Universitatea Transilvania din Brașov

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Clinical-paraclinical and treatment correlations in the evolution of patients with schizophrenia

SUMMARY

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List of Abbreviations

BACS - Brief Assessment of Cognition in Schizophrenia
CBD – Cannabidiol
CI – Confidence Interval
CONTROL - Control Group
CT - Computed Tomography
E - Excitatory
E/I – Excitatory/Inhibitory Balance
FGA – First Generation Antipsychotics
fMRI - Functional Magnetic Resonance Imaging
fMRS – Functional Magnetic Resonance Spectroscopy
GABA - Gamma-Aminobutyric Acid
I - Inhibitory
IQ – Intelligence Quotient
LAI - Long-Acting Injectable Antipsychotics
LAI-AP – Cohort of Patients Treated with Long-Acting Injectable Antipsychotics
MATRICS - Measurement and Treatment Research to Improve Cognition in Schizophrenia
MCCB – MATRICS Consensus Cognitive Battery
MRS - Magnetic Resonance Spectroscopy
NIMH - National Institute of Mental Health
NMDA - N-Methyl-D-Aspartate
OAP – Cohort of Patients Treated with Oral Antipsychotics
PET - Positron Emission Tomography
SCH – Cohort of Patients Diagnosed with Schizophrenia
SGA – Second Generation Antipsychotics
SPECT - Single Photon Emission Computed Tomography
TAAR1 - Trace Amine-Associated Receptor 1 Agonists
PES – Cohort of Patients with First Episode Schizophrenia
VIP - Vasoactive Intestinal Peptide

ABSTRACT

Introduction: Neuroimaging serves as an essential tool in assessing patients with schizophrenia, offering a comprehensive understanding of the morphological and functional alterations within the brain linked to this disorder. These cerebral changes unveil the underlying physiopathological mechanisms of the disease, aiding in the formulation of targeted therapeutic approaches. A thorough examination of the side effects of antipsychotic medications is essential for weighing treatment benefits against potential risks and advocating for the implementation of safer and more tolerable treatment protocols. Additionally, the evaluation of cognitive deficits, prevalent in schizophrenia, is essential for enhancing patients' everyday functioning and facilitating their integration into society.

Objectives: This thesis aims to investigate structural brain changes in individuals diagnosed with schizophrenia. The main objective is to highlight the patterns and extent of these changes using neuroimaging techniques. Secondary objectives include longitudinal tracking of structural changes from the onset of the disease, evaluating brain changes in correlation with age, type of treatment, and results obtained from paraclinical investigations to exclude brain tumors, including prolactinomas in patients with high prolactin levels. Additionally, a comparative evaluation of cognitive function was conducted between patients treated with oral atypical antipsychotics and those undergoing treatment with long-acting injectable atypical antipsychotics.

Materials and Methods: The research, consisting of three separate studies, received approval from the Ethics Committee of the Clinical Hospital of Psychiatry and Neurology in Brasov (Approval No. 6/18.12.2018). Database construction was carried out using Microsoft Excel 2021 software, and statistical analysis was performed using SPSS version 20.00 and MedCalc software. A significance level of $\alpha = 0.05$ was chosen for all analyses, with a confidence interval (CI) of 95%. Statistical methods included descriptive statistics. Study I, titled "***Brain abnormalities in schizophrenia: A comparative imagistic study***," conducted a prospective comparative analysis over a 36-month period involving 150 patients, comparing the first schizophrenia episode with schizophrenia. Study II, " ***Cerebral computed tomographic findings in schizophrenia: relation with second-generation antipsychotics and hyperprolactinemia***," was a cross-sectional study involving 152 patients over a 51-month period. Study III, " ***Cognitive outcomes in patients with schizophrenia treated with long-acting injectable antipsychotics vs. Oral antipsychotics*** " was a cross-sectional study involving 100 patients over a 24-month period.

Results: Study I conducted a comparison of neuroimaging findings across three distinct groups: 51 patients in their first schizophrenia episode, 49 patients diagnosed with schizophrenia for over five years, and a control group of 50 individuals without schizophrenia or any other psychotic disorders. Analysis of cerebral imaging revealed notable differences among these groups. Patients diagnosed with

schizophrenia displayed significant enlargement of the frontal and lateral ventricles compared to those experiencing their first schizophrenia episode, who, in turn, exhibited greater ventricular enlargement than the control group. Additionally, frontal lobe density was found to be highest in patients with schizophrenia, followed by those in their first schizophrenia episode, with the lowest densities observed in the control group.

In Study II, a cohort of 152 patients diagnosed with schizophrenia, all stabilized on a single atypical antipsychotic, was examined. Assessments included CT brain scans, prolactin level measurements, and monitoring of treatment side effects. Although more than half of the patients showed abnormal prolactin levels, CT scans did not reveal the presence of prolactinomas or other cerebral tumors. These findings suggest that the observed hyperprolactinemia was most likely induced by antipsychotic treatment. The most commonly observed adverse effects associated with antipsychotic treatment were weight gain, tremors, and dizziness.

Study III comprised 50 patients diagnosed with schizophrenia treated with long-acting injectable antipsychotics and 50 patients treated with oral antipsychotics. Cognitive assessments were conducted using the Romanian version "A" of the Brief Assessment of Cognition in Schizophrenia (BACS) and the Raven's Progressive Matrices (RPM). Patients treated with long-acting injectable antipsychotics exhibited a higher intelligence quotient and superior performance in all BACS evaluations. While regression analysis did not reveal significant variations in IQ scores, there were notable differences in BACS scores, favoring treatment with long-acting injectable antipsychotics for improved cognitive outcomes.

Conclusions: This research utilized neuroimaging techniques and cognitive assessments to explore brain changes and the impacts of antipsychotic treatments in individuals diagnosed with schizophrenia. The analysis uncovered notable variations in cerebral structure among schizophrenia patients in comparison to those experiencing their initial schizophrenia episode and individuals without psychiatric disorders, emphasizing the enlargement of the frontal and lateral ventricles and heightened frontal lobe density in schizophrenia patients. Hyperprolactinemia was determined to be most likely a result of atypical antipsychotic usage, without evidence of prolactinomas or other brain tumors. Additionally, patients receiving long-acting injectable antipsychotics demonstrated superior cognitive functioning compared to those treated with oral antipsychotics. These results suggest that long-acting injectable antipsychotics may offer enhanced cognitive advantages, highlighting the importance of carefully assessing treatment options to optimize daily functioning and social integration in individuals with schizophrenia.

INTRODUCTION. MOTIVATION FOR CHOOSING THE THEME

Neuroimaging explorations in schizophrenia represent a continually expanding field that aims to decipher the complex neural mechanisms of this severe mental disorder. Schizophrenia, characterized by symptoms such as hallucinations, delusions, and cognitive deficits, presents significant challenges for diagnosis and treatment. Neuroimaging techniques, including computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), and functional magnetic resonance imaging (fMRI), have become essential for understanding the structural and functional brain abnormalities frequently associated with schizophrenia e(Keshavan et al., 2020). CT was among the first techniques used, revealing abnormalities such as ventricular enlargement and cortical volume reduction, which are of great importance in the management of patients with schizophrenia (Reveley, 1985). By integrating neuroimaging data with genetic, clinical, and cognitive information, progress is being made in identifying biomarkers for early diagnosis, predicting disease progression, and developing targeted interventions.

Cognitive deficits are a central feature of schizophrenia and significantly affect the quality of life and daily functioning of individuals with this disorder. These deficits can occur in various cognitive domains, including attention, working memory, executive function, learning and memory, processing speed, and the ability to process social information. Cognitive deficits are often present from the early stages of the disease and can persist even when psychotic symptoms are effectively managed with medication (Gebreegziabhere et al., 2022). Antipsychotic treatment is essential for managing the symptoms of schizophrenia. In managing patients with schizophrenia on oral antipsychotic treatment, noncompliance is often a challenge. Noncompliance with treatment can lead to relapses, which are associated with a progressive deterioration of cognitive function. Treatment with long-acting injectable antipsychotics ensures consistent medication administration, thus reducing the risk of nonadherence and relapses. By maintaining symptom stability and preventing relapses, long-acting injectable antipsychotic treatment helps protect cognitive function. Long-term symptom stability facilitates the maintenance of higher cognitive functions, allowing patients to function effectively in daily life and actively participate in social and professional activities (Correll et al., 2016).

The choice of the theme for this thesis is anchored in the potential of neuroimaging assessments to bridge the gap between clinical symptoms and the underlying neurobiological mechanisms in schizophrenia. By analyzing neuroimaging results and comprehensive evaluations of cognitive function, this research aims to contribute to the understanding of the disease and improve the long-term outcomes of patients. The thesis will focus on identifying structural brain changes in patients with schizophrenia, changes that are present from the first schizophrenia episode, and analyzing these as the disease progresses. Additionally, it will investigate the prevalence of prolactinomas and brain

tumors in patients with schizophrenia treated with atypical antipsychotics, their link to hyperprolactinemia, and how the type of antipsychotic treatment administered can influence the progression of patients' cognitive function. Addressing these aspects will contribute to a better understanding of schizophrenia and pave the way for innovations in early diagnosis and patient treatment.

CHAPTER 2 - IMAGING EXPLORATIONS IN SCHIZOPHRENIA

2.2 THE EVOLUTION OF BRAIN IMAGING IN SCHIZOPHRENIA

The evolution of neuroimaging techniques in schizophrenia research has been significant, progressing from computed tomography (CT), which provided limited insights into anatomical brain changes, to magnetic resonance imaging (MRI), which allows the visualization of subtle changes in brain structure. MRI has revealed more complex alterations, such as changes in specific brain regions and variations in gray matter volume and cortical thickness, providing a deeper understanding of schizophrenia (van den Heuvel et al., 2019).

The emergence of functional imaging techniques, such as positron emission tomography (PET) and single-photon emission computed tomography (SPECT), has revolutionized the study of brain function in schizophrenia. These methods enable the exploration of cerebral blood flow, metabolism, and receptor binding, offering insights into the neurochemical and functional substrates of the disorder. The development of functional magnetic resonance imaging (fMRI) has further solidified this field, allowing the investigation of neuronal activation and connectivity patterns during cognitive tasks, revealing intricate disruptions in brain networks associated with schizophrenia (Wong et al., 2018).

In Romania, CT and MRI are the most commonly used imaging tools, each with distinct advantages and disadvantages. CT is fast and more accessible, making it useful in emergencies and for patients who cannot remain still, but it uses ionizing radiation and has lower resolution for soft tissues. In contrast, MRI, which does not involve ionizing radiation, is safer for repeated investigations and provides superior resolution for detailed evaluation of brain structure. However, MRI procedures are longer, more expensive, and not suitable for patients with metal implants or pacemakers (Lewis, 1990; Okubo et al., 2001).

2.3 STRUCTURAL BRAIN CHANGES IN SCHIZOPHRENIA

In schizophrenia research, structural neuroimaging studies have become essential for identifying brain structural abnormalities. Structural neuroimaging methods, particularly magnetic resonance imaging

(MRI) and computerized tomography (CT), provide detailed insights into the brain architecture in individuals with schizophrenia. These techniques allow for quantification of structural changes, including gray matter volume, cortical thickness, ventricular enlargement, and white matter integrity. Analysis of these changes has provided valuable information about neuroanatomical alterations in patients with schizophrenia, contributing to a deeper understanding of this condition.

Gray matter abnormalities, such as volumetric deficits and cortical thinning, are observable both before and after the onset of psychosis in schizophrenia and are associated with neuropsychological deficits and post-mortem neuropil loss. These anomalies exceed normal age-related atrophy, showing accelerated gray matter volume loss in individuals with schizophrenia up to middle age, followed by a plateau after age 50. The most significant gray matter loss is found in the medial prefrontal cortex, hippocampus, and thalamus. Additionally, white matter integrity deteriorates progressively with age, correlating with basic cognitive deficits in schizophrenia and other degenerative conditions. Studies have demonstrated significant reductions in fractional anisotropy in patients with schizophrenia, highlighting patterns of accelerated neurodevelopment and aging. The use of machine learning technologies has enabled estimation of "brain age of white matter," revealing significant differences between chronological age and brain age in schizophrenia patients, correlated with cognitive functions such as working memory and processing speed (Cropley et al., 2017; Dietsche et al., 2017; Wang et al., 2021).

2.4 FUNCTIONAL BRAIN IMAGING IN SCHIZOPHRENIA

2.4.1 PET and SPECT Imaging Studies

PET and SPECT imaging allow visualization of brain activity and neurochemical processes using radioactive substances. PET provides insights into neurotransmitter functions and their links to schizophrenia, while SPECT focuses on cerebral perfusion and neuroreceptor activity, providing information about the neurobiological mechanisms of the disorder (Cumming et al., 2021).

PET and SPECT studies have highlighted abnormalities in dopamine receptor binding, particularly D2 receptors, and increased dopamine synthesis in the striatum, supporting the dopamine hypothesis of schizophrenia. These techniques have also investigated other neurotransmitter systems, such as the serotonin system, identifying alterations in 5-HT2A receptors, suggesting serotonin involvement in schizophrenia (Howes et al., 2009; Takano, 2018).

2.4.2 Functional Magnetic Resonance Imaging (fMRI) and Resting-State Studies

Functional Magnetic Resonance Imaging (fMRI) and resting-state studies provide insights into brain activity and connectivity in the absence of specific tasks. These methods offer information about the organization and dynamics of brain networks, elucidating the neurobiological basis of the disorder.

fMRI during cognitive tasks reveals altered patterns of brain activation in schizophrenia, highlighting anomalies in regions involved in memory, attention, and emotional regulation. Resting-state studies show disruptions in the functional connectivity of networks implicated in higher cognitive functions, such as the default mode network and the salience network, underscoring deficits in the functional organization of the brain even in the absence of tasks (Picó-Pérez et al., 2022; Algumaei et al., 2022).

2.4.3 Cognitive Tasks and Activation Studies in Schizophrenia

Cognitive tasks and fMRI activation studies in schizophrenia allow for the observation of brain activity while individuals perform various cognitive tasks, helping to identify neural correlates of cognitive deficits. Researchers use tasks such as working memory, attention, and emotion recognition to assess affected cognitive functions in schizophrenia, revealing anomalies in brain regions responsible for these functions (Cruz-Martinez et al., 2022).

fMRI activation studies in individuals with schizophrenia show altered patterns of brain activation, indicating disruptions in networks involved in cognitive functions such as working memory, where aberrant activation in frontal and parietal regions is observed (Picó-Pérez et al., 2022). These studies contribute to understanding the neural mechanisms behind cognitive deficits in schizophrenia, providing valuable insights into altered brain activity and functional connectivity.

CHAPTER 3 - COGNITION IN SCHIZOPHRENIA

3.2 COGNITIVE DEFICITS IN SCHIZOPHRENIA

Cognitive deficits in schizophrenia are distinct from the positive and negative symptoms of the illness. Factor analyses of the PANSS (Positive and Negative Syndrome Scale) have identified a five-factor model (positive, negative, disorganized, excited, and depressed) that more accurately captures the complexity of symptoms compared to the traditional grouping into positive, negative, and general symptoms (Wallwork et al., 2012). In this context, the disorganization factor, which includes difficulties in abstract thinking and reduced attention, strongly correlates with cognitive deficits, although it does not fully explain these aspects (Rodriguez-Jimenez et al., 2013). Additionally, deficits in social cognition

are clearly separated from the five PANSS dimensions and have a significant impact on social and everyday functioning (Fett et al., 2011).

The question of whether cognitive deficits in schizophrenia are generalized or specific to particular domains remains debated. Patients with schizophrenia often exhibit widespread impairment in cognitive performance, with processing speed being most commonly affected (August et al., 2012; Fatouros-Bergman et al., 2014). Studies have identified seven distinct cognitive domains, including attention, working memory, verbal and visual learning, reasoning, and social cognition, which are affected to varying degrees among these patients (Burton et al., 2013). However, uncertainties regarding the specificity of these deficits are reinforced by concerns about the effects of medication treatments and the current limitations of available cognitive tests (Harvey, 2019).

Variability in cognitive functioning among individuals with schizophrenia is significant, with cluster analyses showing diversity in cognitive performance similar to that observed in the general population. These findings suggest that there are varied patterns of cognitive deficits among patients, reflecting individual variations in premorbid cognitive abilities and disease progression (Shin et al., 2013). It is clear that understanding this variability and its impact on daily and social functioning is crucial for the effective management and treatment of schizophrenia.

3.5 COGNITIVE ASSESSMENT METHODS IN SCHIZOPHRENIA

Assessing cognition in individuals with schizophrenia is an important aspect of understanding and addressing the challenges associated with this mental health disorder. Cognitive impairment has emerged as a significant treatment target, recognizing its profound impact on daily functioning, quality of life, and overall well-being of affected individuals. Evaluating cognitive function in schizophrenia involves a diverse range of methods, including neuropsychological testing, clinical interviews, brain imaging techniques, and innovative technologies. This multidimensional approach is essential for capturing the complex nature of cognitive deficits in schizophrenia and for facilitating targeted interventions aimed at improving cognitive outcomes. In this context, integrating state-of-the-art assessment tools not only enhances our understanding of the neurobiological underpinnings of cognitive deficits but also paves the way for the development of effective treatments.

3.5.1 Neuropsychological Tests

Neuropsychological tests play an important role in assessing cognitive function in individuals with schizophrenia, providing a detailed picture of the various cognitive deficits associated with this disorder. These tests are meticulously designed to explore multiple domains of cognition that can significantly impact daily functioning and quality of life for affected individuals. They allow for evaluation of both general cognitive deficits and individual profiles of strengths and weaknesses, thereby facilitating

personalized therapeutic interventions and treatment adjustments based on each patient's specific needs.

The MATRICS Consensus Cognitive Battery (MCCB) stands as a cornerstone in assessing cognitive function in schizophrenia. Developed by the National Institute of Mental Health (NIMH) in collaboration with experts in schizophrenia, this comprehensive battery of standardized tests measures ten essential cognitive domains for evaluating this disorder. The MCCB not only provides a detailed assessment of cognitive performance in domains such as processing speed, attention, and memory but also allows for the generation of individualized cognitive profiles, crucial for tailoring treatment and specific therapeutic interventions to each patient's needs (Nuechterlein et al., 2008).

The Brief Assessment of Cognition in Schizophrenia (BACS) complements the MCCB by focusing on rapid and efficient evaluation of cognitive function in key domains. Developed for use in busy clinical settings, BACS includes tests that assess verbal memory, working memory, verbal fluency, motor function, and executive functions, among others. This instrument is adaptable to diverse cultural and linguistic contexts, having been translated and validated in multiple languages to ensure its global applicability. Its extensive use in clinical practice and research has solidified its status as a reliable and efficient cognitive assessment tool in schizophrenia, supporting accurate diagnosis and monitoring of patient progress over time (Keefe et al., 2004).

Together, the MCCB and BACS represent two key instruments in the toolkit for assessing cognitive function in schizophrenia. These test batteries have redefined assessment standards, facilitating a more precise and comparable evaluation of cognitive deficits on a global scale. Their continued use in research and clinical practice not only contributes to a deeper understanding of the disorder but also informs the development of new therapeutic strategies aimed at improving cognitive functioning and, consequently, the quality of life for individuals affected by schizophrenia.

3.5.2 Clinical Interviews

Clinical interviews for assessing cognition in schizophrenia represent an interactive and flexible method through which clinicians evaluate various aspects of patients' cognitive functioning. Unlike standardized neuropsychological tests, interviews allow for a deeper exploration of cognitive abilities within a structured or semi-structured conversational framework. These interviews can cover a wide range of cognitive domains, including attention, memory, language, problem-solving, and executive functions. Their structure enables clinicians to adapt questions and tasks based on individual responses, providing valuable qualitative insights into cognitive capacities and difficulties experienced by the patient.

Clinical interviews may include assessing attention and concentration by observing how individuals maintain focus during the interview. Memory evaluation could involve tasks testing the ability to recall

recent information or events from the past. Clinicians also explore language comprehension and expression abilities to assess coherence and fluency of speech. Assessment of executive functions may include discussions about planning, organization, and problem-solving ability, offering a detailed picture of how individuals manage complex tasks. With their holistic and adaptable approach, clinical interviews complement standardized neuropsychological tests, providing a comprehensive assessment of cognitive functioning in schizophrenia and guiding personalized intervention strategies (Bucci et al., 2023).

CHAPTER 4 – THE PRACTICAL PART

4.1 OBJECTIVES

Schizophrenia represents a complex psychiatric disorder characterized by disturbances in perception, cognitive function, affective symptoms, and behavioral changes. Despite extensive research in the field of schizophrenia, there are still unclear aspects regarding imaging changes in patients, the progressive impairment or degradation of cognitive function, and the impact of treatment on disease progression. This doctoral thesis aims to provide additional insights into this area through three distinct studies, each addressing important aspects of the disease.

The first study starts from the hypothesis that there are structural brain differences between patients experiencing their first psychotic episode and those already diagnosed with schizophrenia. Its objective is to highlight structural brain changes during the first psychotic episode using imaging techniques and to compare these changes with structural alterations that occur after more than 5 years of illness.

The second study aims to investigate whether patients with schizophrenia are at increased risk of developing brain tumors, prolactinomas, or other brain anomalies that could cause psychiatric or neurological symptoms, and whether there is an association with second-generation antipsychotics.

The third study aims to determine if there is a difference in cognitive ability between patients with schizophrenia treated with oral antipsychotics versus those treated with long-acting injectable (LAI) antipsychotics, using the BACS assessment results obtained from both groups for comparison.

4.2 RESEARCH HYPOTHESES

For conducting the research, I considered the following hypotheses:

Hypothesis 1: There are patients who exhibit structural brain changes from the very first episode of schizophrenia.

Hypothesis 2: There are no brain tumors that justify the neurological manifestations, and hyperprolactinemia is caused by antipsychotic treatment and not by prolactinomas.

Hypothesis 3: The treatment with long-acting injectable (LAI) antipsychotics might result in a higher level of neuroprotection and consequently a better level of cognitive performance compared to oral antipsychotics.

4.3 GENERAL METHODOLOGY

The research conducted in this thesis was non-interventional in nature. All participants in the three studies were diagnosed with schizophrenia according to DSM-5 criteria. All individuals involved in this investigation were aged 18 years and above but not exceeding 45 years; all were voluntarily admitted and signed informed consent upon admission. Clear inclusion and exclusion criteria were established for each study and adhered to by all participants. All stages of the research within the thesis were approved by the Ethics Committee of the Brașov Clinical Hospital of Psychiatry and Neurology (Approval No. 6/18.12.2018).

Regarding statistical significance assessment, T-tests, F-tests, or Chi-square tests were used depending on the situation. Data analysis was performed using SPSS software version 20.00. Adjusted Odds Ratios (AOR) were calculated with a 95% confidence interval using the t-test method. Multivariable logistic regression was implemented where necessary to highlight significant associations. Statistical significance was considered for p-values < 0.05.

4.4 STUDY 1. BRAIN ABNORMALITIES IN SCHIZOPHRENIA: A COMPARATIVE IMAGISTIC STUDY

4.4.2 Objective

The objective of this study is to highlight the presence of structural brain changes during the first schizophrenia episode through imaging investigations and to compare these changes with the structural alterations that occur after more than 5 years of schizophrenia.

4.4.3 Hypothesis

There are patients who exhibit structural brain changes from the very first episode of schizophrenia.

4.4.4 Materials and methods

4.4.4.1 Study design

This study is a prospective study conducted on 100 patients and a control group of 50 subjects. The enrollment period was from January 1, 2019, to December 31, 2021, at the Clinical Hospital of Psychiatry and Neurology in Brașov, a medical facility equipped with 160 beds for acute patients and 315 beds for long-term psychiatric admissions.

4.4.4.9 Statistical analysis

The statistical analysis was comprehensive and utilized various tests to rigorously evaluate the study data. The F-test, applied to assess the equality of variances among different groups, served as an initial exploration of variability. Subsequently, independent samples t-tests were employed for comparisons between two groups, providing valuable insights into specific contrasts within the data. For analyses involving three or more groups, analysis of variance (ANOVA) was utilized, allowing the examination of mean differences. When ANOVA results indicated significance, post hoc tests were conducted to pinpoint specific group variations. All statistical tests were executed at a predetermined significance level of 0.05. The statistical software SPSS version 20.00 facilitated the execution of these analyses, providing a robust foundation for interpreting the observed differences and relationships within the dataset and ensuring the reliability of study findings.

4.4.5 Results

Of the 160 patients initially identified as eligible for the study, after applying the inclusion and exclusion criteria, 60 patients were eliminated. The remaining 100 patients were divided into two groups: the FES group, which included 51 patients experiencing their first schizophrenia episode, and the SCZ group, consisting of 49 patients with schizophrenia and a disease duration of more than 5 years. The control group (Control) was composed of 50 subjects without any psychiatric illness. Regarding the demographic data of the groups, in the FES group, the mean age was 26.35 years, and the mean age of onset was around 25 years (Table 1). The percentage of male patients was 54.9%, and all patients were experiencing their first episode of the illness, with a mean duration of illness of 1.2 years. In the SCZ group, the mean age was 40.08 years, and the mean age of onset was around 25 years. The mean duration of illness was 15.12 years, and the percentage of male patients was 48.98%. In the control group, the mean age of participants was 34.60 years, with a percentage of male patients of 68%.

Table 1. Demographics and clinical characteristics of the study population.

	FES	SCH	*p* value	CONTROL
Number of patients	51	49	-	50
Male patients (n,%)	28, 54.9%	24, 48.98%	0.5556	34, 68%
Mean age (years ± SD)	26.35±3.81	40.08±2.89	< 0.0001	34.60±8.01
Onset age (years ± SD)	25.12±3.75	24.96±2.99	0.8145	NA
Duration of illness (years ± SD)	1.20±0.63	15.12±4.04	< 0.0001	NA
Antipsychotic treatment				

	FES	Mean dose (mg)	Chlorpromazine equivalent (mg)	SCH	Mean dose (mg)	Chlorpromazine equivalent (mg)	*p* Value
Amisulpride (n,%)	3, 5.88%	533.33	533.33	4, 8.16%	650	650	0.65
Aripiprazole (n,%)	6, 11.77%	25	333.33	3, 6.12%	20	222.22	0.32
Clozapine (n,%)	0	-	-	8, 16.33%	312.5	312.5	-
Olanzapine (n,%)	16, 31.37%	19.06	381.25	21, 42.86%	16.75	285.71	0.23
Quetiapine (n,%)	7, 13.73%	414.29	555.55	3, 6.12%	666.67	766.66	0.21
Paliperidone (n,%)	5, 9.80%	7.2	360	3, 6.12%	9	450	0.49
Risperidone (n,%)	14, 27.45%	3.93	196,43	7, 14.29%	5.14	256.14	0.11

Table 1 also presents details regarding the antipsychotic treatment administered to the study participants. Amisulpride was used by 5.88% of patients, with an average dose of 533.33 mg and a chlorpromazine equivalent of 533.33 mg, with no significant differences between the evaluated groups. Aripiprazole was administered to 11.77% of participants, with an average dose of 25 mg and a chlorpromazine equivalent of 333.33 mg. Clozapine was not used in the FES group but was administered to 16.33% of patients with schizophrenia, with an average dose of 312.5 mg. Olanzapine was used by 31.37% of participants in the FES group, with an average dose of 19.06 mg and a chlorpromazine equivalent of 381.25 mg, and in the SCH group, it was administered to 42.86% of patients, with an average dose of 16.75 mg and a chlorpromazine equivalent of 285.71 mg. Quetiapine was administered to 13.73% of patients in the FES group, with an average dose of 414.29 mg and a chlorpromazine equivalent of 555.55 mg, and in the SCH group, to 6.12% of patients, with an average dose of 666.67 mg and a chlorpromazine equivalent of 766.66 mg. Paliperidone was used by 9.80% of participants in the FES group, with an average dose of 7.2 mg and a chlorpromazine equivalent of 360 mg, and in the SCH group, by 6.12% of patients, with an average dose of 9 mg and a chlorpromazine equivalent of 450 mg. Risperidone was administered to 27.45% of participants in the FES group, with an average dose of 3.93 mg and a chlorpromazine equivalent of 196.43 mg, and to 14.29% of patients with schizophrenia, with an average dose of 5.14 mg and a chlorpromazine equivalent of 256.14 mg. The P values associated with these treatments showed no significant differences between the groups.

The frontal horns, lateral ventricles, third ventricle, and fourth ventricle were measured in patients from all three groups. A greater widening of the frontal horns and lateral ventricles was observed in SCZ patients compared to FES, and similarly, FES patients compared to the Control group. Regarding the third ventricle, we noted a difference in the SCZ group compared to FES, but no difference was observed between FES and the control group. As for the fourth ventricle, the average values were the same for the FES and SCZ groups, both of which were higher than the Control group (Figure 1).

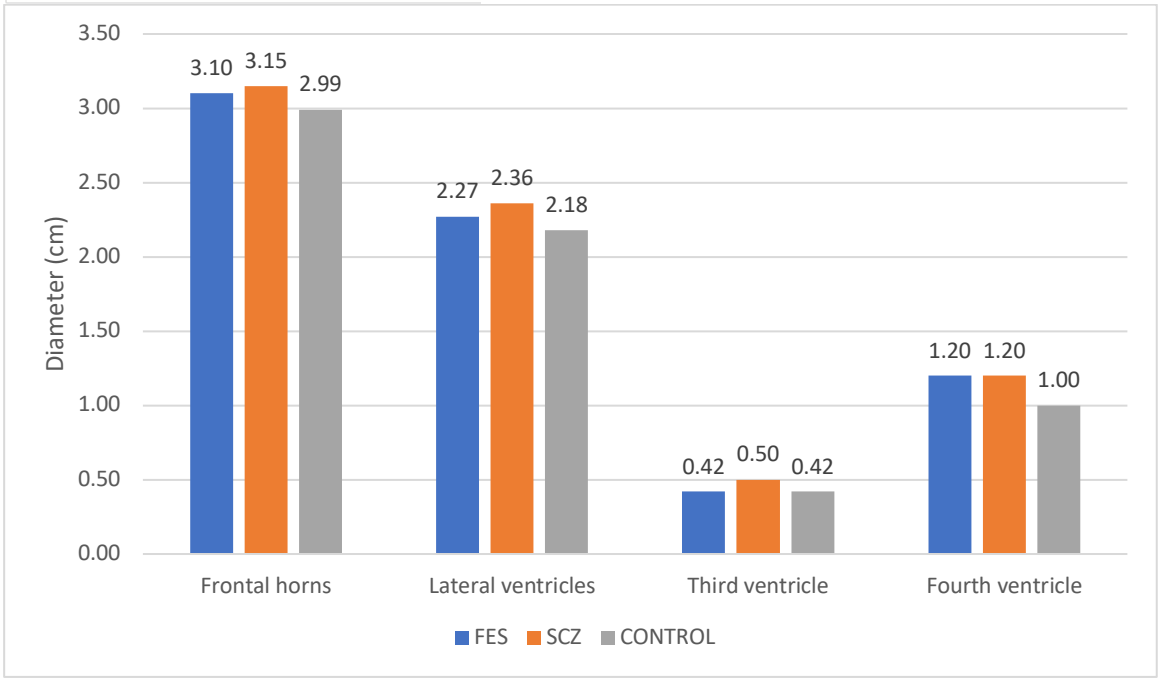

Figure 1. Variations in diameter among the three groups concerning the frontal horns and cerebral ventricles.

The densities of structures in the frontal lobe were measured using cerebral CT explorations. In the cortical region, a higher density is evident in both the anterior right and left portions, as well as in the posterior right portion, in patients with schizophrenia compared to those in the first episode of the illness and those in the control group. As per the cortical area of the left posterior region, the highest density is observed in patients in the FES group. Notably, in the subcortical portion, a higher density is recorded in the anterior left region of the frontal lobe in schizophrenia patients, with the highest densities observed across all other regions in the FES group. The lowest densities across all measured structures were consistently found in the control group (Figure 2).

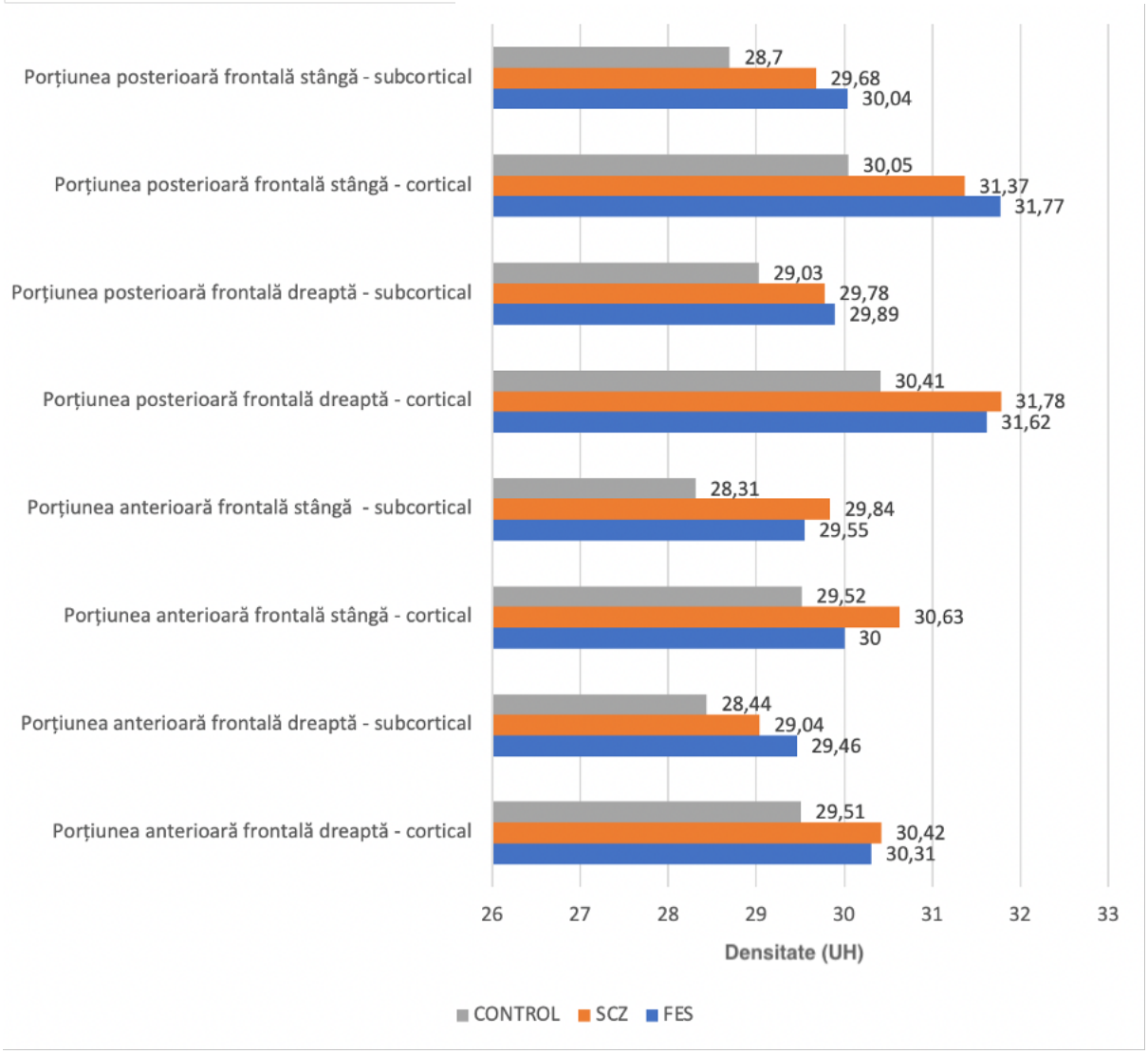

Figure 2. Densities across frontal lobe structures.

Figure 3 provides data on the measured densities of various brain structures for the three distinct groups: FES (first episode schizophrenia), SCH (schizophrenia), and CONTROL (control group). Overall, subtle variations are observed between these groups concerning the densities of the investigated brain structures. However, certain trends and subtle differences are noticeable between the groups. For instance, the measured densities for the right and left caudate nucleus are relatively similar among the three groups, with no significant differences. In the case of the putamen, the densities are generally comparable, with a slight increase in the SCH group for the right putamen. The right and left globus pallidus show comparable densities between groups, with no significant differences. Similarly, the densities for the right and left thalamus do not significantly differ between groups. The right and left amygdala exhibit relatively constant densities among the FES, SCH, and CONTROL groups. Concerning the right and left hippocampus, the densities are generally homogeneous across groups, with no significant variations. From the data presented in the table, we can observe that the SCH group recorded higher densities compared to the other two groups at the level of the right and left caudate nucleus,

right putamen, right globus pallidus, right and left thalamus, right amygdala, and right and left hippocampus. Patients in the FES group recorded higher densities than the other two groups only at the level of the left globus pallidus, and patients in the control group recorded maximum densities compared to the other two groups at the level of the left amygdala and left putamen.

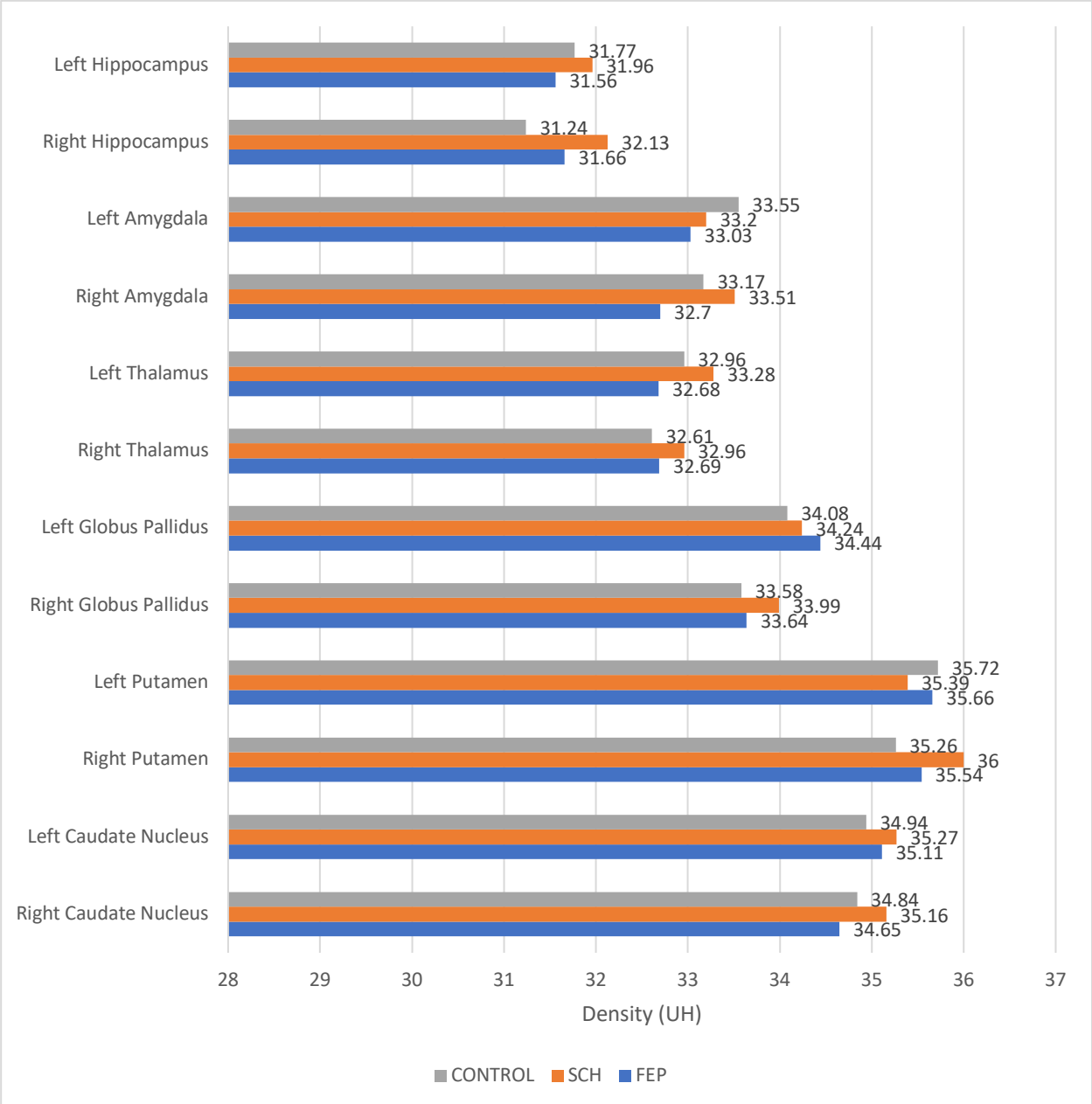

Figure 3. Densities in other brain structures

Table 2 illustrates the localization of brain atrophy in the three studied groups. Regarding the overall presence of brain atrophy, it is observed that this phenomenon is more frequent in the SCH group, with 30 patients representing 58.82% of the total in this group. In comparison, the FES group shows a lower

prevalence, with 18 patients (36.73%), and the control group has the smallest proportion, with only 6 patients (12%).

Concerning the localization of brain atrophy, notable differences between groups are highlighted. For example, frontal lobe atrophy is more commonly observed in the SCH group, with 26 patients (50.98%), while it is present in 16 patients (32.65%) in the FES group and only 5 patients in the control group (10%). Regarding parietal lobe atrophy, it is more prevalent in the FES group, with 18 patients (35.29%), compared to the SCH group, which records 9 patients (17.65%), and the control group, with just 2 patients (4%). Additionally, atrophy in the vermis is more frequently found in the SCH group, with 15 patients (29.41%), while the FES group presents 15 patients (29.41%), and the control group has 2 patients (4%). These findings indicate that there are significant variations in the distribution of brain atrophy among different psychiatric disorders and overall mental health.

Table 2. Distribution of atrophy areas in the SCH and FES group and Control

Cerebral atrophy			
	SCH (N, %)	FES (N, %)	CONTROL (N, %)
Number of patients with atrophy	30, 58.82%	18, 36.73%	6, 12%
	Localizare		
Frontal lobe	26, 50.98%	16, 32,65%	5, 10%
Parietal lobe	9, 17.65%	18, 35.29%	2, 4%
Temporal lobe	1, 1.96%	1, 1.96%	1, 2%
Insular lobe	13, 25.49%	4, 7.84%	1, 2%
Vermis	15, 29.41%	9, 17,64%	2, 4%
Occipital lobe	1, 96%	0	0

The atrophy severity in the SCH, FES, and Control groups is presented in Figure 4, divided into three categories: mild, moderate, and severe. Analyzing the prevalence of atrophy severity relative to the number of patients presenting atrophy in each group, a difference in the prevalence of mild atrophy can be observed, with 77.78% of individuals in the FES group compared to 43.34% in the SCH group, and 50% in the control group. In the SCH group, 46.67% of patients exhibit moderate atrophy, in the FES group 16.67% of patients, and in the Control group, this percentage is 33.34%. Of the total 18 patients in the FES group, 5.56% present severe atrophy; of the total 30 patients presenting atrophy in the SCH group, 10% present severe atrophy; and of the total 6 patients in the Control group who present atrophy, 16.67% present severe atrophy.

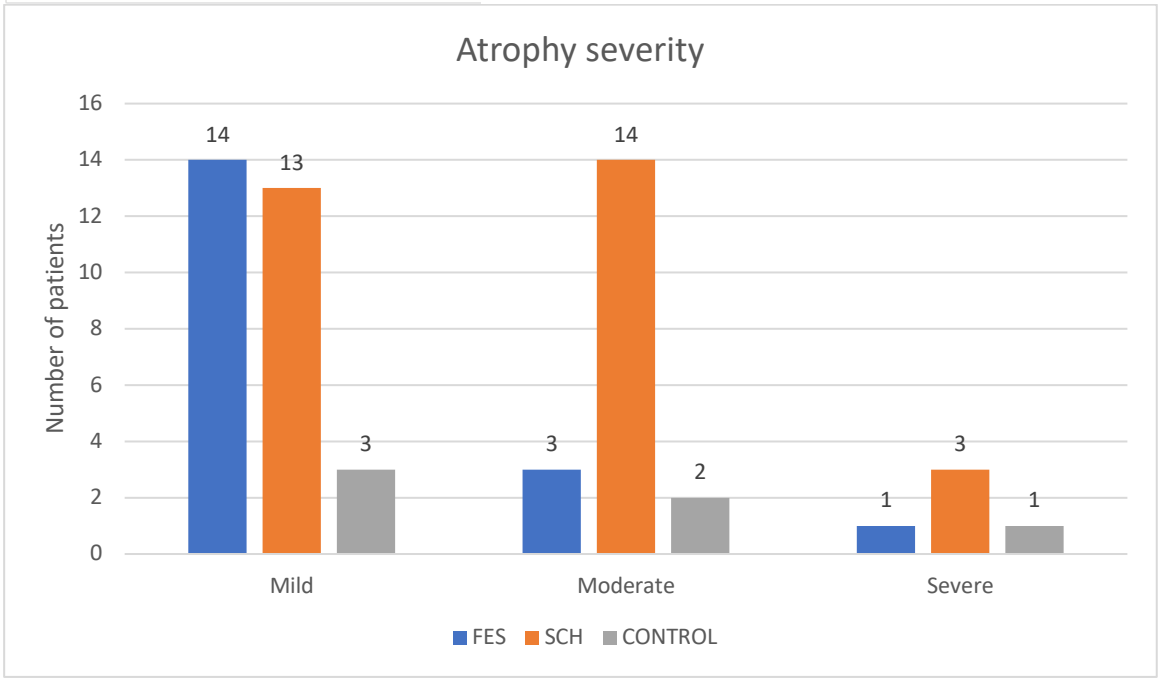

Figure 4. Severity of atrophy in the studied groups

All patients were at the first episode of illness requiring hospitalization, with a maximum illness duration of 2 years. All patients were on atypical antipsychotic treatment: 27.78% were on olanzapine, 11.12% on aripiprazole, 11.12% on quetiapine, 33.34% on risperidone, and 16.67% on paliperidone. The 30 patients diagnosed with schizophrenia who presented with atrophy had an average age of approximately 40 years (SD ± 2.97), with an average illness onset around 26 years (SD ± 3.01). The average duration of the illness was 15 years, marked by an average of 25 episodes requiring hospitalization. All patients were on atypical antipsychotic treatment, as follows: 50% received olanzapine, 6.67% aripiprazole, 3.34% quetiapine, 6.67% risperidone, 3.34% paliperidone, 6.67% amisulpride, and 23.34% clozapine. The frequency of rehospitalizations in this cohort highlights the potential challenges in maintaining adherence to antipsychotic medications. This observation underscores the importance of further exploring the factors influencing medication adherence and its impact on the clinical trajectory of individuals with schizophrenia and associated brain atrophy.

CT evaluations showed the presence of choroid plexus calcifications. Thus, 35.29% of the FES group, 69.39% of the SCH group, and 35.29% of the CONTROL group exhibited these calcifications. While choroid plexus calcifications are often incidental findings, they have been linked to regional brain atrophies, particularly affecting the frontal cortex, parietal-temporal regions, and cerebellum. Identifying these calcifications, especially in the SCH group, may support the neurodevelopmental etiology of schizophrenia and explain the cognitive impairment associated with the disorder.

4.4.7 Conclusion

Brain imaging explorations of patients with schizophrenia, those at the first episode of schizophrenia (FES), and a control group revealed significant differences in brain morphology. Patients with chronic schizophrenia (SCH) show marked expansions of the frontal horns and lateral ventricles, indicating the progression of structural changes throughout the course of the disease. In contrast, patients with FES have larger ventricles compared to the control group, suggesting structural impairment at the onset of the illness. Additionally, the SCH group exhibits increased cortical densities in the frontal lobe, while the FES group shows the highest cortical density in the left posterior region, reflecting variations in the distribution of cortical changes depending on the stage of the illness. These findings underscore the importance of understanding the evolution and clinical implications of brain changes in schizophrenia.

4.5 STUDY 2. Cerebral Computed Tomographic Findings in Schizophrenia: Relationship to Second-Generation Antipsychotics and Hyperprolactinemia

4.5.2 Objective

This study aimed to explore the presence of brain tumors, prolactinomas, and other structural brain changes in schizophrenia patients treated with second-generation antipsychotics using cerebral computed tomography (CT) scans.

4.5.3 Hypothesis

There are no brain tumors that justify the neurological manifestations, and hyperprolactinemia is caused by antipsychotic treatment and not by prolactinomas.

4.5.4 Materials and methods

4.5.4.1 Study design

The present study is a retrospective, cross-sectional study conducted on 152 patients diagnosed with schizophrenia from January 1, 2020, to March 31, 2024, at the Clinical Hospital of Psychiatry and Neurology Brașov, Romania. This academic hospital has 150 beds for acute patients and 300 beds for

chronic patients. It serves a heterogeneous population of over 500,000 inhabitants, including Romanians, Germans, and Hungarians.

All patients were between 18 and 45 years old, diagnosed with schizophrenia, and treated with atypical antipsychotics. The database included basic demographic data, treatment information such as type and dosage, cerebral CT examinations, and prolactin levels.

4.5.4.9 Statistical analysis

A statistician conducted the statistical analysis, employing a range of tests to assess the study data thoroughly. We used Student's t-test to determine statistical significance for comparing means and the chi-square test for comparing proportions. All statistical tests adhered to a p-value of 0.05. The statistical software SPSS version 20.00 was instrumental in executing these analyses, providing a robust framework for interpreting observed differences and relationships within the dataset, thereby ensuring the reliability of study findings.

4.5.5 Results

4.5.5.1 Patient characteristics

Upon analyzing the demographic characteristics, it was observed that the cohort had an average age of 42.79 (±11.66 SD) years, of which 39.04% were male participants. The average duration of illness was 17.89 years (±11.56 SD) with an average of 25 hospitali-zation episodes throughout the illness (Table 1).
Table 1 also presents the distribution and dosage characteristics of various antipsy-chotic medications. Notably, olanzapine was the most frequently prescribed antipsy-chotic, constituting 46.05% of the cohort, with a mean dosage of 14.5 mg/day (±4.43 SD). Risperidone was prescribed to 36.84% of the patients, with a mean dose of 3.33 mg (±1.61 SD), and under 10% of the patients received treatment with amisulpride, aripiprazole, quetiapine, paliperidone, and clozapine.

Tabel 3. Caracteristicile demografice și clinice ale populației de studiu

Parameters	
Number of patients	152
Male gender (n;%)	57; 37.5%
Mean age (years ± SD)	42.79 ± 11.66
Illness duration (years ± SD)	17.89 ± 11.56
Number of episodes (n ± SD)	25.19 ± 13.56
Smoker (n;%)	93; 61.18%

Antipsychotic treatment			
	Number, %	Mean dose (mg) ± SD	Chlorpromazine equivalent (mg)
Amisulpride (n; %)	4; 2.63%	450 ± 100	450
Aripiprazole (n; %)	9; 5.92%	16.12 ± 7.41	214.94
Clozapine (n; %)	4; 2.63%	400 ± 70.71	400
Olanzapine (n; %)	70; 46.05%	14.5 ± 4.43	290
Quetiapine (n; %)	6; 3.94%	566.66 ± 150.55	755.55
Paliperidone (n; %)	3; 1.97%	8 ± 1.73	400
Risperidone (n;%)	56; 36.84%	3.33 ± 1.61	333

In both male and female patients, the most commonly prescribed antipsychotic treatment was olanzapine, with 43.86% of the male patients and 47.37% of the female patients receiving it. Following olanzapine, risperidone was the second most prescribed treatment in both groups, with 40.35% male and 34.73% female patients being prescribed it (Table 4).

Tabel 4. Tratamentul antipsihotic în funcție de gen

Antipsychotic Medication	Male N=57	Female N=95	*p value*
Amisulpride (n;%)	2, 3.51%	2, 2.11%	0.60
Aripiprazole (n;%)	0	9, 9.47%	-
Clozapine (n;%)	2, 3.51%	2, 2.11%	0.60
Olanzapine (n;%)	25, 43.86%	45, 47.37%	0.67
Quetiapine (n;%)	3, 5.26%	3, 3.16%	0.52
Paliperidone (n;%)	2, 3,51%	1, 1.05%	0.29
Risperidone (n;%)	23, 40.45%	33, 34.73%	0.48

4.5.5.2 Antipsychotic medication side effects

The side effects of the antipsychotic medication were extracted from patient files and categorized using the Uku Side Effect Rating Scale as reference [33]. These adverse effects were broadly divided into four categories: psychic, neurological, autonomic, and other side effects. Psychic side effects included concentration difficulties, asthenia, sedation, memory impairment, depression, inner tension/restlessness, changes in sleep duration and dream activity, and emotional numbness. Neurological side effects included dys-tonia, rigidity, decreased or increased movement, tremors, akathisia, seizures, pares-thesia, and headaches. Autonomic side effects involved disturbances in accommodation, salivation changes (either increased or reduced leading to dry mouth), gastrointestinal issues (nausea/vomiting, diarrhea, constipation), urinary problems, orthostatic dizziness, tachycardia, and increased sweating tendency. The other side effects category included weight changes, menstrual irregularities, galactorrhea, gynecomastia, alterations in sexual desire and function, and vaginal dryness. Out of 152 patients, 97 (61.78%) experienced side effects, while 55 (36.18%) did not have any specified in their records. Among the 97 patients with side effects, 56 (57.73%) were women.

Within the category of psychiatric side effects, the most commonly reported side effect was concentration difficulties, reported by 23 (23.71%) patients, followed by asthenia, reported by 18 (18.55%) patients. The least reported adverse effect from this category was increased dream activity, mentioned by only two (2.06%) patients (Figure 5).

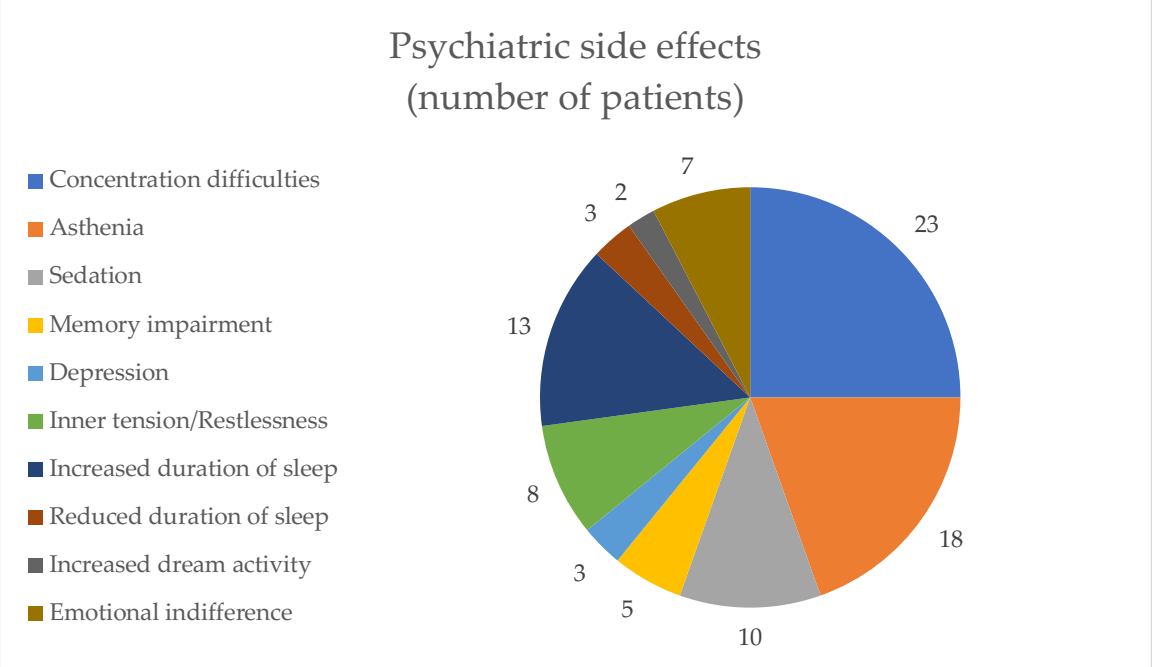

Figura 5. Psychiatric side effects

In terms of neurological adverse effects, 25 (25.77%) patients reported tremors and 15 (15.46%) patients reported rigidity. Only one (1.03%) patient reported epileptic seizures (Figure 6).

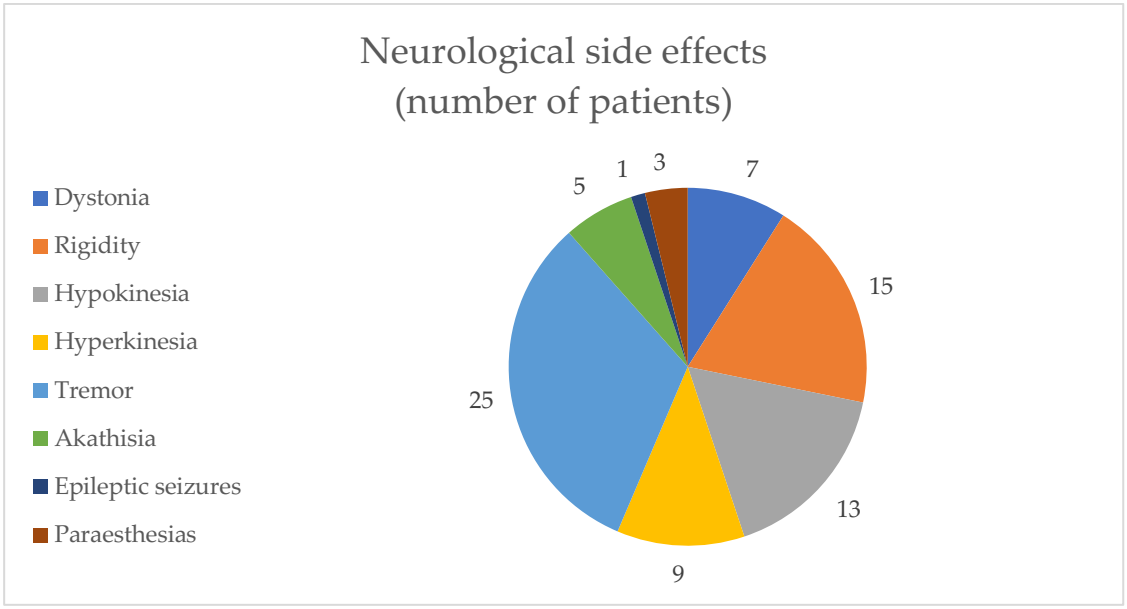

Figura 6. Neurological side effects

Among the autonomic side effects category, orthostatic dizziness was the most commonly experienced adverse effect, reported by 19 individuals (19.59%). This was followed closely by palpitations/tachycardia, noted by 16 individuals (16.49%). Micturi-tion disturbances were the least encountered adverse effect, affecting only two individuals (2.06%) (Figure 7).

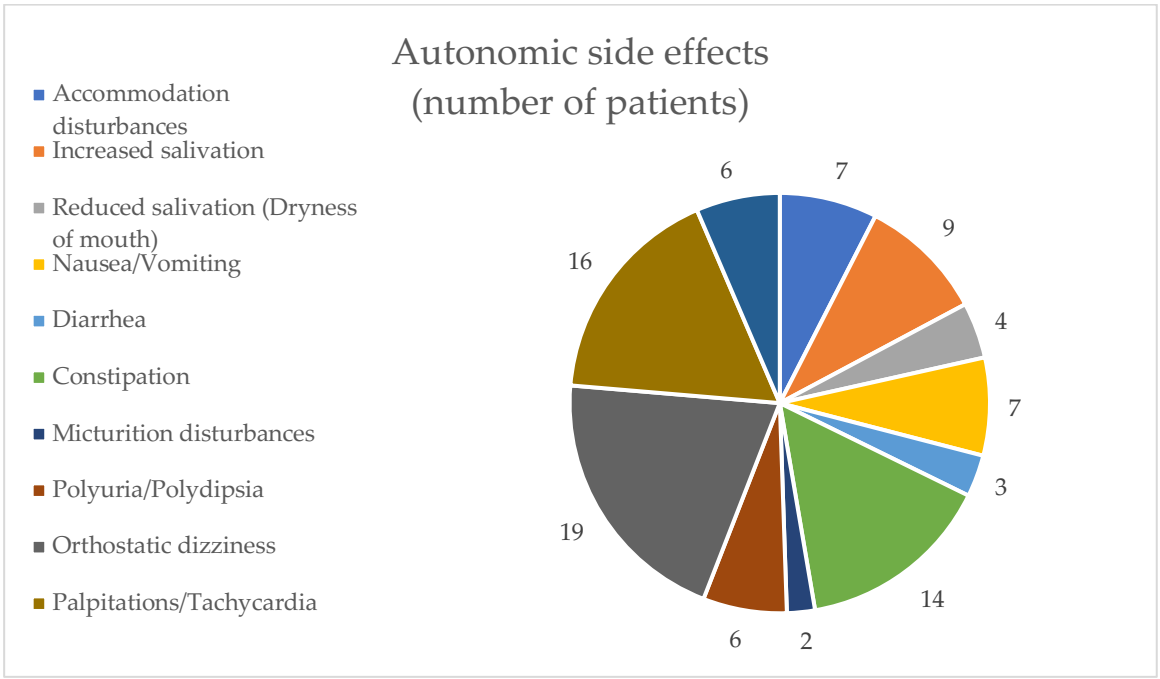

Figura 7. Autonomic side effects

In the other side effects category, weight gain was the most prevalent side effect, reported by 23 individuals (23.71%), followed by diminished sexual desire, experienced by 19 individuals (19.59%). Gynecomastia was the least reported side effect, affecting only two individuals (2.06%). None of the patients experienced weight loss or increased sexual desire (Figure 8). Given that a significant portion of patients experienced adverse effects in this category, many of which are symptoms associated with hyperprolactinemia, we hypothesized that elevated prolactin levels may induce these effects.

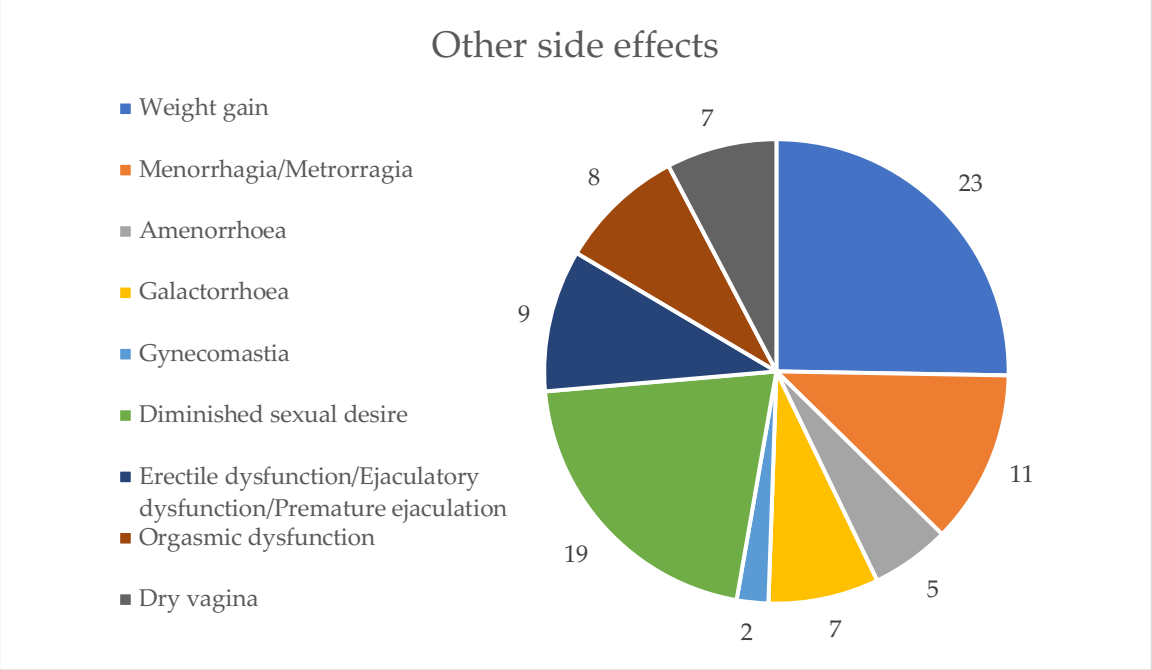

Figura 8. Other side effects

4.5.5.3. Prolactin levels

I examined prolactin levels in all patients enrolled in the study. Out of the 152 patients, 82 (53.95%) had abnormal prolactin levels. Among those 82 patients with ab-normal levels, 30 (36.58%) were men and 52 (63.41%) were women.

Table 5 presents the characteristics of patients with elevated prolactin levels. Among men with elevated prolactin levels, risperidone is the most commonly prescribed anti-psychotic, at 12 cases (40%), while among women with elevated prolactin levels, olanzapine is the most common, at 32 cases (61.54%). None of the patients receiving treatment with aripiprazole exhibited high levels of prolactin.

Table 5. Characteristics of patients with elevated prolactin levels.

	Male		Female	*p* value
Number of patients	30		52	-
Meanage (± SD)	37.67 ± 7.98		39.85 ± 6.52	0.25
Antipsychotic treatment				
	Male		Female	
	Number of patients (n;%)	Mean dose (mg) ± SD	Number of patients (n;%)	Mean dose (mg) ± SD
Amisulpride	1; 3.33%	-	2; 3.85%	500 ± 141.42
Aripiprazole	0	-	0	-
Clozapine	3; 10%	416.67 ± 160.73	0	-
Olanzapine	11; 36.67%	16.82 ± 4.04	32; 61.54%	15.74 ± 4.98
Quetiapine	2; 6.67%	500 ± 141.42	2; 3.85%	500 ± 141.42
Paliperidone	1; 3.33%	-	1; 1.92%	-
Risperidone	12; 40%	4.67 ± 1.3	15; 28.84%	4.8 ± 1.01

In male patients with abnormal prolactin levels, the lowest recorded value was 18.49 ng/mL and the highest was 45.64 ng/mL. For female patients with abnormal prolactin levels, the lowest value observed was 32.31 ng/mL and the highest was 111.56 ng/mL (Figure 9).

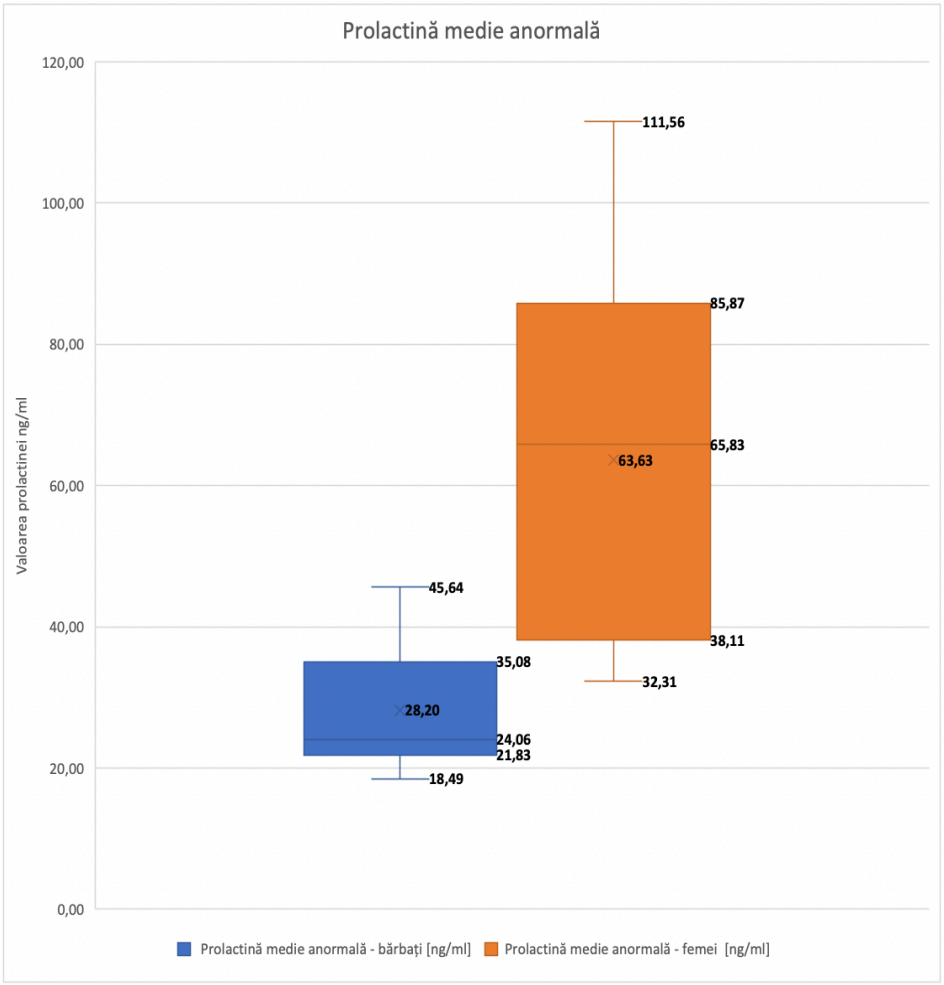

Figure 9. Abnormal prolactin levels

4.5.5.4 CT Scan Results

In all 152 cases, the CT examinations revealed no presence of prolactinomas or other brain tumors. However, the results align with a prior study conducted by our team, in-dicating notable findings concerning brain morphology [34]. Specifically, patients ex-hibited the widening of the frontal horns and lateral ventricles, along with early indi-cations of atrophy. Additionally, 7% of the patients presented with sinus issues, including sinusitis and nasal polyps.

Atrophy was observed in a significant number of patients (n = 98, 64.47%), despite their young age. The frontal (n = 72, 73.47%) and temporal (n = 56, 57.14%) lobes were the most commonly affected regions, with many patients exhibiting atrophy in multiple areas. The severity of atrophy, presented in Figure 10, was categorized as mild, moderate, or severe. The majority of patients had mild atrophy (n = 68, 69.39%), followed by 26 (26.53%) with moderate atrophy, and only 4 (4.08%) with severe atrophy.

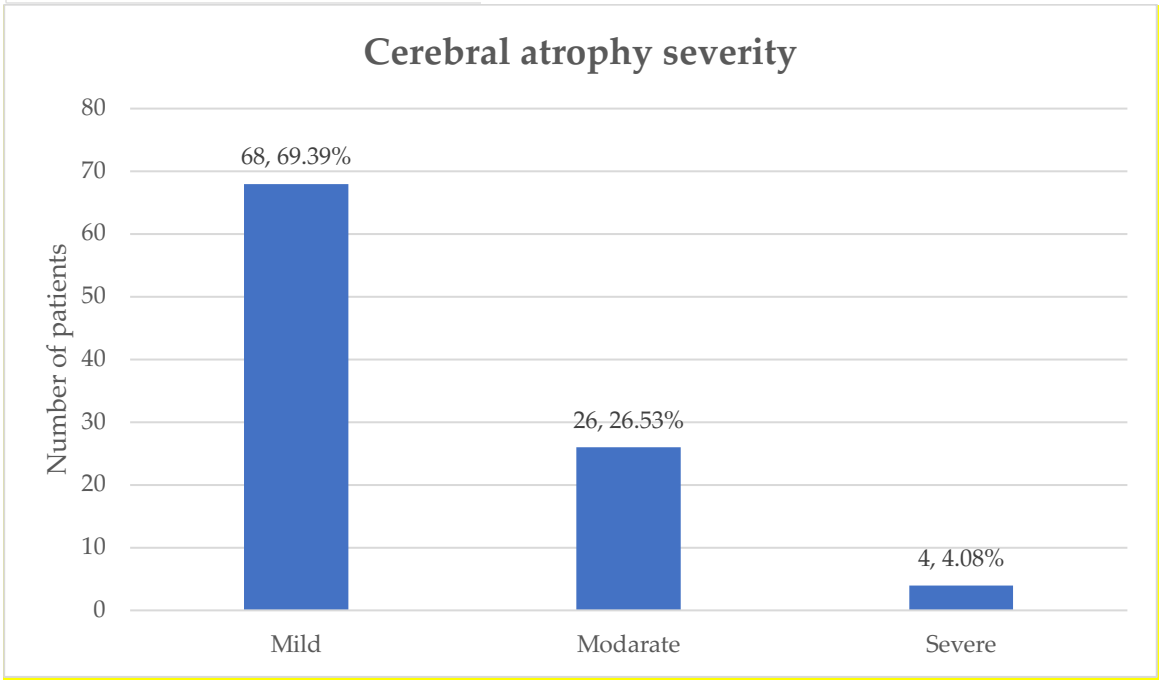

Figura 10. Cerebral atrophy severity

4.5.7 Conclusion

Despite the challenges of an unhealthy lifestyle and limited access to medical investigations associated with schizophrenia, the incidence of brain tumors and prolactiomas in these patients is relatively low. Regular monitoring of prolactin levels is essential in the management of schizophrenia, optimizing therapeutic strategies and reducing adverse effects.

4.6 STUDY 3. COGNITIVE OUTCOMES IN PATIENTS WITH SCHIZOPHRENIA TREATED WITH LONG-ACTING INJECTABLE ANTIPSYCHOTICS VS. ORAL ANTIPSYCHOTICS

4.6.2 Objective

This study aimed to investigate whether there are differences in the results of cognitive assessments between patients who received oral antipsychotics and those who received long-acting injectable antipsychotics. The main objective is centered on a comparative analysis of BACS assessment results between these two groups.

4.6.3 Hypothesis

The treatment with long-acting injectable (LAI) antipsychotics might result in a higher level of neuroprotection and consequently a better level of cognitive performance compared to oral antipsychotics.

4.6.4 Materials and methods

4.6.4.1 Study design

The present study is a cross-sectional study using analytical methods. Patients were enrolled between January 1, 2020, and January 1, 2022. The study was conducted at the Clinical Hospital of Psychiatry and Neurology Brașov, a medical facility with 150 beds for acute psychiatric hospitalizations and 315 beds for prolonged psychiatric hospitalizations.

4.6.4.10 Statistical analysis

Descriptive analyses were conducted to characterize the patient demographic and clinical characteristics profile. The means ± SD (standard deviation) or percentage data were utilized for summarizing group attributes. Statistical analyses were performed using SPSS Statistics version 27.0 (SPSS Inc., 2020), employing the t-test for mean comparisons and the chi-square test for proportions. Statistical significance was set at a p-value less than 0.05. The study incorporated regression analysis techniques to examine and summarize the key features and patterns within the collected data.

4.6.5 Results

4.6.5.1 Demographic and clinical characteristics

The demographic and clinical characteristics of the study population are shown in Table 1. The mean age was higher in the ORAL-AP group and the onset age was higher in the LAI-AP group. The educational level between the two groups was almost the same: approximately 12 years in both groups.

All patients in both groups received treatment with atypical antipsychotics, and none of the subjects were prescribed more than one atypical antipsychotic as part of their treatment regimen. In the ORAL-AP group, the most commonly used oral atypical antipsychotic was olanzapine (n=20, 40%), followed by clozapine (n=10, 20%). Mean daily doses of oral atypical antipsychotics in the ORAL-AP group were 650

100 for amisulpride, 22.5 8.66 for aripiprazole, 305 92.65 for clozapine, 18.25 3.35 for olanzapine, 9 4.24 for paliperidone, 450 100 for quetiapine and 4 1.26 for risperidone. In the LAI-AP group the most used atypical antipsychotic was olanzapine (n= 24, 48%) with a mean dose of 425 151.08. (Table 1) In recent years, more efforts have been made to better inform patients and their relatives about the benefits of LAI treatment and the consequences of maintaining OAP in non-adherent patients. It is thus natural that the age of those who receive LAI is younger than those with OAP.

Tabel 6.Caracteristici clinice și demografice

Characteristic	LAI-AP n=50	OAP n=50	*p* value
Male (n, %)	18 (36%)	27 (54%)	0.07
Age (years, mean SD)	32.12 ± 3.28	35 ± 5.99	0.0036
Smoker(n, %)	29 (58%)	33 (66%)	0.41
Age of onset (years, mean SD)	24.28 ± 2.76	25.1 ± 5.57	0.35
Duration of illness (years, mean SD)	7.84 ± 1.46	10.18 ± 5.79	0.0067
Education (years, mean SD)	12.02 ± 1.63	11.84 ± 2.21	0.63
Medication used in the LAI-AP group			

Medication	Number of patients (n, %)	Mean dose (mg)± SD	Oral dose equivalent (mg)	Chlorpromazine equivalent (mg)
Aripiprazole LAI	9, 18%	400	20	266,66
Olanzapine LAI	24, 48%	425 ± 151.08	14.16	250
Paliperidone LAI	2, 4%	100	9	450
Risperidone LAI	15, 30%	71.67 ± 8.79	2,39	250
Medication used in the OAP group				
Medication	Numărul de pacienți	Doză medie (mg) ± SD		Echivalentul în clorpromazină (mg)
Amisulpride	4, 8%	650 ± 100		650
Aripiprazole	4, 8%	22.5 ± 8.66		275
Clozapine	10, 20%	305 ± 92.65		600
Olanzapine	20, 40%	18.25 ± 3.35		375
Quetiapine	4, 8%	450 ± 100		600
Paliperidone	2, 4%	9 ± 4.24		450

Risperidone	6, 12%	4 ± 1,26	400

4.6.5.2 Intelligence quotient

The group treated with long-acting injectable antipsychotics exhibits a slightly higher intelligence quotient compared to oral antipsychotics group (102.2 vs 101.32, p=0.5401). (Figure 2) This observation implies that the use of long-acting injectable antipsychotics may be associated with improved cognitive functioning, as evidenced by elevated IQ scores when contrasted with individuals undergoing oral antipsychotic therapy. Age can be a factor that makes the difference between two groups. In our case, there is a possibility that the previous treatment with several relapses in the case of the OAP group may cause cognitive impairment and decreasing IQ score or that LAI may offer this protection precisely by avoiding the neurotoxicity of acute psychotic episodes. This hypothesis is more likely since the two groups have about the same duration of schooling, come from the same geographical area and are young people.

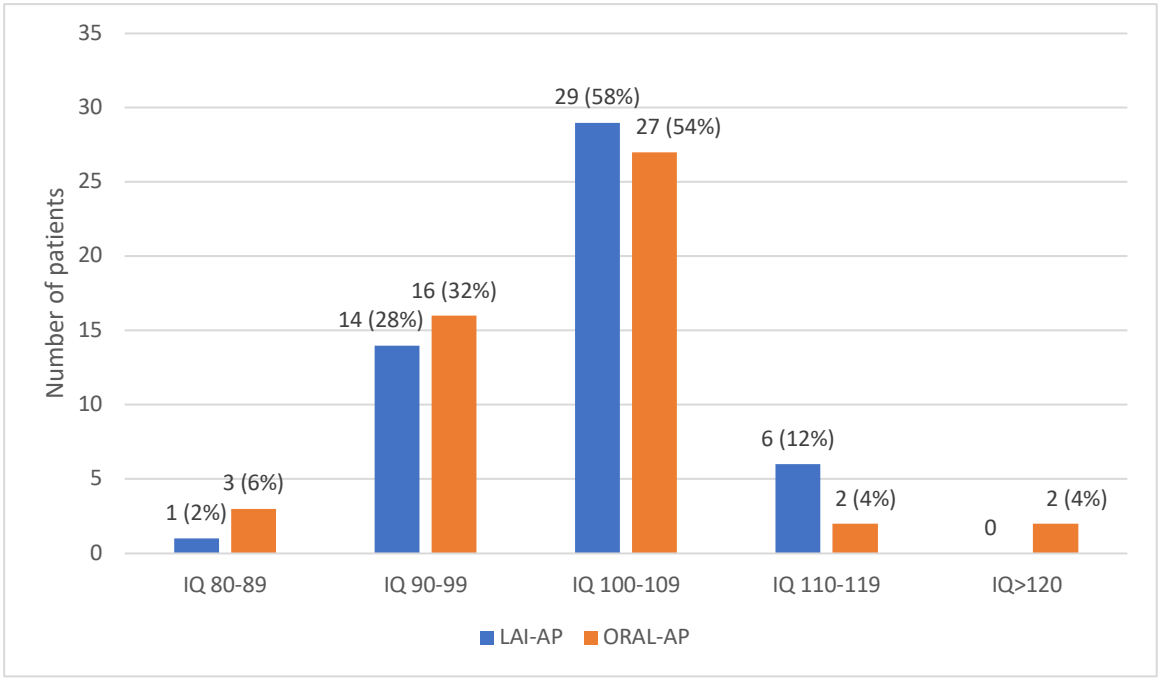

Figura 11. Number of patients in IQ intervals

4.6.5.3 BACS results

Table 7 shows the results obtained by the two groups at the BACS evaluation. Verbal memory, digit sequencing, token motor, semantic and letter fluency, symbol coding, and the Tower of London test were analyzed.

Tabel 7. BACS evaluation

BACS evaluation	**LAI-AP group n=50**		**OAP group n=50**		***p* value**
	Medie ± SD	Interval	Medie ± SD	Interval	
Verbal memory	36.58 ± 2.88	30-44	30.02 ± 5.68	19-41	< 0.0001
Digit sequencing	17.24 ± 2.15	13-23	14.60 ± 3.45	4-23	< 0.0001
Token motor	57.78 ± 17.03	10-76	50.04 ± 18.82	8-78	0.0335
Semantic fluency	19.70 ± 2.10	17-26	15.48 ± 4.61	5-24	<0.0001
Letter fluency	21.74 ± 2.75	16-28	19.68 ± 6.47	4-32	0.0409
Symbol coding	34.30 ± 12.84	7-50	30.48 ± 10.69	10-58	0.10
Tower of London	17.26 ± 2.61	8-22	15.48 ± 3.47	7-22	0.0046
Total	204.60 ± 21.89	141-245	175.78 ± 28.07	118-227	<0.0001

The LAI-AP group performed better in all evaluations. The most significant difference was in token motor (57.78 17.03 vs. 50.04 18.82, p=0.0335), while the smallest difference was at the Tower of London test (17.26 2.61 vs. 15.48 3.47, p=0.0046). In terms of the range of scores obtained by the

OAP group has a higher minimum than the LAI-AP group only in symbol coding and a higher maximum in token motor, letter fluency and symbol coding. The LAI-AP group has a higher total than the OAP group (204.6 21.8 vs. 175.78 28.07, p<0.0001). There was statistical significance in verbal memory, digit sequencing, token motor, semantic fluency, letter fluency and the Tower of London.

4.6.7 Conclusion

The use of long-acting antipsychotic treatment in individuals with schizophrenia offers promising advantages in preserving cognitive function. Our study reveals the protective impact of long-acting antipsychotics on cognition, as indicated by enhanced cognitive performance, particularly in terms of better cognitive functioning. Long-acting antipsychotic treatment is associated with more effective symptom control, reduced relapse frequency, and protective cognitive abilities. The findings underline the substantial benefits of long-acting antipsychotic medications in mitigating cognitive decline and preserving cognitive abilities in individuals with schizophrenia.

CHAPTER 6 – FINAL CONCLUSIONS. THESIS ORIGINALITY. DISSEMINATION OF RESULTS. FUTURE RESEARCH DIRECTIONS

6.1 FINAL CONCLUSIONS

The doctoral thesis investigated two perspectives on schizophrenia: the assessment of brain structural changes and the incidence of brain tumors among patients, as well as the evaluation of cognitive function in relation to different antipsychotic treatment variants.

The first study compared imaging results of patients with first episode schizophrenia, chronic schizophrenia diagnosed for over 5 years, and a control group. Patients with schizophrenia exhibited enlarged lateral ventricles and frontal horns compared to those with acute psychotic disorder, who in turn had larger enlargements compared to the control group. Significant differences were observed in the dimensions of the third ventricle between patients with schizophrenia diagnosed for over 5 years and those with acute psychotic disorder, while the fourth ventricle showed similar sizes in both patient groups but larger compared to the control group. CT scans indicated increased density in the frontal lobe in patients with schizophrenia in both anterior and posterior cortical regions, compared to those with acute psychotic disorder and the control group. Brain atrophy was identified in over half of the patients with schizophrenia and over 35% of those in the first psychotic episode, contrasting with only 6% in the control group. These findings have sparked debates regarding the nature of atrophy as a result of the illness, treatment, or both (Petric et al., 2024).

The second study investigated the prevalence of prolactinomas and brain tumors among patients with schizophrenia, a common consequence of antipsychotic treatment associated with hyperprolactinemia. While imaging explorations did not confirm the presence of prolactinomas, several patients exhibited abnormal levels of prolactin, suggested to be caused by antipsychotic treatment. Measures to normalize prolactin levels were implemented to minimize the impact on the well-being of patients with schizophrenia and to improve treatment adherence. Regular monitoring of prolactin levels in patients with schizophrenia receiving antipsychotic treatment is crucial, considering associated risks such as reproductive disorders, sexual dysfunctions, osteoporosis, psychological and metabolic issues. This monitoring is essential for the proper management of treatment and the improvement of patient health (Petric et al., 2024).

The third study comparatively evaluates cognitive function in patients treated with oral antipsychotics versus long-acting injectable (LAI) antipsychotics. The use of LAI antipsychotics represents a significant advancement in the treatment of schizophrenia, offering several advantages over oral formulations, including benefits for cognitive function. Firstly, LAI provides reliable and consistent medication delivery, ensuring treatment compliance without the daily administration effort. Regular medication

administration has been shown to positively impact cognitive functioning, which is often impaired in schizophrenia. Additionally, LAI administration is associated with a lower risk of relapse, with studies demonstrating that any relapse affects the functional and cognitive levels of patients. Incorporating LAI antipsychotics into treatment plans not only improves medication adherence and symptom control but also holds promise for optimizing cognitive function and promoting better functional recovery in individuals with schizophrenia (Petric et al., 2024).

This study utilized the Brief Assessment of Cognition in Schizophrenia (BACS) battery, which was administered to a group of schizophrenia patients treated with oral antipsychotics and another group treated with LAI (Long-Acting Injectable) antipsychotics under the same conditions of administration. Patients receiving LAI antipsychotics demonstrated better results across all evaluated domains, highlighting the promising advantages of LAI antipsychotic therapy for patients with schizophrenia, especially in preserving cognitive function.

This research underscores the importance of a multidisciplinary approach in managing patients diagnosed with schizophrenia. Careful investigation of structural brain changes and the risk of brain tumors among these patients has emphasized the need for early diagnosis and prompt therapeutic intervention. Additionally, the assessment of cognitive function and comparison between oral and depot antipsychotic therapy have highlighted the benefits of depot therapy in protecting and enhancing cognitive function in this vulnerable population.

6.2 THESIS ORIGINALITY

The thesis's originality lies in its comprehensive exploration of schizophrenia management, from structural brain changes and brain tumor incidence to cognitive function evaluation and comparison of oral versus depot antipsychotic therapies. It includes:

- The first study correlating brain imaging in patients experiencing their first episode of schizophrenia with those diagnosed with schizophrenia for over 5 years, alongside a control group from Romania.
- The first study correlating brain imaging with prolactin levels in patients stabilized on atypical antipsychotics in Romania.
- The first study comparing BACS evaluation results between patients treated with LAI antipsychotics versus those treated with oral antipsychotics in Romania.

This research represents a novel contribution to the field, providing a better understanding of schizophrenia and its management, ultimately enhancing the quality of life for patients.

6.3 DISSEMINATION OF RESULTS

The research results from this thesis have been published in renowned international journals with significant impact factors. Additionally, these findings have been presented at national conferences in the form of papers, thereby substantially contributing to the advancement of current knowledge in the fields of neuroimaging and cognitive assessment in schizophrenia. (Table 14, Appendix 1, Appendix 2)

Tabel 2. Dissemination of research results

	Papers on the thesis topic	Papers on conex topics
Number of articles	3	9
The number of papers presented at conferences	2	4

6.4 FUTURE RESEARCH DIRECTIONS

Based on the results obtained in the doctoral thesis research, the following future research directions are proposed:

- Extending studies to larger and more representative samples of the national population.
- Conducting research projects that use advanced imaging techniques (MRI, fMRI, PET, SPECT).
- Carrying out longitudinal studies to explore the long-term progression of the disease and assess the impact of various treatments.
- Exploring correlations between structural and functional brain changes and clinical symptoms.
- Evaluating the long-term adverse effects of antipsychotics and developing strategies to minimize them.
- Investigating the impact of different types of antipsychotics on cognitive functions and the quality of life of patients.
- Engaging in research on therapeutic interventions to improve cognitive dysfunctions associated with schizophrenia.

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APPENDICES

APPENDIX 1. LIST OF PAPERS PRESENTED AT CONFERENCES

1. Ifteni P, **Petric PS**, Moga S. Potențialul efect protectiv al antipsihoticelor În infecția cu SARS-CoV-2, Conferința Zilele Institutului de Psihiatrie "Socola" Iași, Iași, 11-13 noiembrie 2021
2. Teodorescu A, Ifteni P, Miron AA, Petric PS, Dima L. Clozapine for treatment-refractory aggressive behavior, "Congresului Națională de Psihiatrie", 12-15 iulie 2022
3. Miron AA, Ifteni PI, Popa A, **Petric PS**, Teodorescu A. Provocări ale inițierii LAI la pacienții cu tratament concomitent cu antipsihotice și benzodiazepine. Zilele Medicale și Științifice ale Spitalului Clinic de Psihiatrie "Prof. Dr. Al. Obregia", București, 16-20 mai 2023
4. Ifteni PI, Teodorescu A, Popa A, **Petric PS**, Miron AA. Algoritm decizional în vederea inițierii tratamentelor de tip LAI. Zilele Medicale și Științifice ale Spitalului Clinic de Psihiatrie "Prof. Dr. Al. Obregia", București, 16-20 mai 2023
5. Moga S, **Petric PS**, Teodorescu A, Miron AA, Ifteni P. Outcome of COVID-19 Vaccination in Pattients Treated with Clozapine Who Previously Went Through SARS-CoV-2 Infection, European Conference of Psychiatry and Mental Health "Galatia 2023", Galați, 17-21 mai 2023
6. Ifteni P., **Petric PS**. Evaluarea cognitivă a pacienților cu schizofrenie utilizând bateria de teste BACS. Congresul pentru studenți și tineri medici "KronMed". Brașov, 16-19 Noiembrie 2023

LIST OF PUBLICATIONS

1. **Petric, P. S.,** Ifteni, P., Miron, A. A., Sechel, G., & Teodorescu, A. (2024). Brain Abnormalities in Schizophrenia: A Comparative Imagistic Study. Medicina, 60(4), 564. Link: Brain Abnormalities in Schizophrenia: A Comparative Imagistic Study
2. **Petric P.S.,** Ifteni P, Popa AV, Teodorescu A. (2024) Cerebral Computed Tomographic Findings in Schizophrenia: Relationship to Second-Generation Antipsychotics and Hyperprolactinemia. Healthcare.; 12(13):1343. Link: Cerebral Computed Tomographic Findings in Schizophrenia: Relationship to Second-Generation Antipsychotics and Hyperprolactinemia
3. **Petric, P. S.,** Teodorescu, A., Miron, A. A., Manea, M. C., & Ifteni, P. (2024). Cognitive Outcomes in Nonacute Patients With Schizophrenia Treated With Long-Acting Injectable Antipsychotics Versus Oral Antipsychotics. American Journal of Therapeutics, 31(3), e219-e228. Link: Cognitive Outcomes in Nonacute Patients With Schizophrenia Treated With Long-Acting Injectable Antipsychotics Versus Oral Antipsychotics
4. **Petric, P.S.,** Dima, L., Ifteni, P., Teodorescu, A., Gavris, C., Pascu, A. M., ... & Burtea, V. (2019). Clozapine Efficacy, Type of Titration and Therapeutic Drug Monitoring Using Chemical Methods for Serum Level Assessment. REVISTA DE CHIMIE, 70(8), 2866-2868. Link: Clozapine Efficacy, Type of Titration and Therapeutic Drug Monitoring Using Chemical Methods for Serum Level Assessment
5. Andreea, T., Petru, I., Miron, A. A., **Paula-Simina, P.,** & Lorena, D. (2021). Clozapine for treatment-refractory aggressive behavior. Psychiatric Quarterly, 92(2), 721-733. Link: Clozapine for treatment-refractory aggressive behavior
6. Moga, S., Teodorescu, A., Ifteni, P., Gavris, C., & **Petric, P. S**. (2021). Inflammatory response in SARS-CoV-2 infection of patients with schizophrenia and long-term antipsychotic treatment. Neuropsychiatric Disease and Treatment, 3053-3060. Link: Inflammatory response in SARS-CoV-2 infection of patients with schizophrenia and long-term antipsychotic treatment
7. Ifteni, P., **Petric, P. S**., & Teodorescu, A. (2021). Rating opportunity for long-acting injectable antipsychotic initiation index (ROLIN). Frontiers in Psychiatry, 12, 767756. Link: Rating opportunity for long-acting injectable antipsychotic initiation index (ROLIN)
8. Moga, S., Teodorescu, A., Ifteni, P., **Petric, P. S**., & Miron, A. A. (2022). Clozapine and neutropenia in patients with schizophrenia and SARS-CoV-2 infection. Neuropsychiatric disease and treatment, 18, 977. Link: Clozapine and neutropenia in patients with schizophrenia and SARS-CoV-2 infection
9. Miron, A. A., Teodorescu, A., Ifteni, P., Irimie, C. A., Dima, L., & **Petric, P. S**. (2022). Switch from olanzapine long-acting injectable to its oral equivalent during COVID-19 pandemic: a real world observational study. Psychiatric Quarterly, 93(2), 627-635. Link: Switch from olanzapine long-acting injectable to its oral equivalent during COVID-19 pandemic: a real world observational study
10. Miron, A. A., Ifteni, P. I., Teodorescu, A., & **Petric, P. S**. (2022, July). Long-acting injectable antipsychotics (LAIs) prescribing trends during the COVID-19 Pandemic in Romania. In

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11. Miron, A. A., **Petric, P. S**., Teodorescu, A., Ifteni, P., Chele, G., & Szalontay, A. S. (2023). Benzodiazepines and mood stabilizers in schizophrenia patients treated with oral versus long-acting injectable antipsychotics—an observational study. Brain Sciences, 13(2), 173. Link: Benzodiazepines and mood stabilizers in schizophrenia patients treated with oral versus long-acting injectable antipsychotics—an observational study
12. Moga, S., **Petric, P. S**., Miron, A. A., Ifteni, P., & Teodorescu, A. (2023). Outcome of COVID-19 mRNA Vaccination in Patients Treated With Clozapine WHO Previously Went Through SARS-COV-2 Infection. American Journal of Therapeutics, 30(3), e186-e196. Link: Outcome of COVID-19 mRNA Vaccination in Patients Treated With Clozapine WHO Previously Went Through SARS-COV-2 Infection