety, depression, obsessive-compulsive symptoms, dissociation, sleep disorders and changes in neurophysiological parameters.

Our results show that resistant schizophrenia manifests itself early in the course of the disease, age of onset, duration of untreated symptoms, the effect of the first antipsychotic drug and the outcome of the first two weeks of therapy.

The other differences we observe can be discussed in the context of the progression of schizophrenia over time with the formation of a gradient transformation of neurophysiological indicators, changes in some scales, social dysfunction and the deepening of cognitive and dissociative indicators.

We believe that our comparative clinical-neurophysiological and psychological assessment of the differences between patients with resistant schizophrenia and those in remission have primarily practical applications and are mainly theoretical. The differences we studied are easily applicable and can be used in the assessment of patients and the preparation of a therapeutic plan in order to achieve maximum control of psychotic symptoms and prevention of psychosocial consequences resulting from the development of schizophrenia.

At the end of the analysis, we should note that based on the more excellent dispersion of results within the group in the evaluation of some indicators, we can expect that there will be a "jump" of patients from one group to another over time. Despite this fact, which is inevitable due to the lack of logic in the course of the disease and the possibility of spontaneous remissions / in our study, we aimed to derive indicators that may guide and essentially determine in direct clinical work.

Contributions:
Original contributions

1. A comprehensive summary assessment of the differences associated with the course of schizophrenia in patients with resistance to psychotic symptoms and those in remission.

2. Resistance factors have been assessed by bringing out some new aspects.

3. A parallel assessment of the relationship between the various factors related to resistance allowed its conceptual modelling.

4. A comparative assessment of the changes in the standard EEG finding, the paroxysmal and focal indicators, and the quantitative parameters in the neurophysiological indicators: absolute and relative powers.
5. An analysis of therapeutic interventions as an indicator with early diagnostic value has been prepared.

6. The type of cognitive indicators is assessed as a factor related to resistance and derivable from it.

Contributions of a confirmatory and practical nature

1. Some factors related to psychosis resistance have been reaffirmed.

2. A conceptual model for assessment and analysis of the resistant patient has been developed.

3. An algorithm of differences depending on the effect of the applied treatment is developed.

Publications on the topic of the dissertation

1.Panov G. (2022) Dissociative Model in Patients With Resistant Schizophrenia. *Frontiers in Psychiatry* 13: 845493. doi: 10.3389/fpsyt.2022.845493 **Impact Factor – 4, 157**

2. Panov G. (2022) Comparative Analysis of Lateral Preferences in Patients With Resistant Schizophrenia. *Front. Psychiatry* 13:868285. doi: 10.3389/fpsyt.2022.868285 **Impact Factor -4,157**

3. Panov G. (2022) Early markers in resistant schizophrenia. Effect of the first antipsychotic drug**.** Advances in the Diagnosis and Management of Psychosis. *Diagnostics*. 2022; 12(4): 803. https://doi.org/10.3390/ diagnostics12040803 **Impact factor – 3,70**

4. Panov G. Djulgerova S, Panova P. The effect of education level and sex differences on resistance to treatment in patients with schizophrenia. Bulgaria Medicine.2022; 1; 12 / in press/

5. Panov G. Comparative anthropometric criteria in patients with resistant schizophrenia. Bulgarian Medicine 2022; 1; 12 /in press/

Participation in scientific forums and presentations related to the dissertation

1. Panov G. Mental disorders and neurodegeneration "Neurodegenerative diseases, symptoms and complications", Sunny Beach. 24-25.09.2021
2. Panov G. Schizophrenia and sleep, Conference Somnology, Sofia Hotel Marinela. 2021. 5-7.11
3. Panov G. Dissociation, mental disorders and epilepsy - Psychosomatics, Borovets. 2021, 25-27
4. Panov G. Pain and psyche - Psychosomatics. 25 - 27.06.2021
5.Panov G. Inflammation, sleep, depression - Psychosomatics, 25 - 27.06.2021
6. Panov G. Sleep disorders in mental illness - Psychosomatics, Hissar 25 - 27.09.2020
7. Panov G. Dissociative disorders - Psychosomatics, Borovets 25 - 27.09.2020
8. Panov G. Gender differences in the course of mental disorders. BPA. Pomorie. 2019
11. Panov G. Neuroplasticity and neurodegeneration. BPA. Pomorie. 2019