UNIVERSITATEA DE MEDICINĂ ŞI FARMACIE
"CAROL DAVILA" din BUCUREŞTI

UNIVERSITATEA DE MEDICINĂ ŞI FARMACIE

„CAROL DAVILA", BUCUREŞTI

ŞCOALA DOCTORALĂ

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TEZĂ DE DOCTORAT

Conducător de doctorat:

PROF. HABIL. DR. CIOBANU ADELA MAGDALENA

Student-doctorand:

PETRESCU CRISTIAN

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DISCIPLINA PSIHIATRIE

NEUROLOGICAL SOFT SIGNS IN PATIENTS WITH SCHIZOPHRENIA

SUMMARY OF THE DOCTORAL DISSERTATION

(ENGLISH VERSION)

Conducător de doctorat:

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Introduction

Schizophrenia is a severe neuropsychiatric disorder that affects thinking, perception, and behavior, significantly impacting patients' quality of life [1-4]. **Neurological Soft Signs (NSS)** have been proposed as diagnostic and prognostic markers with implications for personalized therapies. This study examines the relationship between NSS severity, negative symptoms, neuroleptic treatment, and quality of life, contributing to the integration of clinical approaches in schizophrenia.

The findings highlight the high prevalence of NSS in patients with predominantly negative symptoms, their negative impact on quality of life, and the lack of influence of neuroleptic treatment on NSS severity. These results support the hypothesis that NSS are intrinsic neurobiological markers of the disease, emphasizing the need for a standardized assessment tool and their integration into clinical practice to improve diagnosis and therapeutic interventions.

I. General Section

1. Neurological Soft Signs (NSS)

Neurological Soft Signs (NSS) are subtle neurological abnormalities with no identifiable cause, encompassing difficulties in sensory integration, motor coordination, and sequencing of motor acts [5-7]. Initially, motor disturbances in schizophrenia were classified into "hard" signs, associated with dysfunctions of the pyramidal and extrapyramidal systems, and "soft" signs, which are not part of a clearly defined neurological syndrome [6]. However, this distinction remains controversial, as neuroimaging studies suggest the involvement of complex brain networks in the pathogenesis of these manifestations [8-10].

Research indicates that NSS play a crucial role in schizophrenia and are considered "target traits," resulting from the interaction of genetic and environmental factors [11-14]. Torrey et al. [17] demonstrated that twins affected by schizophrenia exhibit more neurological abnormalities than their unaffected siblings. Meehl [18] introduced the concept of schizotaxia, suggesting that NSS reflect an integrative neuronal defect predisposing individuals to psychotic disorders.

Consequently, NSS are regarded as markers of neurocognitive and neurodevelopmental vulnerability, contributing to a better understanding of the neurobiology of schizophrenia [19-26].

NSS frequently occur in patients with schizophrenia, being present even in those experiencing their first psychotic episode who have not yet been exposed to neuroleptic treatment. This suggests that these abnormalities are intrinsic features of the disease [39-42]. Studies on relatives of patients and unaffected twins confirm a genetic predisposition, as NSS are more common in first-degree relatives than in the general population [43-48]. NSS tend to be less pronounced in patients with a favorable therapeutic response but persist in treatment-resistant cases, correlating with negative symptoms and cognitive deficits [7-8, 49-50]. Moreover, NSS are associated with early-onset schizophrenia and may predict the risk of psychosis in adolescents [39-40, 52-55]. Meta-analyses indicate that up to 73% of schizophrenia patients exhibit significantly increased NSS, supporting the hypothesis that they could be used for disease staging [49, 56-57].

Assessment of NSS is conducted using several standardized scales. The Neurological Evaluation Scale (NES) is the most widely used clinical tool, providing a simple and structured method for quantifying NSS, although score interpretation may be influenced by antipsychotic side effects [28]. The Heidelberg Scale is another reliable instrument, including 17 items evaluating motor coordination, sensory integration, and primitive reflexes, making it applicable in both research and clinical practice [20, 65-67]. The Cambridge Neurological Inventory (CNI) combines NSS evaluation with extrapyramidal symptoms and catatonia, being used to study NSS prevalence in patient relatives and their correlation with cognitive function [68-71]. The Woods Scale, which includes both "hard" and "soft" NSS, allows for etiological classification of these signs, highlighting the role of treatment and other factors in their manifestation [72].

2. Integration of Neurological Soft Signs in Psychiatric Pathology

Dysfunction of the cortico-cerebello-thalamo-cortical circuit is considered the central mechanism underlying NSS in schizophrenia, as these signs have been correlated with morphological abnormalities in structures such as the thalamus, caudate nucleus, putamen, globus pallidus, cerebellum, and brainstem [26, 78, 93-103]. Neuroimaging studies have shown that

schizophrenia patients experiencing their first psychotic episode exhibit NSS correlated with gray matter loss in the lingual gyrus, parahippocampal gyrus, and superior temporal gyrus [98].

Most studies indicate that neuroleptic treatment does not significantly influence NSS, as they are present in both treated patients and those naive to treatment or in their first psychotic episode [50, 107-117]. Regarding the evolution of NSS under treatment, findings are contradictory. Some studies have reported NSS improvement following antipsychotic administration [80, 133], while others found no significant correlation between daily antipsychotic dose and NSS severity [77, 81, 98, 103, 128-130]. Additionally, certain studies suggest that NSS could be a predictor of treatment-resistant schizophrenia [64]. This supports the idea that there may be two distinct patient groups: one that exhibits clinical and NSS improvement under treatment and another in which NSS persist or worsen.

2.3. Correlation of NSS with Schizophrenia Symptoms, Sociodemographic Characteristics, and Disease Stage

Studies on the relationship between NSS and sociodemographic characteristics of schizophrenia patients yield contradictory results. While some research associates NSS with lower educational levels [59, 133, 134], others have found no significant correlations with sex, age, or education [7]. Some analyses suggest that NSS worsen with age and disease duration [81, 97, 130, 135], whereas others do not support this trend [49, 101, 103, 133]. Recent meta-analyses indicate a progressive increase in NSS in schizophrenia, unlike the U-shaped pattern observed in healthy individuals [40]. Additionally, NSS appear more pronounced in patients with predominantly negative symptoms, with some authors proposing that these signs may predict symptom progression [80, 128].

Structural imaging research has highlighted reduced connectivity between the caudate nucleus and core brain networks in schizophrenia patients compared to their healthy relatives and control groups [99]. Furthermore, patients with schizophrenia tend to exhibit more severe NSS than those in early stages of the disease [133]. Longitudinal studies have shown that patients following a remissive disease course experience a reduction in NSS, unlike those with chronic progression, where NSS either remain stable or worsen over time [41, 133].

2.4. Neurological Soft Signs as an Endophenotype of Schizophrenia

NSS are considered a potential endophenotype of schizophrenia, as they meet essential criteria such as heritability, relative stability over time, and presence in unaffected relatives of patients [136-140]. These neurological abnormalities can be detected before disease onset and occur at an intermediate frequency in patient relatives, supporting the hypothesis of a common genetic mechanism [48, 100, 147]. Studies indicate that NSS are more frequent in relatives of early-onset schizophrenia patients than in those with late-onset schizophrenia, suggesting a strong genetic component [149].

Current evidence suggests that NSS may be used to identify individuals at high risk of schizophrenia, with significant relevance for understanding the disease's neurobiology. While open questions remain regarding their specificity, existing data indicate that NSS represent a stable neurobiological marker of schizophrenia, with implications for early diagnosis, genetic studies, and neurodevelopmental research.

3. The Concept of Quality of Life in Schizophrenia

Schizophrenia profoundly impacts patients' quality of life, negatively affecting physical health, psychological well-being, social relationships, and environmental interactions [150-152]. Factors contributing to poor physical health include antipsychotic side effects, sedentary lifestyle, and inadequate nutrition [154-155]. Psychologically, positive and negative symptoms, alongside comorbidities such as depression and anxiety, further deteriorate patients' quality of life [156-157].

Social deficits are among the most affected aspects, influenced by stigma, isolation, and difficulties in professional integration [158-159].

3.2. Impact of Motor Disorders on Quality of Life in Schizophrenia

Schizophrenia involves motor dysfunctions, significantly impairing patients' daily functioning. Extrapyramidal symptoms such as medication-induced parkinsonism, tardive dyskinesia, acute dystonia, and akathisia negatively affect patients' autonomy [170-171].

Tardive dyskinesia severely impacts quality of life, affecting physical, psychological, and social functioning [175-176]. Quantitative motor assessments suggest that schizophrenia involves a primary motor deficit independent of treatment, with typical antipsychotics exacerbating motor impairments [177].

II. Personal Contributions

4. Working Hypothesis and General Objectives

General Hypotheses:

1. Neurological Soft Signs (NSS) are intrinsic characteristics of schizophrenia and are not solely the result of antipsychotic treatment side effects. Their severity is influenced by clinical and demographic factors.
2. Patients with predominantly negative symptoms (PNS) exhibit a higher degree of NSS compared to other schizophrenia patients. This suggests a link between sensorimotor dysfunctions and the negative symptomatology of schizophrenia.
3. Antipsychotic treatment has a limited effect on NSS severity, and the daily neuroleptic dose is not a significant predictor of their intensity. NSS may be intrinsic manifestations of schizophrenia rather than adverse effects of treatment.
4. Extrapyramidal side effects of neuroleptics may partially explain the expression of NSS.
5. Clinical and demographic factors (e.g., disease duration, age at onset, number of hospitalizations) influence the severity of NSS and extrapyramidal symptoms (EPS), potentially playing a role in disease progression and treatment response.
6. The quality of life in schizophrenia patients is affected by the severity of NSS and negative symptoms, independent of antipsychotic treatment. NSS may serve as a predictive factor for disability and reduced socio-professional integration.

General Objectives:

1. To determine the impact of antipsychotic treatment on NSS in schizophrenia patients by assessing the extent to which medication influences their severity.
2. To compare NSS severity between PNS and non-PNS patients to investigate possible correlations between negative symptoms and neurological dysfunctions.
3. To evaluate the presence of extrapyramidal symptoms (EPS) and correlate them with NSS severity, analyzing whether motor side effects of treatment contribute to NSS expression.

4. To analyze the influence of daily neuroleptic dose on NSS and EPS severity to determine whether there is a dose-dependent relationship between antipsychotic treatment and neurological impairment.
5. To explore the relationships between clinical and demographic variables (e.g., age, disease duration, number of hospitalizations) and the severity of NSS and EPS to identify potential risk factors for worsening motor symptoms in schizophrenia.
6. To identify potential predictive factors of quality of life in schizophrenia patients by analyzing the relationships between NSS, clinical symptoms, disease duration, and treatment history.

5. General Research Methodology

5.1 Study Design

This prospective observational study investigated Neurological Soft Signs (NSS) in schizophrenia patients admitted to the "Prof. Dr. Alexandru Obregia" Psychiatric Hospital, Bucharest, Romania. The study adhered to international ethical standards and was approved by the hospital's Ethics Committee (approval no. 89/June 7, 2022). Participants were consecutively selected based on inclusion and exclusion criteria, and evaluations were conducted by a multidisciplinary team consisting of a psychiatrist and a neurologist. Patients were initially assessed during hospitalization, re-evaluated after one month, and then again after six months.

The exclusion criteria targeted patients with intellectual disabilities, organic neurological pathologies, substance abuse, a history of severe traumatic brain injury, other non-schizophrenic psychoses, and ages outside the 18–65 range to ensure a homogeneous sample.

5.2. Measurement Instruments

Neurological Evaluation Scale (NES)

The NES assesses NSS through 28 items grouped into four domains:

- Motor coordination
- Sensory integration
- Sequencing of complex motor acts
- Primitive reflexes

The total score reflects NSS severity and allows comparative analysis between patients.

Positive and Negative Syndrome Scale (PANSS)

The PANSS is a standardized tool used to measure the severity of schizophrenia symptoms. It consists of 30 items divided into three subscales:

- Positive symptoms
- Negative symptoms
- General psychopathology

PANSS is used for monitoring clinical evolution and treatment response.

Simpson-Angus Scale (SAS)

The SAS evaluates antipsychotic-induced parkinsonism, analyzing muscle rigidity, tremor, and other extrapyramidal signs. High scores suggest severe motor impairment, and the scale is useful for treatment adjustments.

WHOQOL-BREF Scale

Developed by the World Health Organization (WHO), this instrument measures quality of life across four domains:

- Physical health
- Psychological well-being
- Social relationships
- Environment

As a validated international tool, WHOQOL-BREF allows for an assessment of the impact of schizophrenia symptoms on patients' quality of life.

These methods were chosen to provide a comprehensive evaluation of the relationship between NSS, schizophrenia symptom severity, and quality of life in affected individuals.

6. The Impact of Antipsychotic Treatment on Neurological Soft Signs in Schizophrenia Patients with Predominantly Negative Symptoms

6.1. General Hypotheses

The primary objective of this study is to assess the impact of antipsychotic treatment on the severity of Neurological Soft Signs (NSS) by comparing patients with predominantly negative symptoms (PNS) to those without this predominance. One of the central hypotheses suggests that patients with PNS exhibit a higher degree of NSS. Additionally, the study investigates whether NSS severity is influenced by demographic factors, extrapyramidal symptoms (EPS), and clinical characteristics of schizophrenia, as well as whether antipsychotic treatment has a significant effect on these symptoms.

6.2. Materials and Methods

This research was conducted on a sample of 99 inpatients at the "Prof. Dr. Alexandru Obregia" Psychiatric Hospital in Bucharest, Romania. All participants received antipsychotic treatment, with a mean daily dose of 424 mg chlorpromazine equivalent (CPZE). The sample was divided into two subgroups:

- Patients with predominantly negative symptoms (PNS)
- Patients with non-predominantly negative symptoms (NPNS)

To assess the severity of clinical and neurological symptoms, several standardized instruments were used:

- The Positive and Negative Syndrome Scale (PANSS) was applied to quantify schizophrenia symptom severity.

- The Neurological Evaluation Scale (NES) was used to evaluate NSS.
- The Simpson–Angus Scale (SAS) was used to determine the severity of extrapyramidal symptoms.

Statistical analysis was conducted using linear regression models and t-tests for group comparisons.

6.3. Results

Demographic and Clinical Characteristics

The mean age of patients included in the study was 30.6 years, and the mean disease duration was 8.15 years. The majority of patients (86%) received atypical antipsychotics, while 4% were treated with typical neuroleptics, and 9% received a combination of two atypical antipsychotics.

Assessment of NSS and Extrapyramidal Symptoms

- The severity of NSS, measured using the NES, showed a mean score of 10.5 (SD = 5.5).
- Extrapyramidal symptoms, assessed using the SAS, had a mean score of 3.04 (SD = 2.01).

A comparative analysis between the PNS and NPNS groups revealed significant differences:

- Patients in the PNS group exhibited significantly higher NES scores (12.49 vs. 9.13, $p = 0.003$).
- Regarding individual NES components, patients with PNS obtained significantly higher scores in:
    - Sensory integration ($p = 0.024$)
    - Motor coordination ($p = 0.013$)
    - Sequencing of complex motor acts ($p = 0.03$)

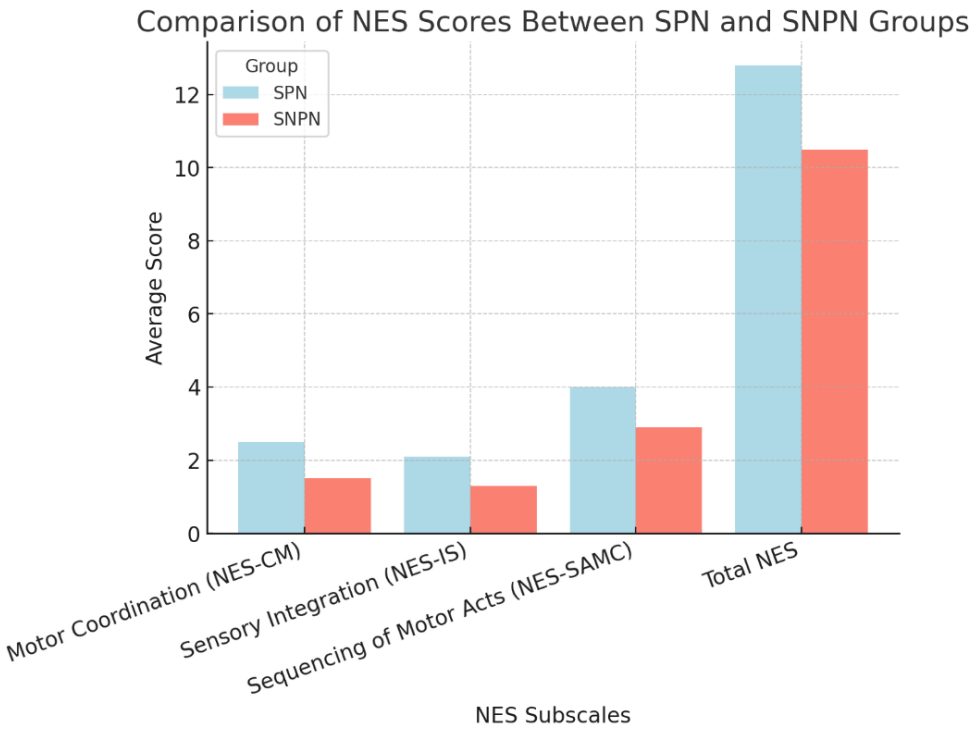

Figure 6.1. Distribution of NES Neurological Evaluation Scores for Patient Subgroups

Correlation Analysis

Demographic and clinical variables were analyzed to identify potential correlations with the severity of Neurological Soft Signs (NSS). The results indicate that male patients exhibited significantly higher NES scores than females ($p = 0.002$). Additionally, an older age at disease onset was associated with higher NES scores ($p = 0.048$), and a longer disease duration was a predictor of increased NSS severity ($p < 0.001$). Furthermore, a higher number of hospitalizations and a longer cumulative hospitalization period were positively correlated with NSS severity ($p < 0.001$).

An analysis of the relationship between the daily CPZE dose and NSS severity did not reveal a significant correlation ($p = 0.438$), suggesting that NSS are more likely an intrinsic characteristic of schizophrenia rather than a consequence of antipsychotic treatment.

Extrapyramidal Side Effects

The findings indicate that CPZE dose was positively correlated with the severity of extrapyramidal symptoms (EPS), as measured by the Simpson–Angus Scale (SAS) ($p < 0.001$),

suggesting a dose-dependent relationship between neuroleptic treatment and the severity of these adverse effects. Additionally, patients treated with typical antipsychotics exhibited higher SAS scores compared to those receiving atypical antipsychotics ($p < 0.001$). Moreover, the absence of anticholinergic treatment was associated with lower SAS scores ($p = 0.010$), suggesting a potential protective effect of anticholinergic medication against EPS.

6.4. Conclusions

The results of this study provide new insights into the relationship between schizophrenia, NSS, and antipsychotic treatment. The key findings are summarized as follows:

1. NSS are more frequent and more severe in patients with predominantly negative symptoms (PNS), suggesting a strong association between sensorimotor dysfunctions and the negative symptomatology of schizophrenia.
2. Antipsychotic treatment does not significantly influence NSS severity, supporting the hypothesis that NSS are primarily a neurobiological characteristic of schizophrenia rather than a side effect of medication.
3. Demographic and clinical factors influence NSS severity, with male patients, those with late-onset schizophrenia, and those with a higher number of hospitalizations exhibiting higher NES scores.
4. The severity of extrapyramidal symptoms is correlated with the daily CPZE dose, unlike NSS severity, which is not significantly affected by treatment.

7. Neurological Soft Signs in Schizophrenia Patients: Sociodemographic Correlations, Clinical Implications, and Quality of Life

7.1 General Hypotheses

Previous studies have demonstrated an association between the severity of negative symptoms and the presence of NSS, and recent research suggests that NSS may have prognostic value, being considered markers of disease progression. In this context, the present study aims to

investigate the relationship between NSS severity and the clinical, therapeutic, and demographic factors of schizophrenia patients. The central hypothesis of this study is that NSS are correlated with the intensity of psychotic symptoms and social dysfunction, and their severity is not significantly influenced by antipsychotic treatment. Additionally, this study sought to analyze the impact of symptomatology on patients' quality of life and explore the correlations between NSS and sociodemographic characteristics.

7.2. Materials and Methods

This study was conducted on a sample of 81 inpatients from the "Prof. Dr. Alexandru Obregia" Psychiatric Hospital in Bucharest, Romania. The patients included in the study were between 18 and 64 years old, with a mean age of 33.08 years. The diagnosis of schizophrenia was established according to DSM-V criteria, and patients were receiving antipsychotic treatment prescribed by their attending physicians, without intervention from the research team in selecting the therapy.

For clinical assessment, the following standardized instruments were used:

- Positive and Negative Syndrome Scale (PANSS) – applied to measure schizophrenia symptom severity.
- Neurological Evaluation Scale (NES) – used to quantify NSS, including subscales for motor coordination, sensory integration, and sequencing of complex motor acts.
- Simpson–Angus Scale (SAS) – used to assess extrapyramidal symptoms.
- WHOQOL-BREF Scale – used to evaluate patients' quality of life.
- Clinical Global Impression Scale (CGI) – applied to assess initial symptom severity and clinical evolution during the study.

Statistical analysis was conducted using linear regressions and mixed-effects models, aiming to identify predictors of NSS severity and evaluate their variations over time.

7.3. Results

Demographic and Clinical Characteristics

The analysis of demographic and clinical characteristics revealed that the mean age at disease onset was 23.43 years, while the average duration of schizophrenia progression was 9.65 years. Patients included in the study had experienced an average of 6.35 hospitalizations since the onset of the disease. Regarding pharmacological treatment, the mean daily antipsychotic dose was initially 412 mg CPZE and increased to 475 mg CPZE after six months of treatment.

Schizophrenia Symptom Evolution

The assessment of clinical symptoms indicated a significant improvement over the course of the study. The PANSS scores showed a statistically significant reduction in psychotic symptoms, with the Positive PANSS Score decreasing from 21.19 to 19.28 ($p < 0.001$), the Negative PANSS Score decreasing from 22.10 to 20.89 ($p < 0.001$), and the Total PANSS Score decreasing from 85.79 to 79.21 ($p < 0.001$).

NSS Severity

The analysis of NSS severity over the six-month assessment period did not reveal any statistically significant variations, with the total NES score remaining relatively stable (initial: 11.58; final: 11.37, $p = 0.065$). These findings suggest that NSS are stable characteristics of schizophrenia, independent of symptom improvement under treatment, and may serve as potential neurobiological markers of the disease.

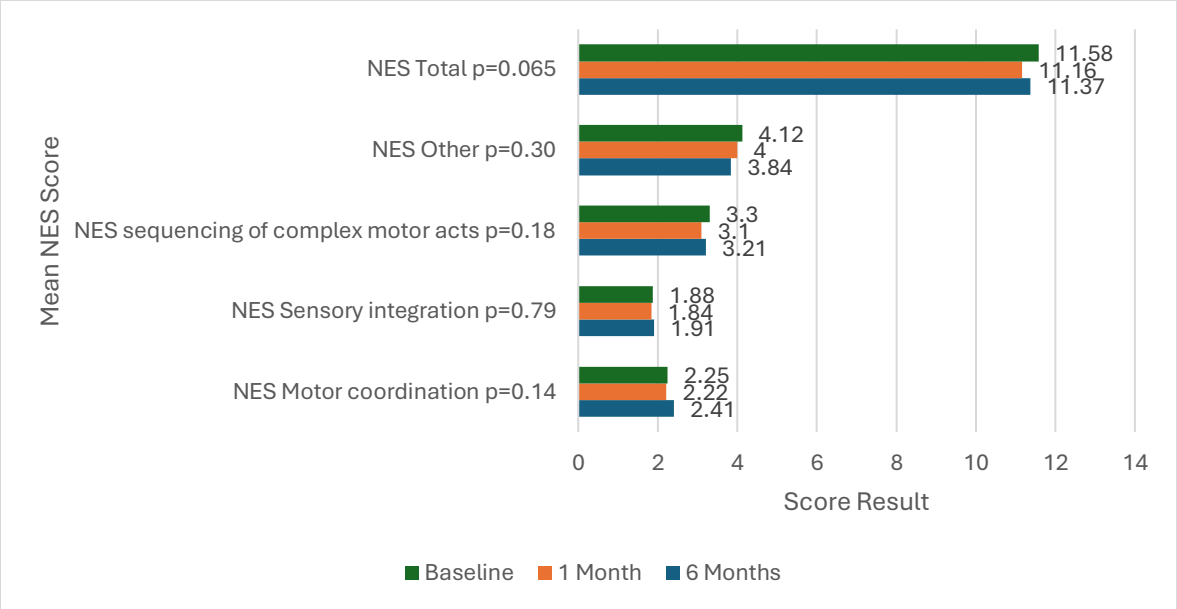

Figure 7.1. Evolution of NES Scores from Baseline to 6 Months.

Regarding predictive factors, male patients exhibited higher NES scores compared to females ($p = 0.013$). A longer disease duration was identified as a significant predictor of higher NES scores ($p = 0.029$), as were the total number of hospitalizations and cumulative hospitalization duration ($p < 0.001$). In contrast, the daily CPZE dose was not correlated with NSS severity ($p = 0.12$), suggesting that NSS are an intrinsic feature of schizophrenia, independent of neuroleptic treatment.

Table 7.1. Statistically Significant Predictors for the Total NES Score

Predictors	**Beta (95% TI) ***	***p*-value**
Sex		
Female	—	
Male	1.6 (0.05 la 3.1)	0.043
Duration of illness	0.13 (0.05 la 0.22)	0.002
CGI Improvement	2.0 (1.3 la 2.7)	<0.001
PANSS Negative	0.11 (0.03 la 0.19)	0.005
PANSS General	0.07 (0.02 la 0.12)	0.005
SSA	0.28 (0.07 la 0.49)	0.01
Total Hospitalization Period (months)	0.62 (0.16 la 1.1)	0.009
WHOQOL Social	-0.03 (-0.06 la 0.00)	0.029

Extrapyramidal Symptoms and Treatment Side Effects

The severity of extrapyramidal symptoms (EPS), as measured by the Simpson–Angus Scale (SAS), remained stable throughout the study ($p = 0.16$). The use of anticholinergic treatment was associated with higher SAS scores ($p < 0.001$), while the CPZE dose showed a positive correlation with EPS severity ($p < 0.001$).

Quality of Life and the Impact of Symptoms

The quality-of-life analysis revealed significant improvements in the psychological domain (+7.89%) and social domain (+8.35%), whereas changes in physical health (+2.36%) and environmental factors (+1.22%) were minimal. Furthermore, the severity of schizophrenia

symptoms, as measured by the PANSS, was negatively correlated with patients' perception of quality of life ($p < 0.001$) (Figure 7.2).

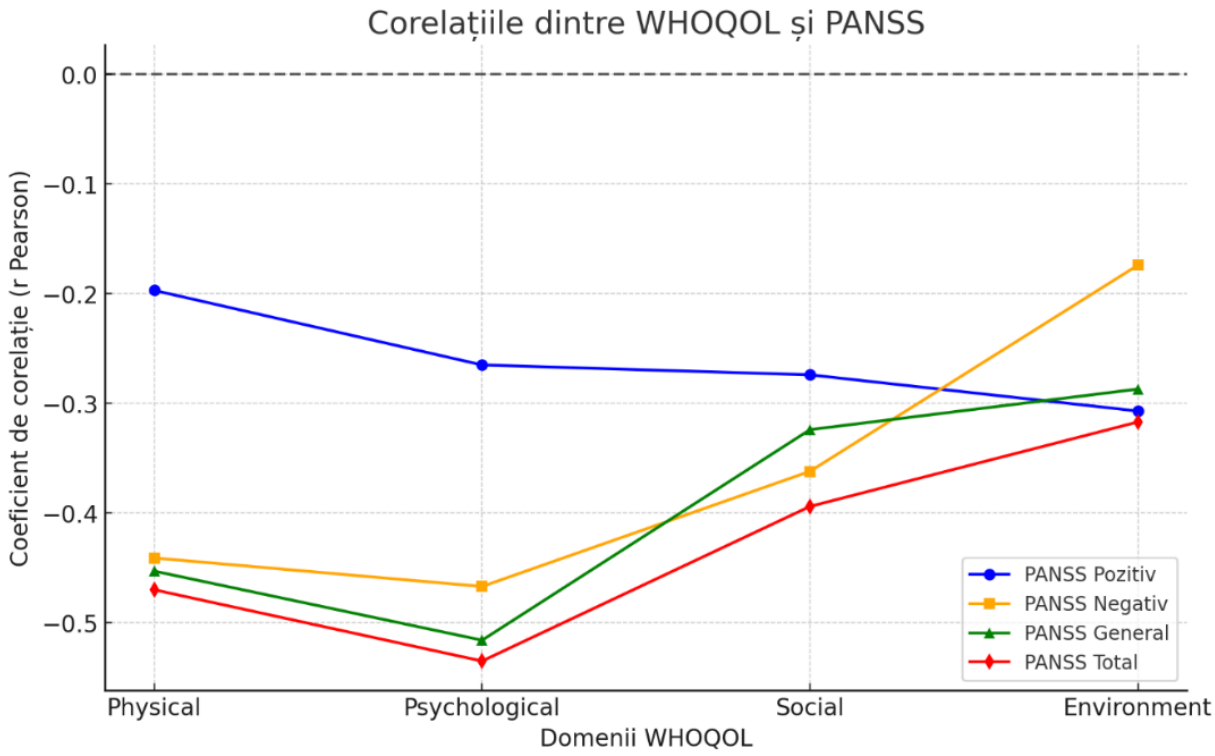

Figure 7.2. Correlations Between WHOQOL and PANSS

7.4. Conclusions

The findings of this study suggest that Neurological Soft Signs (NSS) are correlated with schizophrenia severity but are not influenced by antipsychotic treatment. Their severity is primarily determined by clinical factors, such as disease duration and hospitalization history, whereas extrapyramidal symptoms (EPS) are dependent on the administered neuroleptic dose.

Regarding patients' quality of life, the amelioration of psychotic symptoms contributed to an improvement in psychological and social health perception. However, the effects on physical health and environmental factors were less pronounced.

8. General Conclusions

This study contributes to the understanding of Neurological Soft Signs (NSS) in schizophrenia, reinforcing the evidence regarding their correlation with psychotic symptoms and disease progression, independent of antipsychotic treatment. While the clinical utility of NSS requires further investigation, the obtained data highlight their potential as diagnostic and prognostic markers in schizophrenia. Previous longitudinal studies have supported this hypothesis, but the current findings emphasize the need for a standardized approach to NSS assessment, including objective criteria and well-defined cutoff scores. Furthermore, the use of advanced imaging techniques could help validate NSS as biomarkers of disease progression.

Key Research Findings

1. Correlation Between Negative Symptoms and NSS

Patients with predominantly negative symptoms (PNS) exhibited significantly higher NES scores compared to those without this predominance, indicating a link between the severity of negative symptoms and sensorimotor dysfunctions.

2. Impact of Antipsychotic Treatment

Statistical analysis did not identify a significant relationship between the daily antipsychotic dose and NSS severity, suggesting that NSS are an intrinsic feature of schizophrenia rather than a side effect of medication. Conversely, SAS scores were significantly correlated with CPZE dose, confirming the association between extrapyramidal symptoms and high neuroleptic doses.

3. Relationship Between NSS and Clinical-Demographic Variables

Factors such as age at disease onset, schizophrenia duration, number of hospitalizations, and cumulative hospitalization duration were identified as predictors of NSS severity. Patients with a longer disease duration or an extensive hospitalization history had significantly higher NES scores.

4. Correlation Between NSS and Quality of Life

The severity of NSS was a negative predictor of quality of life, with patients exhibiting pronounced NSS reporting lower well-being levels, particularly in the psychological and social

domains. Deficits in motor coordination and sensory integration were most strongly associated with quality-of-life deterioration.

5. NSS Evolution Over Time

Over the six-month follow-up period, NSS severity remained relatively stable, showing no statistically significant changes, regardless of schizophrenia symptom evolution. While PANSS scores improved under treatment, NSS did not follow the same trajectory, supporting the hypothesis that they represent a phenomenon relatively independent of psychotic symptom severity.

Original Contributions of the Study

One of the main contributions of this study is the identification of a significant correlation between negative symptoms and Neurological Soft Signs (NSS). The results indicate that patients with predominantly negative symptoms (PNS) exhibit more severe sensorimotor deficits compared to those without this predominance. This finding emphasizes the importance of NSS as potential markers of negative symptom severity in schizophrenia, offering a new perspective on the neurobiological basis of the disorder.

Another key contribution of the study is the confirmation of NSS independence from antipsychotic treatment. Statistical analysis demonstrated the lack of a significant relationship between NSS severity and the daily chlorpromazine-equivalent (CPZE) dose, suggesting that these manifestations are not merely side effects of medication but rather intrinsic features of schizophrenia. This discovery reinforces the hypothesis that NSS may reflect neurodevelopmental dysfunctions rather than purely treatment-induced abnormalities.

Based on the obtained data, the study proposes the hypothesis that sensorimotor dysfunctions could serve as prognostic markers for schizophrenia progression, with relevant clinical implications. In this context, NSS could be utilized to identify patients at higher risk of functional deterioration, facilitating early interventions to prevent symptom exacerbation.

The results also demonstrate that patients with a higher degree of sensorimotor impairment exhibit distinct clinical-functional characteristics, necessitating the development of personalized

therapeutic strategies. Integrating NSS assessment into clinical practice could contribute to optimizing treatment plans and ensuring better adaptation of interventions to each patient's profile.

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List of published scientific articles

[1] **Petrescu C**, Papacocea IR, Vîlciu C, Mihalache OA, Vlad DM, Marian G, Focșeneanu BE, Sima CT, Ciobanu CA, Riga S, et al. The Impact of Antipsychotic Treatment on Neurological Soft Signs in Patients with Predominantly Negative Symptoms of Schizophrenia. *Biomedicines*. 2022; 10 (11) : 2939 . https://doi.org/10.3390/biomedicines10112939

F.I. = 4.1

(Study 1 – Chapter 6)

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(Chapter 1)

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