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DYNAMICS OF DIAGNOSIS IN PATIENTS WITH A FIRST PSYCHOTIC EPISODE INDUCED BY THE USE OF PSYCHOACTIVE SUBSTANCES

THESIS SUMMARY
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The thesis is presented on 148 pages and is illustrated with 43 tables and 60 figures, including five appendices. The bibliography includes 201 sources, of which 11 are in Cyrillic and 190 are in Latin.

Note: The numbering of tables and figures in the thesis summary does not correspond to the numbering in the thesis itself.

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The thesis documentation is available at the Scientific Department of the university and is published on the MU-Varna website.

CONTENTS

Abbreviations

2-AG – 2-arachidonoylglycerol
AEA – Endogenous cannabinoid anandamide
BAD – Bipolar affective disorder
CB1R – Cannabinoid receptor type 1
CBs – Cannabinoids
CNS – Central nervous system
CUD – Cannabis use disorder
DAST 10 – Drug Abuse Screening Test
DAT – Dopamine transporter
DSM-5, DSM-5-TR – Diagnostic and Statistical Manual of Mental Disorders
DUP – Duration of untreated psychosis
eCBs – Endogenous cannabinoids
ECS – Cannabinoid system
FPE – First psychotic episode
GABA – gamma-aminobutyric acid
GAF – Global Assessment of Functioning Scale
ICD-10, ICD-11 – International Classification of Diseases
MDMA – 3, 4-methylenedioxymethamphetamine, ecstasy
METH – Methamphetamine
NC – Natural cannabis
NET – Noradrenergic transporter
PANSS (PANSS+//-, G) – Positive and Negative Syndrome Scale
PAS – Psychoactive substances
PEA – Phenethylamine
SCI-PANSS – Structured Clinical Interview for PANSS
SCs – Synthetic cannabinoids
SERT – Serotonin transporter
SIPD – Substance-induced psychotic disorder
THC – Tetrahydrocannabinol, delta-9-tetrahydrocannabinol

I. Introduction

1. Relevance of the subject

The first psychotic episode (FPE) is a defining moment in chronic psychotic disorder development and is associated with high diagnostic, therapeutic, and prognostic significance. The diversity of disease manifestations, their temporal dynamics, and treatment outcomes often lead to complex clinical diagnostic challenges.

Patients with first-episode psychosis are a heterogeneous group, which determines the instability of initial diagnoses over time. The initial manifestations of psychosis can hardly be attributed to a specific nosological entity, but rather are categorised within a spectrum of mental disorders. The use of psychoactive substances (PAS) is an additional complicating factor affecting the intensity and duration of symptoms and prolonging the process of differential diagnosis.

In recent decades, there has been a steady increase in the number of registered mental disorders induced by the use of PAS, both nationally and internationally. Their frequency follows the trends of increasing drug use and drugs diversity. Data from the European Drug Report 2025: Trends and Developments show that approximately 8.4% of the adult Europeans (24 million aged 15 to 64 years) have used cannabis in the past year, and 1.5% (4.3 million) are daily or near-daily users. Cocaine is the second most commonly reported illicit drug among individuals entering specialised treatment for drug dependence for the first time. It is the most commonly reported substance in cases of acute intoxication in emergency departments. The presented results demonstrate that the combined use of PAS (the use of two or more substances, simultaneously or sequentially) is widespread among individuals with substance abuse and is associated with increased risk of health and social problems [European Union Drugs Agency, 2025].

Clinical experience and numerous studies link the use of PAS with the appearance of transient psychotic symptoms during acute intoxication. Chronic PAS use is associated with the triggering of a psychotic episode and subsequent development of a chronic disorder from the schizophrenia or bipolar spectrum. The probability of developing PAS-induced psychosis is associated with multiple currently unclear factors, including the type of substance, duration of use, degree of addiction, presence of comorbid dependencies, and hereditary predisposition.

According to available literature data, the frequency of dual diagnosis – a disorder due to PAS use and psychosis from the schizophrenia spectrum – can

reach up to 50%, with more severe symptomatology and poorer response to treatment compared to patients with primary psychosis.

The conclusions from the literature review indicate that the observed comorbidity between psychosis and addiction suggests the presence of common pathogenetic mechanisms. The diagnostic transition after the first psychotic episode linked to PAS use represents a complex and multifactorial process. Monitoring these characteristics is essential for early diagnosis, prognostic assessment, and individualised treatment in patients with a first psychotic episode.

2. Scientific and practical significance

Experience from daily clinical practice shows that the differential diagnosis of primary and PAS-induced psychosis is sometimes difficult and even impossible, raising the following insufficiently clarified questions:

- How do the duration of use and type of PAS affect the onset, frequency, and severity of the clinical picture of psychotic disorder, as well as the final diagnosis and prognosis?
- Is it possible to identify risk factors, characteristic clinical manifestations, course type, and therapeutic response that could help the clinician in distinguishing primary psychosis from psychosis resulting from PAS use?

The dynamics of diagnosis in patients with FPE induced by PAS use is a relevant and insufficiently studied problem in Bulgarian psychiatry, which justifies the choice of our research topic.

II. Objectives, tasks and working hypotheses of the study

1. Objective

The thesis aims to track the variability (dynamics) of diagnosis in patients with FPE after PAS use within a two-year period.

2. Main tasks

• To perform an analysis of the type of diagnosis at the first and subsequent psychotic episodes, comparing the final diagnosis within a two-year period in the studied subjects from the target group with psychosis induced by PAS use, and the control group with psychosis without PAS use.

• To analyse the severity of clinical syndromes and quality of life at the initial and final diagnosis in the study group with PAS use, as well as comparative analysis with the control group.

• To perform a comparative analysis of the demographic indicators in both groups and to identify the most common risk factors for triggering psychotic disorder with PAS use.

• To determine the frequency of subsequent psychotic episodes and hospitalisations, as well as the severity of the course and duration of use at the end of the study period.

• To investigate how the duration and type of PAS used influence the age of onset of psychotic disorder, the severity of the clinical picture, dynamics of course, quality of life and final diagnosis, as well as the prognosis of the disease.

• To derive prognostic-diagnostic criteria for the reliability and dynamics of diagnosis within a two-year period after FPE induced by PAS use.

• To formulate recommendations for applying screening tests and questionnaires for early detection of psychotic symptoms in individuals abusing or dependent on PAS.

3. Working hypotheses

Hypothesis 1: In patients with FPE induced by PAS use, greater variability (dynamics) of diagnosis is observed within the two-year follow-up period, compared to patients without PAS use.

Hypothesis 2: Prolonged and combined use of PAS (especially cannabis, amphetamines and methamphetamines) has a significant influence on the age of

onset of FPE, with these patients more frequently showing earlier manifestation of psychotic symptomatology compared to the control group without PAS use.

Hypothesis 3: Patients with psychosis related to PAS use have more severe clinical manifestations at initial and final diagnosis and lower assessment of functioning and quality of life compared to the control group.

Hypothesis 4: In individuals using PAS, the frequency of subsequent psychotic episodes and hospitalisations within the two-year period is higher compared to the control group.

Hypothesis 5: Demographic characteristics (age, sex, social status, education and professional employment) and the presence of certain risk factors (heredity, comorbidity and early PAS use) have a significant influence on the manifestation and course of psychotic disorders.

Hypothesis 6: The severity of clinical syndromes and dynamics of diagnosis are correlated with the duration and type of PAS used and the initial age of abuse.

Hypothesis 7: The risk of transition to chronic psychotic disorder, most commonly schizophrenia and schizoaffective disorder, is highest in individuals using cannabis and combined PAS.

Hypothesis 8: In cases initially diagnosed with acute psychosis with polymorphic and schizophrenia-like symptoms and PAS use, the risk of transition to chronic psychosis from the schizophrenia spectrum is higher.

Hypothesis 9: Monitoring the dynamics in clinical manifestations and functional recovery within a two-year period allows us to derive prognostic-diagnostic criteria for the reliability and stability of diagnosis in psychotic disorders induced by PAS.

III. Materials and methods

1. Study design

The study is designed as a longitudinal, prospective study with a two-year follow-up period, including initial, intermediate, and final assessment of the studied indicators.

2. Subject and sample of the study

The present study covers a total sample of 81 patients aged 18 to 65 years, divided into two groups. The study (research) group includes 41 individuals with a diagnosis meeting the criteria for FPE after PAS use. The control group consists of 40 individuals with a diagnosis of FPE, in whom no data for preceding PAS use were established. This sample structure allows direct comparison between the two groups with regard to assessing the influence of PAS use on the clinical manifestation, course, and diagnostic features of the first psychotic episode.

The included individuals were hospitalised in the Psychiatry clinics at St. Marina University Hospital – Varna and consulted at the Specialised Psychiatric Outpatient Clinic in Varna, in the period from May 2021 to June 2023. The study started after obtaining permission from the Research Ethics Committee at the Medical University – Varna, which approved the plan-program and gave its positive decision for conducting the study.

Participation in it was completely voluntary, and inclusion was carried out after a conversation with the principal investigator, providing information about the nature, objectives, and benefits of the study. All participants in the study signed a declaration of informed consent (according to a template) and a notice for the processing of personal data. Participants were given the opportunity to withdraw from the study at any time.

Of the initially included 96 patients, 15 dropped out for various reasons, most often due to refusal to sign informed consent or failure to appear for follow-up examinations and tests.

3. Inclusion and exclusion criteria. Study limitations and framework

Inclusion criteria for the study group: Diagnosed FPE and data for use/abuse of PAS, with the exception of alcohol. The clinical picture in all studied individuals in the study group met the criteria for establishing a diagnosis from Section F10-F19 of ICD-10 – "Mental and behavioural disorders due to psychoactive substance use", including Psychotic disorder caused by psychoactive substances

(F1x.5) or Residual and late-onset psychotic disorder caused by PAS (F1x75). Accordingly, the different PAS are differentiated with a third code character – F11 Opioids; F12 Cannabinoids; F13 Sedatives and hypnotics; F14 Cocaine; F15 Other stimulants; F16 Hallucinogens; F18 Volatile solvents; F19 Combined use or use of other PAS.

The study group also included psychotic disorders from Section F20-F29 "Schizophrenia, schizotypal and delusional disorders", including Section F23 "Acute and transient psychotic disorders" and F30-F39 Section "Affective disorders", in the presence of an accompanying diagnosis from Section F10-19 - Harmful use (F1x1) and PAS dependence syndrome (F1x2).

Patients with a diagnosis of psychotic disorder due to alcohol use were excluded from the group, as well as those with states of acute intoxication with PAS and the presence of a withdrawal state with or without delirium. This is justified by the fact that alcohol is usually considered separately from other PAS in epidemiological and clinical studies. Therefore, psychoses in alcohol abuse and dependence are not included in the main group, but are recorded as *accompanying*. Their inclusion in the group with PAS could lead to "distortion of results" due to the high frequency of alcohol abuse in the general population and its related complications.

Inclusion criteria for the control group: Patients diagnosed with FPE, without data for PAS use, meeting the criteria for diagnosis in the sections listed above from ICD-10 (F20-F29 and F30-F39), and psychotic disorders due to organic brain pathology were not included.

Exclusion criteria from the study and control group are: Patients with a definitive clarified diagnosis in clinical terms, registered patients, patients placed under limited or full prohibition, refusal to sign or withdrawal of informed consent, as well as the cases listed above.

Limitations and framework of the study

The limitations in the study result from the lack of cooperation and difficulties in contact with the studied individuals, especially those in the study group with PAS. Another limitation is the relatively short follow-up period of two years, which is considered insufficient in the majority of studies with a similar design. Patient follow-up was periodic, with control examinations – routine, in case of deterioration of mental state and new psychotic episode.

4. Research methods

4.1. Clinical method – clinical interview (anamnesis and mental status)

The information was obtained personally by the principal investigator during clinical examinations. Additional information was collected from the patient's anamnesis and medical documentation, inpatient and outpatient patient files, from close relatives and family members, and from the treating psychiatrist.

A standard clinical psychiatric examination was conducted, including observation and psychiatric interview, with detailed collection of anamnestic data regarding the current illness, previous and concomitant mental and somatic disorders, as well as family and social history. An assessment of the mental status was performed by individual mental spheres with a subsequent summary. As part of the comprehensive examination, an assessment of neurological and somatic status was performed, aimed at identifying possible organic factors related to psychopathology. At the discretion of the treating medical team, patients were prescribed additional tests and consultations.

4.2. Standardised instruments (assessment scales, questionnaires)

At the first and last examination, standardised assessment scales were used to evaluate the severity of the clinical picture:

Positive and Negative Syndrome Scale (PANSS), developed by Kay, Fiszbein and Opler in 1987, with assessment by subscales for positive (PANSS+), negative symptoms (PANSS-), general psychopathological assessment (PANSS G) and total assessment (PANSS total), using the Structured Clinical Interview for PANSS (SCI-PANSS).

Global Assessment of Functioning Scale (GAF) – a widely used instrument for assessing the overall level of psychological, social, and occupational functioning in individuals with mental disorders (American Psychiatric Association, DSM-IV-TR, 2000).

Due to their high consistency and reliability, PANSS and GAF were selected as the main instruments for assessing psychopathological severity and overall functioning of the studied individuals.

Drug Abuse Screening Test (DAST), according to the Methodology for applying screening tests of National Centre of Public Health and Analyses **(**NCPHA, 2021). The shortened version (DAST-10) was used, including 10 questions designed for screening problematic use and dependence on PAS, with the exception of alcohol [Skinner, 1982]. The questionnaire was completed at the patients' last visit. The answer to the questions is "Yes" or "No". In these statements, "drug abuse" refers to:

1) Use of prescription or over-the-counter medications in doses larger than prescribed; 2) Any non-medical use of medications – various categories of PAS are included, such as: cannabis (marijuana, hashish), solvents, tranquilisers (benzodiazepines, sleeping pills), barbiturates, cocaine, psychostimulants, hallucinogenic substances and opiates. 3) Questions do not include alcohol use. 4) Questions refer to the last 12 months before the survey.

For convenience in the present study, DAST-10 responses are grouped according to the scores obtained as: 0 points – no use; 1 to 5 points – episodic use and 6 to 10 points – continuous use.

4.3. Clinical laboratory tests

For the purposes of the study, the results from clinical laboratory tests with paraclinical effectiveness were analysed, including liver transaminases. Results from clinical laboratory tests and combined urine test for PAS, in patients hospitalised at St. Marina University Hospital – Varna, were obtained from data from the disease history and upon admission to the psychiatric clinics. Control clinical laboratory tests in outpatient individuals were performed at a certified medical diagnostic laboratory, and the urine test was conducted by the principal investigator at the initial and final visit (designated as urine test PAS-1 and PAS-2).

The following combined urine tests for PAS were used:

- Clear DOA Combo-6 – Combined rapid urine test for 6 PAS (THC; AMP; COC; OPI; MET/MAMP; BZD)
- Multi Drug-6 (Multi-Panel Test) – Combined 6-position urine test (THC; AMP; COC; OPI; MET, MAM)

Both tests are suitable for examining patients for clinical or screening use and cover the main groups of PAS included by international recommendations.

4.4. Statistical methods

Statistical methods enable us to make objective conclusions regarding the dependencies, patterns, and differences between the observed variables within the sample. In clinical-psychiatric research, statistical analysis is a fundamental tool for assessing the reliability of results, for verification of hypotheses, and for tracking the dynamics of clinical indicators over time. In the present study, the following basic statistical methods were applied in processing the results:

4.4.1. Descriptive statistics

Used to present and summarise the basic characteristics of the studied groups – demographic, clinical, and diagnostic data. Through indicators such as mean value, standard deviation, minimum and maximum values, percentage distributions and frequencies, the main trends in the obtained data are outlined. The application in the present case is a description of the demographic structure of the samples (with PAS and control group) – age, sex, education, work, marital status, comorbid diseases, family burden, as well as data from conducted tests, assessment scales and questionnaires.

4.4.2. Non-parametric tests for independence (χ^2 *and Fisher's exact test*)

These are used in analysing the correlations between categorical variables when the prerequisites for parametric tests are not met. Their application in the study is in comparing groups by demographic and clinical parameters, as well as checking the statistical significance of established differences.

4.4.3. Correlation analysis

It is used to investigate the direction and strength of the correlation between two quantitative variables. The present study aims to investigate the degree and direction of correlations between the main demographic, clinical indicators and behavioural variables in patients with FPE and PAS use. Analysis of correlations between risk factors, duration and intensity of PAS use, type of initial diagnosis, symptom severity by PANSS, number of hospitalisations, adherence to treatment and dynamics of clinical improvement with final diagnosis. The correlation analysis aims to establish whether statistically significant dependencies exist that support the concept of the influence of PAS on the course, chronification and nosology of first-episode psychotic disorders. Pearson's correlation coefficient (Pearson's r) was applied, which measures the strength and direction of linear dependence between pairs of variables. The statistical significance of correlations was assessed through p-values, with values below 0.05 considered significant.

4.4.4. Parametric inferential statistics (*t-test*)

The *t-test* enables comparison of mean values between two groups (t-test for independent samples) or between two measurements within the same group (t-test for dependent samples). Application: analysis of changes in the severity of psychopathological symptoms between initial and final assessment by PANSS in all subscales and comparison between groups. Two main types of t-tests were used in the study: paired t-test and independent t-test.

Paired t-test is applied to compare the mean values of the same group of participants at two different times or conditions – for example, a change in the functional state of patients between the first and second observation period.

An independent t-test is used to compare mean values between two independent groups. In this case, it checks whether there is a statistically significant difference in the given indicators between the patient groups, with the PAS and control groups. It is assumed that the two groups are independent and their data follow a normal distribution.

4.4.5. One-way analysis of variance (*ANOVA/Analysis of Variance*)

This is a statistical test used to compare mean values between more than two independent groups, to assess differences between them on a given indicator. Allows the establishment of statistically significant variations arising from the influence of independent factors. Its application in the study is in comparing mean values of clinical assessments according to the type of diagnosis, duration and pattern of PAS use. If the result from ANOVA is statistically significant ($p < 0.05$), this means that at least one of the groups differs in mean value from the others.

4.4.6. Non-parametric inferential statistics – *Wilcoxon Signed-Rank Test* for paired comparisons in case of non-conformity with normal distribution.

The Wilcoxon test for related samples is used to compare two dependent measurements when the prerequisites for normal distribution are not met, analysing the differences between pairs of observations and accounting for the direction and magnitude of change. Its application in the present study is a comparison of initial and final scores on psychometric scales (e.g., PANSS, GAF) within the same group of patients when data do not follow a normal distribution or the number of observations is small. This allows a reliable assessment of the dynamics of the clinical condition during follow-up.

4.4.7. Effect size – *Cohen's d and biserial correlation* for interpreting the strength of observed effects.

Effect size complements the results from significance (p-values) by showing the practical significance and strength of the observed effect. Cohen's d measures the standardised difference between two mean values and was applied in comparisons of changes in results from psychometric scales (e.g., psychosis severity by PANSS) between initial and final assessment, as well as between groups with and without PAS use. It is generally accepted that values around 0.2 indicate a small effect, around 0.5 – a medium effect, and ≥ 0.8 – a large effect. The biserial correlation assesses the relationship between a dichotomous and

quantitative variable, for example presence/absence of comorbid disease and results on the functional scale (GAF).

The applied statistical methods provide a reliable basis for interpretation of results and for formulating substantiated conclusions regarding the factors affecting the dynamics of diagnosis in patients with FPE, with statistical and clinical significance.

IV. Results and discussion

For the purposes of the study, we performed an assessment and comparative analysis of the results in the two patient groups according to the following main indicators:

- *Demographic characteristics*: age, sex, education, social and professional status;
- *Clinical characteristics*:

- identification of risk and predisposing factors;
- results from clinical laboratory tests and a combined urine test for PAS;
- assessment of severity and dynamics of symptoms through standardised psychometric scales.

  - *Interrelationships between individual variables*: analysis of correlations between risk factors;
  - *Clinical course and quality of life*: assessment of the dependence between severity of course, number of hospitalisations, duration of use and quality of life indicators;
  - *Diagnostic comparison*: comparative analysis between initial and final diagnoses in both groups according to ICD-10.

1. Demographic characteristics of the sample (patients with PAS and the control group)

– Sex: In the group with PAS use, males predominate (90.2%), while females represent 9.8% of the studied individuals. In contrast, the control group shows a prevalence of females (60.0%), with a relatively lower proportion of males (40.0%). There is a pronounced difference in sex distribution between the two groups, with PAS use being significantly more common among males. This corresponds to data from the literature, according to which male sex is associated with a higher risk of PAS use and the development of comorbid mental disorders. The sex distribution in the PAS group is presented in Figure 1.

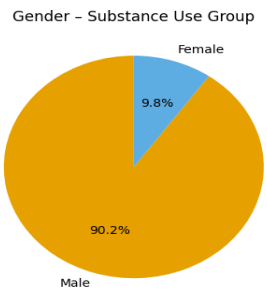


Figure 1

– Age distribution of the studied groups: Distinct differences in age distribution are observed between the two groups. In the group with PAS use, the largest share is of individuals aged 18 to 29 years (48.8%), followed by the age group 30–44 years (43.9%), while participants aged 45–59 years represent a relatively low proportion (7.3%). In the control group, people aged 30–44 years predominate (42.5%), followed by the age group 18–29 years (35.0%), with the smallest share of people aged 45–59 years (22.5%).

The next figure shows the age distribution of participants from the group with PAS use, measured quantitatively – the number of individuals in each age category (see Fig. 2).

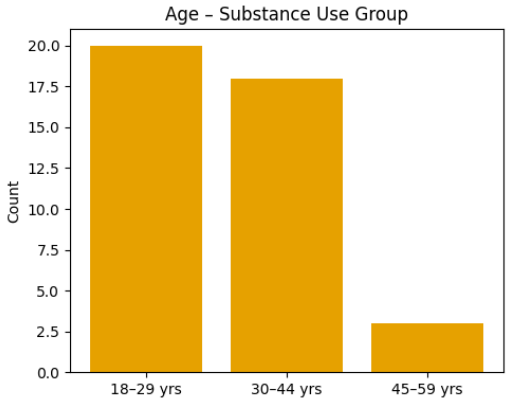


Figure 2

– Education: The distribution in the PAS group is as follows – the largest share consists of patients with secondary education, 22 (53.7%), followed by those with primary education, 14 (34.1%), a small part has elementary – 3 (7.3%) or no education - 2 (4.9%). In the group, there are no individuals with higher education. In this sample, the high number of patients with low levels of education is striking, with young adults predominating in the group. In the control group, people with secondary education also predominate (62.5%), but a significant share of individuals with higher education is observed (32.5%), while those with elementary and primary education are 2.5% each.

– Marital status: Marital status was presented in only two categories (married/unmarried), with the studied individuals given the opportunity to determine which group they fall into. A significantly larger part of PAS users define themselves as unmarried – 35 (85.4%), and only 6 (14.6%) are in a marital relationship. In the control group, the share of unmarried is lower (62.5%), with a significantly higher proportion of married individuals (37.5%).

–Employment: The majority – 28 (68.3%) from the group with PAS use are unemployed, compared to 13 (31.7%) who stated they work; there are no

students. In the control group, the distribution is more even – unemployed are 47.5%, employed 42.5%, and 10% are students.

Comparison of social and demographic characteristics of the two groups:

- There is a pronounced difference in sex distribution between the two groups, with FPE due to PAS use being significantly more common among males.
- The mean age of FPE manifestation in the PAS group is 31.3 years, which is 3 to 4 years earlier onset compared to the control group, 35.4 years.
- In the PAS group, patients with lower levels of education, more unemployed and unmarried individuals dominate, compared to the control group.

2. Clinical characteristics

For the purposes of the study, during the initial and subsequent examinations in both groups, a clinical characterisation of each case was made according to specific indicators from the psychiatric history: Duration of PAS use; Family burden; Comorbid diseases; Number of psychotic episodes; Number of psychiatric hospitalisations; Conducted medication therapy. From the clinical laboratory tests performed at the initial examination and at the end of the study, the following indicators were taken:

- Complete blood count; Biochemical profile; Urine analysis;
- Results from combined urine tests for PAS 1 and 2;

To characterise the severity of the clinical picture in FPE at the beginning and at the last examination, as separate criteria, the results from the applied assessment scales were recorded:

- PANSS with subscales for positive, negative symptoms, general psychopathological symptoms and total score – first and second measurement – PANSS 1, PANSS 2;
- Global Assessment of Functioning Scale – first and second measurement – GAF 1, GAF 2;
- Drug Abuse Screening Test DAST 10;

2.1. Clinical characteristics of the sample with PAS:

Duration of PAS use

The data show that in the study group, patients with long-term PAS use dominate – nearly half (46.3%) have used over 5 years. A significant share is

occupied by people using between 2 and 5 years (36.6%), and relatively small is the group with use up to 2 years (17.1%), which outlines a trend toward prolonged PAS exposure among participants. These results emphasise that the predominant part of the studied patients develop mental symptomatology in the context of years-long use, which is significant both for the therapeutic approach and for prevention (see Table 1 and Fig. 3).

Table 1. Duration of PAS use in the study group

Duration of PAS use	Number	%
Up to 2 yrs.	7	17.1 %
2 – 5 yrs.	15	36.6 %
Over 5 yrs.	19	46.3 %

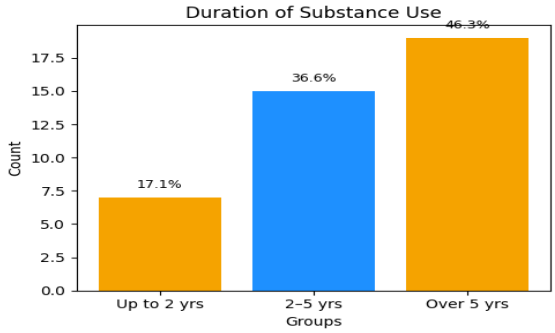


Figure 3

Family burden – In all patients from the study group, there is no data for family burden with mental illnesses.

Urine tests for PAS

First urine test – At the initial examination, the urine test for PAS is not positive in all patients from this group, with the distribution of results presented below (see Table 2).

Table 2. Results of urine test for PAS 1

Urine PAS 1	Number	%
Negative Blue	17	41.5
Positive THC	7	17.1
Methamphetamines (METH)	2	4.9
Amphetamines (AMF)	1	2.4
Combined PAS	14	34.1

From the presented data, the high percentage of patients with negative tests for PAS at the first diagnosis (41.5%) is noticeable, which can be explained by the lack of immediate or recent use. Positive only for THC (cannabis) is 17.1%. This is the most commonly detected substance among positive samples, independently and in combined use. The data correspond to general European trends, in which cannabis is the most widespread illicit substance. A significant part of patients have a positive test for several PAS – combined use (34.1%), with samples most often positive for cannabinoids and methamphetamine, single combinations with cocaine and with opiates. The smallest relative share is occupied by patients who gave a positive test only for methamphetamines and amphetamines, which is a sign of limited independent use.

Second urine test – Results were taken from the last documented visit, respectively discharge summary, regardless that during the studied period other tests were also conducted in part of the patients, mainly during hospitalisation.

The comparison of results between the first and second urine tests is graphically presented in the following Fig. 4.

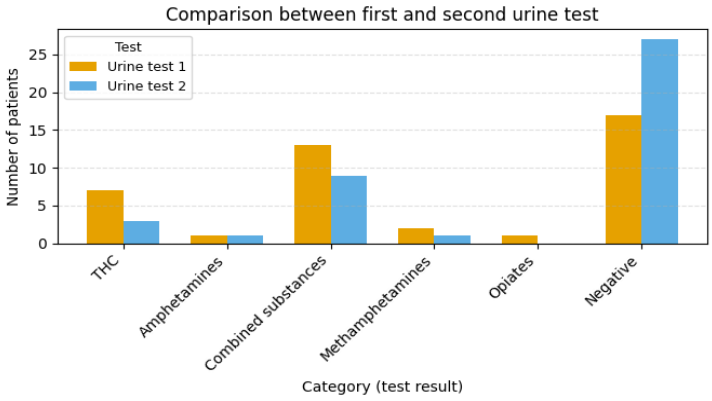


Figure 4

Clinical laboratory tests

From the study group, only three patients (4.9%) showed deviations in laboratory tests – two with elevated liver tests, one of whom was comorbid with alcohol abuse, and one female patient with insignificant changes in blood count.

Number of hospitalisations

Within the studied two-year period, the number of hospitalisations was determined from the history of disease, available information in the hospital information system, as well as from the patient's medical file during consultations conducted in outpatient ambulatory practice. The number of hospitalisations is presented in the following Fig. 5.

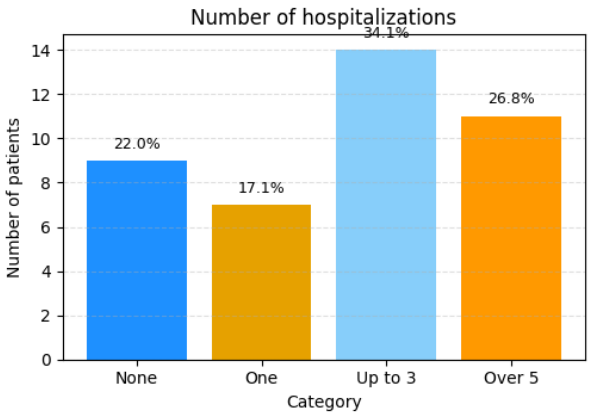


Figure 5

The number of hospitalisations of patients in the study group shows that the largest share had up to three hospitalisations (34.1%). The proportion of those with over five hospitalisations is also significant (26.8%), which testifies to frequent relapses and chronification of psychosis. Patients without hospitalisations who were treated only on an outpatient basis constitute 22.0%, and those with one hospitalisation – 17.1%. These data emphasise that in most patients with PAS use, a more frequent need for hospital treatment is observed, which is an indicator of the severity and persistence of psychopathological symptomatology.

Conducted medication therapy

From the study group, 5 patients (12.2%) state they have not conducted therapy, while for 36 (87.8%), there is data for non-systematic medication therapy conducted with continuing abuse.

Drug Abuse Screening Test DAST-10

For the purposes of the study, the shorter version of DAST with 10 questions was used, which is more convenient in the daily clinical practice. Due to the explainable difficulties in conducting the initial examination, the questionnaire was completed at the patients' last visit. The results are shown in Table 3 and Fig. 6.

Table 3. Interpretation of results from the DAST-10 questionnaire

Result	Interpretation
0 p.	No indications of a problem / no use
1–5 p.	Low to medium risk / occasional use /
6–10 p.	High to very high risk / probable dependence

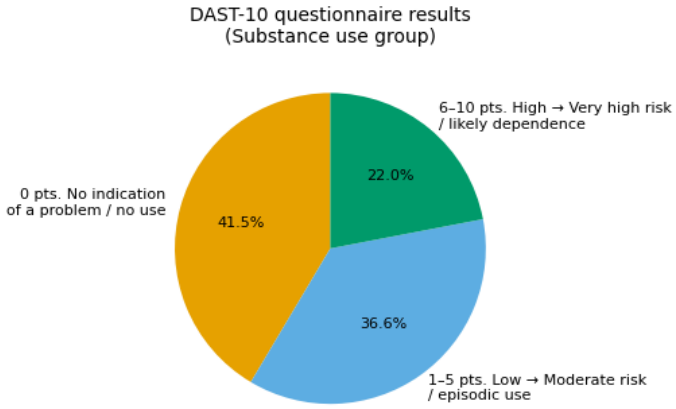


Figure 6

The graphically presented results show that a total of 15 patients (36.6%) fit the "low to medium risk" category, which suggests episodic or experimental use, but with potential for developing problems with the substance. In the high to very high risk group are 9 patients (22.0%), which in this case is an important indicator of probable presence of dependence. The largest number of patients, 17 (41.5%), have no indications for problematic use or a complete absence of PAS use at the end of the research period.

Comorbid diseases

In the present study, comorbid diseases are divided into several categories: absence, somatic disease, comorbid mental illness and separately, comorbidity with alcohol abuse and dependence.

Fig. 7 presents the percentage distribution of comorbid diseases in the PAS group.

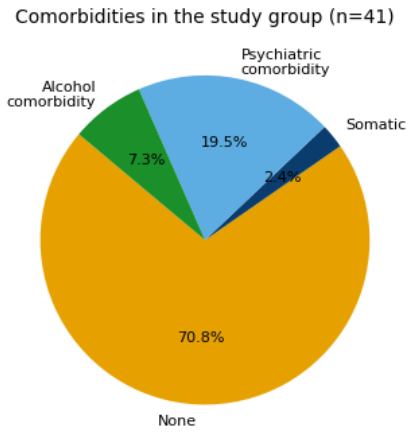


Figure 7

The predominant part of the study group, 29 (70.7%), has no comorbid diseases. Alcohol comorbidity is present in only 3 patients (7.3%), and only one (2.4%) has a somatic disease (very low frequency of physical comorbidity). This relatively small share suggests insufficient data when collecting history. Comorbidity with mental disorders was established in 8 patients (19.5%), with accompanying diagnosis of Obsessive-compulsive disorder (OCD) established in three patients and Personality and behaviour disorder in two of the patients.

Initial and final diagnoses in the study group with PAS (n=41) are distributed percentagewise as follows (see Fig. 8):

• F19 Psychotic disorders related to combined use or use of other psychoactive substances – 65.9%

• F12 Psychotic disorders related to cannabinoid use – 14.6%

• F23 Acute and transient psychotic disorders – 14.6%

• F11 Psychotic disorders related to opioid use – 4.9%

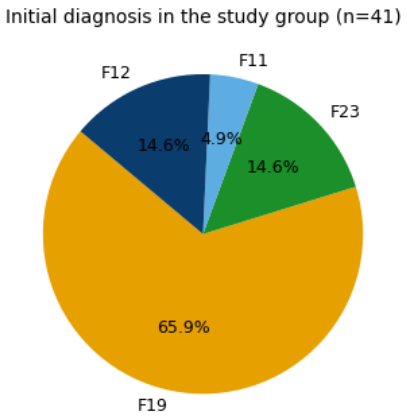


Figure 8

The obtained values show that diagnosis F19 (65.9%) dominates in the sample, which shows that, in most patients it concerns most often the combined use of PAS, a trend characteristic of clinical practice in our country and in international observations.

Psychotic episodes diagnosed with F12 (cannabinoids) and F23 (acute and transient psychotic disorders) have an equal proportion (14.6%), which emphasises the significance of cannabis as a frequently encountered substance in first contacts with psychiatric care and its connection with induced psychotic states.

The final diagnoses in the PAS group show greater diversity, with the observation that again the largest number of patients continue to be diagnosed with Psychotic disorders related to combined use of PAS:

• F19 Psychotic disorders related to combined use or use of other psychoactive substances – 43.9%

• F20.0 Paranoid schizophrenia – 34.1%

• F25 Schizoaffective disorder – 4.9%

• F22 Chronic delusional disorders - 4.9%

• F30 – F39 other affective disorders – 7.3%

• F31 Bipolar affective disorder – 2.4%

• F12 Disorders related to cannabinoid use – 2.4%

As a final diagnosis, psychotic disorders related to cannabinoid use are found in a smaller number of patients compared to the initial ones, probably due to their transition to the combined use group (F19).

There is an apparent pattern that the primary diagnosis was made mainly based on substance use and acute psychotic symptoms, and after a more prolonged observation period, the diagnosis transforms toward chronic psychoses and affective disorders.

This confirms the clinical rule that initial diagnoses in patients with PAS are often temporary and need additional observation and clarification, especially when acute psychotic symptoms are nonspecific and variable (see Fig. 9).

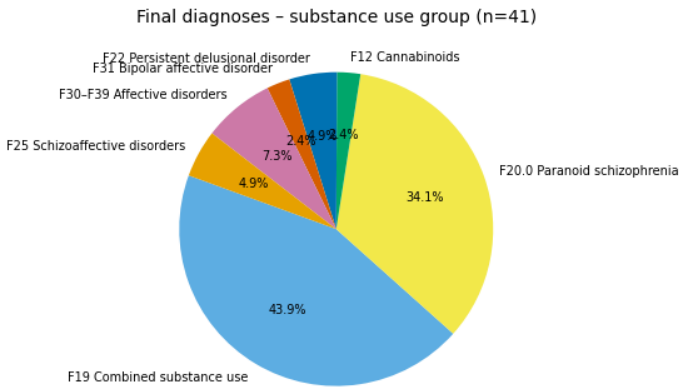


Figure 9

2.2. Clinical characteristics of the control group

Duration of PAS use

In almost all participants in the control group (n = 40) there is no PAS use (which is a requirement for inclusion), with the exception of one patient diagnosed with code F23.1, who is noted to have taken PAS for less than two years and a long clean period before the onset of FPE.

Urine tests for PAS are accordingly negative for all patients in the control group, both the initial and final urine tests.

Family burden

In patients from the control group, family burden with mental illnesses is present in three patients (7.5%).

Drug Abuse Screening Test DAST-10

The result from the questionnaire for all in the group is 0 points - "no indications for use".

Comorbid diseases

Patients from the control group show a higher frequency of comorbid diseases, regardless that in most of them (65%) such diseases are absent. Comorbid mental disorders are 7 patients (17.5%), with patients with OCD again predominating, five cases. With accompanying somatic disease are 5 patients (12.5%), of which one with Hepatitis B and C. Single cases are with comorbid alcohol dependence. Regardless of the small sample, the presented data are clinically significant (see Fig. 10).

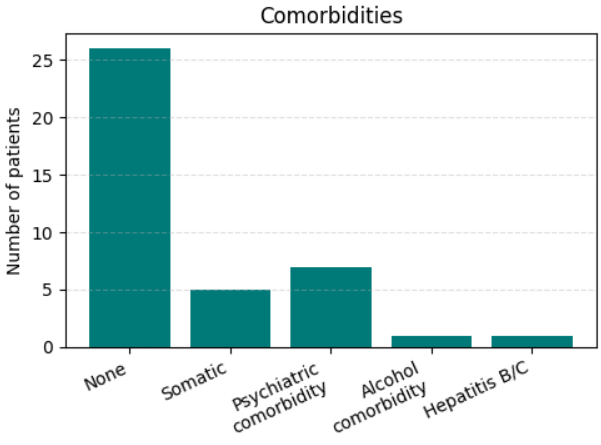


Figure 10

Clinical laboratory tests – in the entire control group, no deviations in laboratory tests were registered.

Within the studied two-year period, the high percentage of non-hospitalised patients is striking – 18 (45.0%), who were treated outpatients, and only one with more than 5 hospitalisations (2.5%), which is also a sign of the lesser severity of psychosis in the control group.

Medication therapy

The majority of patients from the control group declared that they take the prescribed psychotropic medication therapy – 38 (95%), which explains the smaller number of hospitalisations in this group.

The initial diagnoses in the control group are presented in the following table:

Table 4. Initial diagnoses in the control group

Initial diagnosis	Number	%
F25 Schizoaffective disorders	1	2.5
F20.0 Paranoid schizophrenia	1	2.5
F23 Acute and transient psychotic disorders	30	75.0
F22 Chronic delusional disorders	3	7.5
F31 Bipolar affective disorder	4	10.0
F30-F39 Affective disorders	1	2.5

The distribution of initial diagnoses shows predominance of Acute and transient psychotic disorders (F23), which encompass 75.0% of the sample. This suggests that in the predominant part of cases, psychopathological symptoms arise and develop relatively quickly and have a time-limited manifestation. A significantly smaller share is of people diagnosed with Chronic delusional disorders (F22 –7.5%) and BAD (F31–10.0%), with equal cases of diagnoses of Schizoaffective disorders (F25–2.5%), Paranoid schizophrenia (F20.0–2.5%) and other affective disorders (F30-F39–2.5%). These results outline an initial diagnostic profile of the group without PAS, in which the most common clinical manifestation is acute and transient psychosis with schizophrenic symptoms.

Final diagnoses

The acute and transient psychotic disorders dominating in the initial assessment (75.0%) are reduced to single cases (2.5%) in the final diagnosis. At the same time, a significant increase in the diagnosis of Paranoid schizophrenia is observed (F20 – from 2.5% to 37.5%) and Schizoaffective disorders (F25 – from 2.5% to 27.5%). To a lesser extent, an increase in chronic delusional disorders is also recorded (F22 – from 7.5% to 10.0%).

The group of Affective disorders (F31 and F30-39) remains relatively stable, with slight fluctuations. It is important to note that in the control group, there are patients with remission, who are 10.0% of the sample. In these cases, continuous medication therapy is usually present.

The described data demonstrate that the initial acute psychotic episodes in a significant part of cases are later specified as chronic psychoses, which emphasises the importance of the follow-up over time for clarifying nosological affiliation.

The following figure graphically presents the dynamics of diagnoses in the control group.

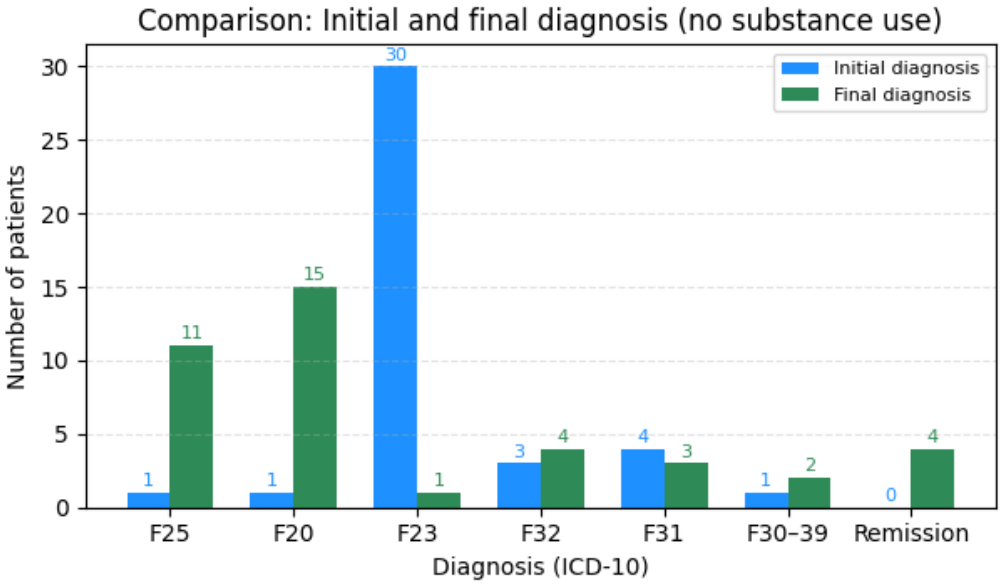


Figure 11

From the presented results regarding the initial and final diagnosis in both groups, we can conclude that the PAS group is characterised by more frequent and more prolonged over time diagnosis of psychotic disorders induced by substance use. In this group, even after a two-year period, a high percentage of

diagnoses with F19.5 (43.9%) is observed. In both groups, the dynamics of diagnoses are similar, with a large part of cases in the control group transforming into chronic schizophrenic and affective psychoses, most often F20.0 (37.5%).

3. Statistical processing and comparative analysis

The statistical processing of data includes comparative analysis and the establishment of interrelationships between individual measurements. Due to the small number of observations in some cells, Fisher's exact test was also applied, suitable for small and rare data and providing an accurate assessment of significance and presence of statistically significant correlation.

3.1. Comparative analysis of family burden

In the PAS group, there is no family burden, and in the control group, it is present in only 3 patients (7.5%). Fisher's exact test showed that the difference between groups is not statistically significant ($p = 0.116$), which means there is no evidence of association between family burden for mental illness and belonging to either of the two groups. From a clinical perspective, however, the lack of family psychiatric burden among individuals with PAS use emphasises the stronger significance of environmental and behavioural factors in this group, compared to hereditary-genetic predispositions, which probably exert greater influence in the control sample.

3.2. Comparative analysis of comorbid diseases

In the PAS group, clinically significant psychiatric comorbidity is recorded – 16.8% with mental disorders (OCD – 3 cases, personality disorder – 2 cases, alcohol dependence – 3 cases), 2.4% with somatic disease. In the control group, clinically significant comorbidity is again recorded – 17.5% with mental disorder (OCD and alcohol dependence), 12.5% with somatic disease. Fisher's exact test shows that there is no statistically significant difference between groups regarding comorbid diseases ($p = 0.311$). The most frequently encountered comorbidity in both groups is of clinical significance – with OCD (total 8 cases – 50%) as well as two cases diagnosed with personality pathology in the PAS group. The results are illustrated in the following figure.

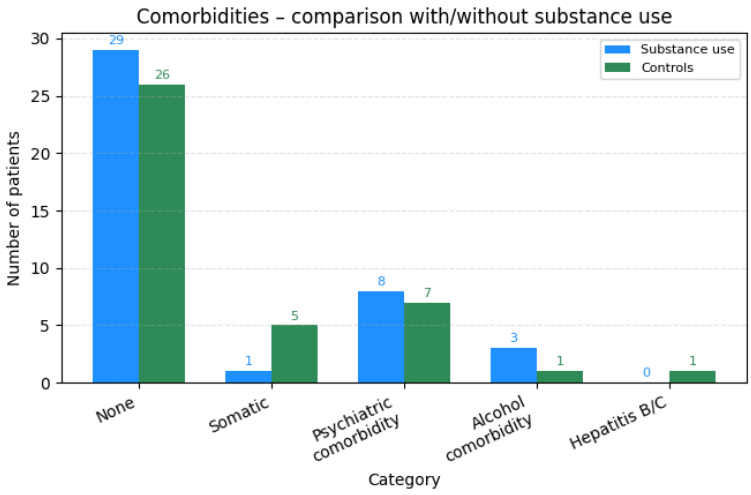


Figure 12

3.3. Comparative analysis of the number of hospitalisations

Results from the Fisher's exact test (p=0.001) show a statistically significant difference between groups regarding the number of hospitalisations. In individuals with PAS use, a larger share has multiple hospitalisations (over 5 – 13.6% and up to 3 – 17.3%), while in the control group cases without hospitalisations (22.2%) or with only one (17.3%) predominate. The share of patients with over 5 hospitalisations is much lower (1.2%). This emphasises the more severe and relapsing clinical course of psychosis with PAS use (see Fig. 13).

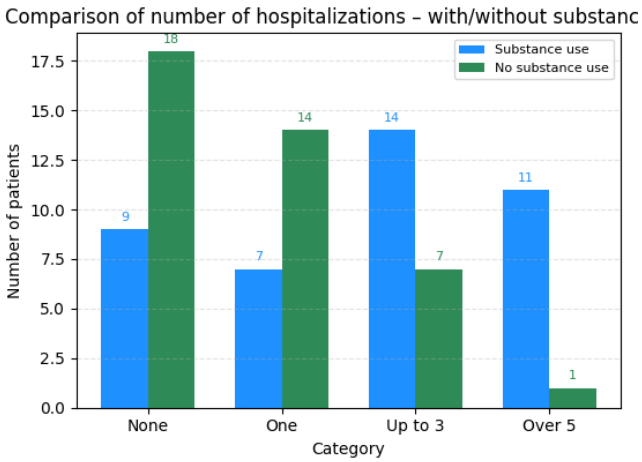


Figure 13

3.4. Correlation between the duration of use and the number of hospitalisations in both groups

The result from Fisher's exact test (p = 0.035) shows that there is a statistically significant association between the duration of PAS use and the number of hospitalisations. In individuals without or with short use (up to 2 years), cases without hospitalisations predominate (9.8% of all). With prolonged use (over 5 years), the share of patients with frequent hospitalisations is highest (over 5 times, 19.5% and up to 3 times, 14.6%). These data outline a clear trend – increasing the duration of use, the probability of more frequent and repeated hospitalisations increases. This supports the hypothesis of the cumulative effect of PAS affecting the severity, frequency of relapses and chronification of psychotic disorders (see Fig. 14).

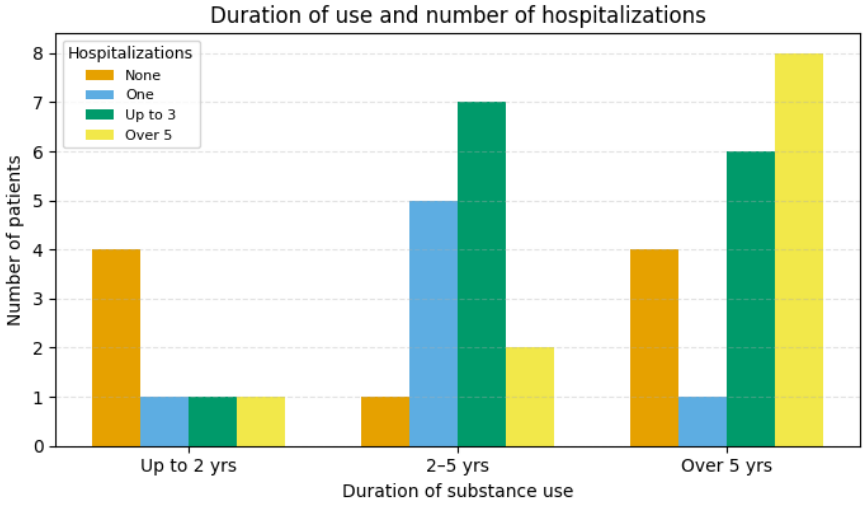


Figure 14

3.5. Correlation between mean age at FPE and duration of PAS use

In analysing the correlation between age and duration of PAS use, it is established that the majority of individuals aged 18–29 years report use up to 5 years (7.3% up to 2 years and 26.8% for 2–5 years). In the age group 29–44 years, the share of users over 5 years is larger (24.4%). In the group 45–59 years, all have with duration of over 5 years (7.3% of the total number).

The Fisher's exact test for correlation between age and the duration of use demonstrates a lack of statistically significant association at the standard significance level ($p < 0.05$). However, we can see a tendency in which with increasing age, the share of individuals with a longer period of use increases. The onset of psychosis differs in both age groups, with the mean age in the PAS sample being 31.3 years, and in the control group, 35.4 years. Our data correspond to the results from other studies showing that the age of psychosis onset in cannabis users is, on average, 2.7 years earlier compared to non-users, and in patients with combined substance use, psychosis onset occurs on average

2.0 years earlier [Murrie et al., 2020]. The onset of PAS use during adolescence, when it usually occurs, is associated with a greater risk because the developing brain is particularly vulnerable to the harmful effects of substances. Meta-analyses describe a dose-dependent correlation between the probability of psychosis and cannabis use among adolescents, with additional risk factors being family history of psychosis as well as combined use of PAS substances [Matheson et al., 2022].

3.6. Comparison of results from urine tests for PAS

Fig. 15 shows a graphical comparison of the results from the two urine tests.

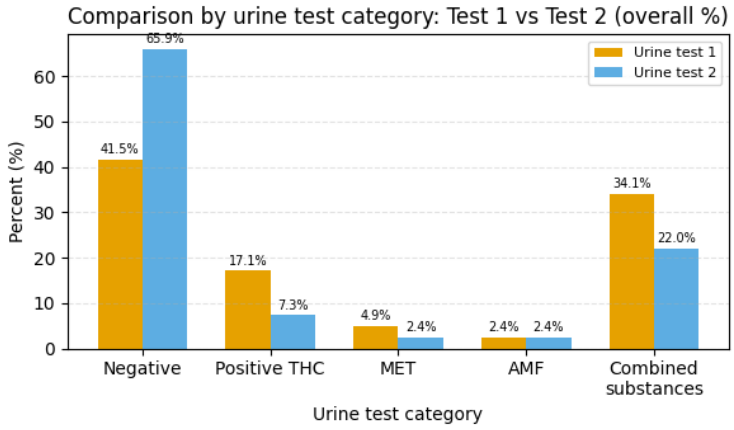


Figure 15

The analysis of results shows the following: There is a significant increase in the share of negative samples in the second examination (n=27). Most patients with a negative first test remain negative in the second. The proportion of positive samples with combined PAS (n=9) and isolated cases for methamphetamines and amphetamines has decreased. As a general trend, a decrease in positive results in the second test can be determined, which can be explained by the treatment being conducted or control over use.

3.7. Comparison of results from the urine tests and final diagnosis in the study group with PAS

Results from Fisher's exact test ($p = 0.316$) do not show a statistically significant correlation between the results from the urine test for PAS 1 and PAS2 and the final psychiatric diagnosis. The established changes in diagnoses and test results are presented in Tables 5 and 6.

Table 5. Interdependence of urine PAS 1 and final diagnosis (Fisher's exact test p = 0.316)

Urinary PAS 2	F25 (N)	F25 (%)	F19 (N)	F19 (%)	F12 (N)	F12 (%)	F20 (N)	F20 (%)	F22 (N)	F22 (%)	F31 (N)	F31 (%)	F30 –39 (N)	F30-39 (%)	Total (N)	Total (%)
Negative	2	4.9 %	9	22.0 %	1	2.4 %	10	24.4 %	2	4.9 %	0	0.0 %	3	7.3 %	27	65.9%
Positive THC	0	0.0 %	0	0.0%	0	0.0 %	2	4.9%	0	0.0 %	1	2.4 %	0	0.0 %	3	7.3%
METH	0	0.0 %	1	2.4%	0	0.0 %	0	0.0%	0	0.0 %	0	0.0 %	0	0.0 %	1	2.4%
AMF	0	0.0 %	0	0.0%	0	0.0 %	1	2.4%	0	0.0 %	0	0.0 %	0	0.0 %	1	2.4%
Combined PAS	0	0.0 %	8	19.5 %	0	0.0 %	1	2.4%	0	0.0 %	0	0.0 %	0	0.0 %	9	22.0%
Total	2	4.9 %	18	43.9 %	1	2.4 %	14	34.1 %	2	4.9 %	1	2.4 %	3	7.3 %	41	100.0%

Table 6. Interdependence of urine PAS2 and final diagnosis (Fisher's exact test p = 0.175)

Urinary PAS 2	F25 (N)	F25 (%)	F19 (N)	F19 (%)	F12 (N)	F12 (%)	F20 (N)	F20 (%)	F22 (N)	F22 (%)	F31 (N)	F31 (%)	F30-39 (N)	F30-39 (%)	Total (N)	Total (%)
Negative	2	4.9%	9	22.0%	1	2.4%	10	24.4%	2	4.9%	0	0.0%	3	7.3%	27	65.9%
Positive THC	0	0.0%	0	0.0%	0	0.0%	2	4.9%	0	0.0%	1	2.4%	0	0.0%	3	7.3%
METH	0	0.0%	1	2.4%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	2.4%
AMF	0	0.0%	0	0.0%	0	0.0%	1	2.4%	0	0.0%	0	0.0%	0	0.0%	1	2.4%
Combined PAS	0	0.0%	8	19.5%	0	0.0%	1	2.4%	0	0.0%	0	0.0%	0	0.0%	9	22.0%
Total	2	4.9%	18	43.9%	1	2.4%	14	34.1%	2	4.9%	1	2.4%	3	7.3%	41	100.0%

The analysis of results shows that diagnoses F19 and F20.0 dominate in both tests, which corresponds to the hypotheses that PAS-induced psychotic disorders are directly dependent on intake, as well as that when establishing a final diagnosis of psychosis (e.g., Paranoid schizophrenia (F20.0)), current PAS use is not infrequently recorded as accompanying /comorbidity/, but not determining for diagnosis.

The lack of statistical significance ($p > 0.05$) in both analyses is most likely due to the limited sample size and distribution of cases in small subgroups. Similar observations have been reported in the literature. Murrie et al. (2020), point out that the correlation between cannabis use and the first psychotic episode is stronger in epidemiological studies, but in clinical cohorts often does not reach statistical significance due to heterogeneity and sample size. From a

clinical perspective, the results suggest that urine tests have more confirmatory than prognostic value, and for assessing diagnosis dynamics, larger samples over a longer time period are needed.

3.8. Comparison of results from DAST 10 questionnaire and final diagnosis

The following table presents the distribution of final diagnosis in the study group according to PAS use, according to results from the DAST 10 questionnaire – absence of use, episodic or continuing. The largest share consists of individuals with F19 (mental and behavioural disorders due to PAS use) – a total of 43.9% - 5 with absence of use, 5 with episodic and 8 with continuing use (19.5%). The diagnosis F20 (schizophrenia) is represented in 34.1% of the individuals, most often with absence or episodic use. The other diagnoses (F25, F12, F22, F31 and F30–39) have lower frequency. Statistical analysis with Fisher's exact test shows no significant dependence between the type of final diagnosis and pattern of PAS use ($p = 0.196$), (see Table 7).

Table 7. Correlation between final diagnosis and PAS use (Fisher's exact test $p = 0.196$)

Urinary PAS 2	F25 (N)	F25 (%)	F19 (N)	F19 (%)	F12 (N)	F12 (%)	F20 (N)	F20 (%)	F22 (N)	F22 (%)	F31 (N)	F31 (%)	F30–39 (N)	F30-39 (%)	Total (N)	Total (%)
Negative	2	4.9%	9	22.0%	1	2.4%	10	24.4%	2	4.9%	0	0.0%	3	7.3%	27	65.9%
Positive THC	0	0.0%	0	0.0%	0	0.0%	2	4.9%	0	0.0%	1	2.4%	0	0.0%	3	7.3%
METH	0	0.0%	1	2.4%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	2.4%
AMF	0	0.0%	0	0.0%	0	0.0%	1	2.4%	0	0.0%	0	0.0%	0	0.0%	1	2.4%
Combined PAS	0	0.0%	8	19.5%	0	0.0%	1	2.4%	0	0.0%	0	0.0%	0	0.0%	9	22.0%
Total	2	4.9%	18	43.9%	1	2.4%	14	34.1%	2	4.9%	1	2.4%	3	7.3%	41	100.0%

Despite the lack of statistical significance, the following trends emerge:

- The largest share is the group of F19 (mental and behavioural disorders due to PAS use) – 43.9%, most often associated with continuing use (19.5%).
- Schizophrenia (F20.0) is also highly represented (34.1%), more often with absence or episodic use.
- Other diagnoses (F25, F12, F22, F31, and F 30-39) have a smaller proportion but show diversity in distribution – for example, F25 occurs only with absence of use, while F31 is associated exclusively with episodic use.

These results suggest that PAS use may influence manifestations of psychotic disorders, but is not a leading factor for final diagnostic determination in this sample, due to the small size of groups and heterogeneity of cases.

The results from the questionnaire in the control group show the distribution of final diagnosis as follows: Participants without PAS use predominate (97.5%), with the largest share being diagnosed with F20.0 and F25 (Schizoaffective disorder) – 27.5%. Episodic use was registered in only 1 case (2.5%) with a diagnosis from section F30–39. The conducted Fisher's exact test shows that no statistically significant dependence was established between the type of final diagnosis and PAS use according to the survey ($p = 0.075$).

In the presented literature references, it is emphasised that in control groups in psychiatric studies with a similar design, minimal and episodic PAS use is often established, which provides a clearer distinction from groups with active and risky use or dependence [Murrie et al., 2020; Murrie, Rognli, 2020].

3.9. Dynamics of diagnoses in both groups (PAS and controls)

The χ^2 (chi-square) statistical test is used to check the dependence between two categorical variables — in this case, initial and final diagnosis in patients. This test compares observed frequencies with those expected under the hypothesis of independence. Due to the small number of observations in some cells, Fisher's exact test was also applied, which is suitable for small and rare data and provides an accurate assessment of significance. The use of these tests allows us to establish whether there is a statistically significant correlation between initial and final diagnosis.

Table 9 presents a *comparison of initial and final diagnosis* (in the PAS group) in quantitative measurement and dynamics (change in type of diagnoses), (see Table 9 and Fig. 16).

Table 9. Comparison between the initial and final diagnosis (PAS group)

Initial/ Final diagnosis	F25 (N)	F25 (%)	F19 (N)	F19 (%)	F12 (N)	F12 (%)	F20 (N)	F20 (%)	F22 (N)	F22 (%)	F31 (N)	F31 (%)	F30-39 (N)	F30-39 (%)	Total (N)	Total (%)
F19	0	0.0 %	15	36.6 %	1	2.4 %	7	17.1 %	2	4.9 %	0	0.0 %	2	4.9 %	27	65.9%
F12	2	4.9 %	1	2.4%	0	0.0 %	1	2.4%	0	0.0 %	1	2.4 %	1	2.4 %	6	14.6%
F11	0	0.0 %	1	2.4%	0	0.0 %	1	2.4%	0	0.0 %	0	0.0 %	0	0.0 %	2	4.9%
F23	0	0.0 %	1	2.4%	0	0.0 %	5	12.2 %	0	0.0 %	0	0.0 %	0	0.0 %	6	14.6%
Total	2	4.9 %	18	43.9 %	1	2.4 %	14	34.1 %	2	4.9 %	1	2.4 %	3	7.3 %	41	100.0 %

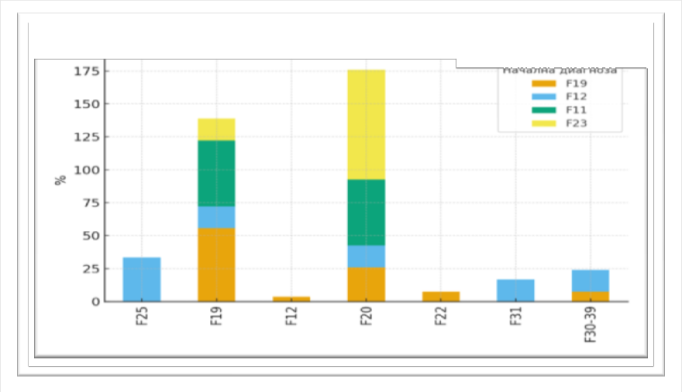


Figure 16

Diagnostic instability in the PAS group:

• Initial diagnosis F19 Mental and behavioural disorders due to combined PAS use (65.9%) remains in the final as 36.6% and transitions to F20 with 17.1%;

• Initial diagnosis F12 – Psychosis with cannabinoid use (14.6%) has diverse transitions to F20, F25, and F31;

• Initial diagnosis F23 (14.6%) shows a tendency for transition mainly to F20 (12.2%);

• Most frequent final diagnoses are F19 (43.9%) and F20 (34.1%).

To compare initial and final diagnosis in the control group, due to the relatively small number of observations, Fisher's exact test was also used (p=0.089). The test does not show statistical significance (see Fig. 17 and Table 10).

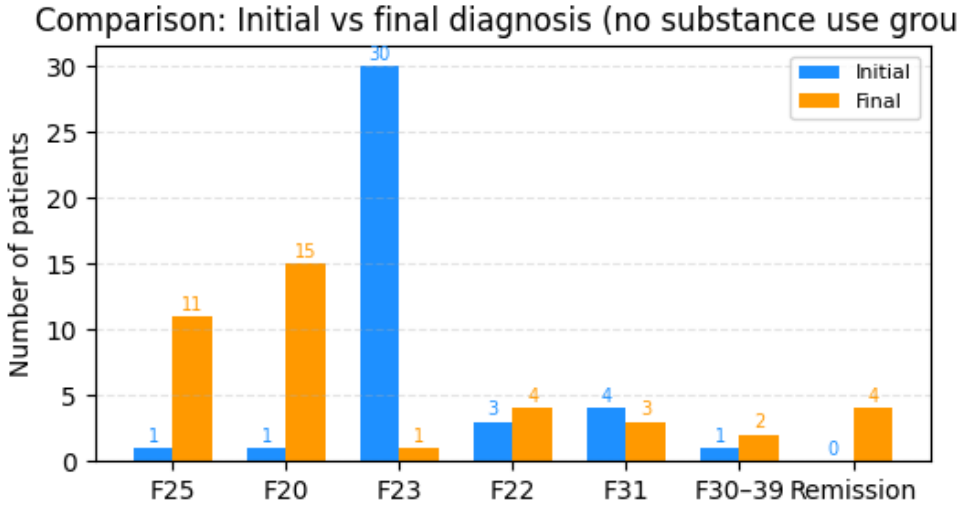


Figure 17

Table 10. Transition from initial to final diagnosis in the control group

Initial diagnosis	Initial frequency (%)	Final diagnosis	Final frequency (%)	Trend
F23 Acute and transient psychotic disorders	75.0%	F20 Schizophrenia / F25 Schizoaffective disorder	37.5% / 27.5%	Transition to chronic psychosis
F20.0 Paranoid schizophrenia	2.5%	F20 Paranoid schizophrenia	37.5%	Stabilisation and confirmation
F25 Schizoaffective disorders	2.5%	F25 Schizoaffective disorders	27.5%	Significant increase
F22 Chronic delusional disorders	7.5%	F22 Chronic delusional disorders	10.0%	Stabilisation
F31 Bipolar affective disorder	10.0%	F31 Bipolar affective disorder	7.5%	Relatively stable
F30–39 Other affective disorders	2.5%	F30–39 Affective disorders	5.0%	Slight increase
—	—	No symptoms/remission	10.0%	Newly formed group

Diagnostic instability in the control group:

• The largest share is patients with initial diagnoses Acute and transient psychotic disorders (F23) – 75.0% (most often with polymorphic picture), F31 – 10.0%, F22 – 7.5%, F25 and F20.0 – 2.5% each, and F30-F39 – 2.5%.

• In the distribution of final diagnoses, the share of F23 (2.5%) substantially decreases – clarification of diagnosis.

• In the final diagnoses, schizophrenia and schizoaffective disorders predominate (F20.0) – 37.5%, (F25) – 27.5%.

• There is a group of patients with absence of symptoms/remission – 10.0%, which conveys a favourable prognosis.

Despite the lack of data for statistically significant change – Fisher's exact test ($p=0.089$), the results possess clinical significance regarding data showing that in patients without PAS, initially diagnosed acute psychotic episodes in a significant part of cases develop into disorders from the schizophrenia spectrum (F20–F25). This corresponds to the described results in other clinical studies where acute psychotic disorders are often a "transitional" diagnosis that is subsequently clarified as chronic psychotic illness. The presence of 10% remission in the control sample points that, despite the small number of patients, favourable development within the studied period is possible, which reflects the heterogeneity of the non-PAS-using group.

4. Correlation analysis examines the statistical relationship between variables

4.1. Correlation analysis between PANSS subscales (+/–/G), total PANSS score and GAF in the PAS group

Correlation analysis is used to investigate interrelationships between continuous variables. In the present study, it aims to investigate the degree and direction of correlations between main demographic, clinical and behavioural variables in patients with a first psychotic episode and PAS use. The goal is to establish whether statistically significant dependencies exist that support the concept of PAS influence on the course, chronification and nosology of first-episode psychotic disorders.

Pearson's correlation coefficient (Pearson's r) was applied, which measures the strength and direction of linear dependence between pairs of variables. Statistical significance of correlations was assessed through p-values, with values below 0.05 considered significant.

Comparison between first and second measurement period (PANSS1–GAF1 subscales and PANSS2–GAF2) in PAS group (see Tables 11-12). Table 11 presents results from the correlation matrix at the first measurement.

Table 11. Correlation matrix between PANSS1 and GAF1 subscales

Variables	PANSS1G	PANSS1+	PANSS1−	PANSS1 total score	GAF1
PANSS1G	—	r = 0.316*, p = 0.044	r = 0.349*, p = 0.025	r = 0.824***, p < .001	r = -0.326*, p = 0.037
PANSS1+	r = 0.316*, p = 0.044	—	r = -0.059, p = 0.714	r = 0.561***, p < .001	r = -0.637***, p < .001
PANSS1−	r = 0.349*, p = 0.025	r = -0.059, p = 0.714	—	r = 0.653***, p < .001	r = -0.185, p = 0.247
PANSS1 total score	r = 0.824***, p < .001	r = 0.561***, p < .001	r = 0.653***, p < .001	—	r = -0.552***, p < .001
GAF1	r = -0.326*, p = 0.037	r = -0.637***, p < .001	r = -0.185, p = 0.247	r = -0.552***, p < .001	—

Note: *p < .05, **p < .01, ***p < .001

In the initially conducted analysis (PANSS1), the general psychopathological assessment scale PANSS1G shows a positive correlation with subscales for positive symptoms (PANSS1+, r = 0.316, p = 0.044) and negative symptoms (PANSS1−, r = 0.349, p = 0.025), as well as with the total score PANSS1 total (r = 0.824, p < 0.001). Moreover, PANSS1+ and PANSS1− demonstrate positive correlation with PANSS1total (r = 0.561 and r = 0.653, respectively, p < 0.001).

Results from GAF1 show negative dependence with PANSS1G ($r = -0.326$, $p = 0.037$), PANSS1+ ($r = -0.637$, $p < 0.001$) and PANSS1 total ($r = -0.552$, $p < 0.001$), which reflects that more severe symptomatology and higher values on the general psychopathology scale are associated with lower levels of functioning.

Interpretation of results:

–*Dependencies between individual subscales in PANSS* – High positive correlations between individual subscales and total PANSS score show that the severity of positive and negative symptoms contributes significantly to overall psychopathological severity.

– *PANSS and overall level of functioning:* Negative correlations between PANSS and GAF show inverse dependence – more pronounced severity of psychopathological symptomatology is associated with a lower level of functioning in all spheres. Most emphasised is the correlation between positive symptoms and functional decline ($r = -0.637$), which can be explained by the influence of hallucinatory-paranoid symptoms and disorganised behaviour.

From a clinical perspective, we can conclude that the established dependencies emphasise that symptom severity in patients with FPE and PAS use is associated with more limited social functioning and more difficult recovery. This corresponds to data from international studies [Addington et al., 2006; Murrie et al., 2020; Murrie B, Rognli EB, 2020], which indicate that concomitant PAS use in the first psychotic episode leads to a more severe course and slower functional improvement. Table 12 presents results from the correlation matrix at the second measurement (Note: * $p < .05$, ** $p < .01$, *** $p < .001$).

Table 12. Correlation matrix between PANSS2 and GAF2 subscales

Variables	PANSS2G	PANSS2+	PANSS2−	PANSS2 total	GAF2
PANSS2G	—	r = 0.504***, p < .001	r = 0.141, p = 0.380	r = 0.887***, p < .001	r = -0.574***, p < .001
PANSS2+	r = 0.504***, p < .001	—	r = -0.203, p = 0.204	r = 0.725***, p < .001	r = -0.650***, p < .001
PANSS2−	r = 0.141, p = 0.380	r = -0.203, p = 0.204	—	r = 0.324*, p = 0.039	r = -0.012, p = 0.939
PANSS2 total	r = 0.887***, p < .001	r = 0.725***, p < .001	r = 0.324*, p = 0.039	—	r = -0.655***, p < .001
GAF2	r = -0.574***, p < .001	r = -0.650***, p < .001	r = -0.012, p = 0.939	r = -0.655***, p < .001	—

Results from correlation analysis for the second assessment period (PANSS2, GAF2) show stable and statistically significant correlation between the main PANSS subscales and GAF. As in the first measurement, PANSS2G is positively associated with the positive symptoms subscale PANSS2+ ($r = 0.504$, $p < 0.001$) and with the total score PANSS2 total ($r = 0.887$, $p < 0.001$). Also, PANSS2+ correlates positively with PANSS2 total ($r = 0.725$, $p < 0.001$). The correlation between negative symptoms PANSS2- and total score is also significant, although weaker ($r = 0.324$, $p = 0.039$).

The GAF2 scale showed a strong negative correlation with PANSS2G ($r = -0.574$, $p < 0.001$), PANSS2+ ($r = -0.650$, $p < 0.001$) and PANSS2total ($r = -0.655$, $p < 0.001$), which confirms that higher symptom severity is associated with lower functional level. The correlation between PANSS2− and GAF2 is insignificant *($r = -0.012$, $p = 0.939$)*, which shows that negative symptoms have weaker dynamics and correspondingly less influence on functional recovery at this stage.

Clinical significance of established dependencies in the PAS group:

The obtained results point out the significance of positive symptomatology reduction as the main predictor of functional recovery after treatment. Negative symptomatology, for its part, is characterised by relative resistance, weaker therapeutic sensitivity and a tendency toward prolonged persistence. This corresponds to data from several studies, which indicate that positive symptoms exhibit greater dynamics and a faster therapeutic response. At the same time, negative and cognitive deficits remain stable over time and have a lasting influence on the global functioning and social adaptation of patients [Addington et al., 2006]. Symptoms related to the production of psychotic symptoms are more important for achieving remission in the immediate period after a psychotic episode. Negative symptoms are more important for long-term remission. In summary, these results emphasise the stable and significant correlation between the intensity of psychosis symptoms and the level of functioning in patients with PAS during both study periods.

4.2. Correlation analysis between PANSS subscales (+/–/G), total PANSS score and GAF in the control group

In control participants, correlation analysis revealed significant correlations between different PANSS subscales and their total score, as well as with the GAF scale.

The following table presents the correlation matrix in the control group at the first measurement (see Table 13).

Table 13. Correlation matrix between PANSS1 and GAF1 subscales in the control group

Variables	PANSS1 G	PANSS1 +	PANSS1 −	PANSS1 total score	GAF1
PANSS1 G	—	r = 0.367*, p = 0.020	r = 0.261, p = 0.103	r = 0.909***, p < .001	—
PANSS1 +	r = 0.367*, p = 0.020	—	r = -0.240, p = 0.135	r = 0.589***, p < .001	—
PANSS1 −	r = 0.261, p = 0.103	r = -0.240, p = 0.135	—	r = 0.402*, p = 0.010	—
PANSS1 total	r = 0.909***, p < .001	r = 0.589***, p < .001	r = 0.402*, p = 0.010	—	—
GAF1	—	—	—	—	—

*Note: Pearson correlation coefficients ®.*df = 38; *p < .05; **p < .01; **p < .001. Explanation: df – degrees of freedom (n–2); p-value – level of statistical significance showing the probability that the correlation is random.*

At the first measurement, PANSS1 G shows a significant positive correlation with positive symptoms (PANSS1+, r = 0.367, p = 0.020) and with the total score PANSS1 total (r = 0.909, p < 0.001). Negative symptoms (PANSS1-) are also positively associated with PANSS1 total (r = 0.402, p = 0.010). Global assessment of functioning GAF1 shows a strong negative correlation with PANSS 1 G (r = -0.625, p < 0.001), PANSS1+ (r = -0.538, p < 0.001) and PANSS1total (r = -0.683, p < 0.001).

At the second measurement (PANSS2), similar trends are observed: PANSS2G correlates positively with PANSS2+ (r = 0.442, p = 0.004) and PANSS2 total (r = 0.532, p < 0.001). Positive symptoms PANSS2+ show a strong correlation with the total score PANSS2 total (r = 0.743, p < 0.001), and negative symptoms PANSS2- also correlate significantly with PANSS2 total (r = 0.651, p < 0.001). GAF2 is strongly negatively associated with PANSS2G (r = -0.420, p = 0.007), PANSS2+ (r = -0.748, p < 0.001), PANSS2- (r = -0.676, p < 0.001) and PANSS2 total (r = -0.742, p < 0.001), which reflects that symptom severity is associated with lowering of functional status (see Table 14).

Table 14. Correlation matrix between PANSS2 and GAF2 subscales in the control group

Variables	PANSS2G	PANSS2+	PANSS2−	PANSS2 total score	GAF2
PANSS2G	—	r = 0.504*** p < .001	r = 0.141 p = 0.380	r = 0.887*** p < .001	r = -0.574*** p < .001
PANSS2+	r = 0.504*** p < .001	—	r = -0.203 p = 0.204	r = 0.725*** p < .001	r = -0.650*** p < .001
PANSS2−	r = 0.141 p = 0.380	r = -0.203 p = 0.204	—	r = 0.324* p = 0.039	r = -0.012 p = 0.939
PANSS2 total	r = 0.887*** p < .001	r = 0.725*** p < .001	r = 0.324* p = 0.039	—	r = -0.655*** p < .001
GAF2	r = -0.574*** p < .001	r = -0.650*** p < .001	r = -0.012 p = 0.939	r = -0.655*** p < .001	—

*Note: Pearson correlation coefficients ®.*df = 38; *p < .05; **p < .01; **p < .001. Explanation: df – degrees of freedom (n–2); p-value – level of statistical significance showing the probability that the correlation is random;*

In summary, the correlations in the control group confirm that more severe symptomatology is associated with a poorer level of global functioning, which also corresponds to observations in patients with PAS.

4.3. Comparison between the first and second measurement period – (PANSS1–GAF1) and (PANSS2–GAF2) in the control group

In both compared measurement periods, a similar correlation structure is observed – positive correlations between PANSS subscales and negative correlations with GAF. This reflects the stability of psychometric dependencies in the control group. The high statistical significance of general psychopathology (PANSS1G) with positive symptomatology ($r = 0.367$, $p = 0.020$) and strong correlation with total score ($r = 0.909$, $p < .001$) is noticeable.

At the second and final assessment by PANSS2, the correlations between subscales remain significant, with a slight decrease in the strength of dependencies observed – for example, PANSS2G ↔ PANSS2+ ($r = 0.442$, $p = 0.004$) and PANSS2G ↔ PANSS2 total ($r = 0.532$, $p < .001$). The dynamics suggest that after therapeutic intervention, the psychopathological profile becomes more homogeneous and less dependent between individual measurements, which reflects a reduction of acute symptoms and stabilisation of the clinical condition. The difference in the control group is more significant compared to the PAS group.

Results by GAF maintain stable negative correlations with PANSS indicators in both periods, which confirms the inverse dependence between the symptom severity and level of functioning.

• PANSS1G ↔ GAF1: $r = -0.625$, $p < .001$

• PANSS2G ↔ GAF2: $r = -0.420$, $p = 0.007$

During the second period, the negative dependence weakens, which shows improvement in functional recovery and reduction of general psychopathology. Similar trend is observed with positive symptomatology ($r = -0.538 \rightarrow r = -0.748$), where the correlation with GAF2 is even stronger, which suggests that reduction of positive symptoms has a direct effect on functional progress.

Regarding the negative subscale in the first period, PANSS1 shows a weak correlation with the total score ($r = 0.402$, $p = 0.010$) and an insignificant correlation with GAF1 ($r = -0.094$, $p = 0.563$). In the second period, dependencies strengthen moderately (PANSS2− ↔ PANSS2 total, $r = 0.651$, $p < .001$; PANSS2− ↔ GAF2, $r = -0.676$, $p < .001$). This again confirms that in control participants, negative symptoms remain relatively more resistant and

their influence on overall functioning intensifies in the second period – probably due to the present reduction of positive symptoms.

Clinical significance of established dependencies in the control group:

A general decrease in symptom intensity over time is established as a result of conducting medication therapy. There is a stable negative correlation between PANSS and GAF, and a more clearly expressed inverse dependence between the positive symptoms and GAF2 compared to the PAS group. These findings also correspond to our previous conclusions.

4.4. Cross-comparative correlation analysis (PAS group and control)

The correlation analysis of results from psychometric tests in both groups shows that strong positive interrelationships exist between individual PANSS subscales, both in the first (PANSS1) and second period (PANSS2). At the beginning of the disease, at the first measurement, a moderate to strong correlation is established between general psychopathology (PANSS1G) and positive and negative symptomatology (PANSS1+, PANSS1-). Total score – PANSS1 total, correlates highly and significantly with all subscales ($p < .001$). In the second period (PANSS2), the structure of correlations is preserved. In both groups, high internal consistency of PANSS is established (correlations between subscales $r > 0.5$).

Assessment of change in GAF in both groups, at both measurements, shows that both groups start with low GAF1 (around 25–30), reflecting significantly impaired functioning. Patients with PAS have slightly higher mean functioning values, but the difference is not clinically significant. Data suggest that the influence of PAS on functioning and the quality of life is not clearly manifested in the initial stage, but probably becomes prominent later (GAF2). In the PAS group, the dependence between PANSS and GAF is stronger and more stable, which shows a more pronounced influence of psychopathological symptoms on functional state.

Summary:

• In the control group, correlations are more moderate, which reflects better clinical stabilisation after treatment.

• In both groups, positive symptomatology remains the main predictor of general psychopathology and functioning, while negative symptomatology shows weaker and less significant correlation.

• The obtained results correspond to literature data emphasising the leading role of positive symptoms for prognosis and remission, as well as the resistance of negative and cognitive deficits.

5. Analysis of PANSS results

5.1. Initial and outcome values by PANSS in the PAS group (n = 41)

To assess differences between the first and second measurement period in the patient group with PAS, paired samples t-tests (parametric and non-parametric Wilcoxon signed-rank test) were used.

The paired t-test was applied for scales PANSS G and PANSS + because data for these indicators are approximately normally distributed and meet the prerequisites for a parametric test. The test compares mean values of the same participants in two consecutive periods, assessing significant changes.

For the negative scale PANSS–, in which data distribution does not satisfy prerequisites for normality, the Wilcoxon signed-rank test was used — a non-parametric test that is suitable for deviation from normality or with smaller samples.

In addition to statistical significance, effect size was also calculated (Cohen's d for t-tests and biserial correlation for the Wilcoxon test) to assess the practical significance of observed differences. Comparative analysis is presented in Table 15.

Table 15. Results from the comparative analysis between the initial/outcome PANSS values

Indicator	Test type	N	(Mean ± SD)	t / W, p-value, 95% CI	Effect size (Cohen's d / r)	Interpretation
PANSSG (general psychopathological symptoms)	Paired t-test	41	53.9 ± 10.18 → 45.2 ± 10.89	t = 5.42, p = 0.001, [0.485–1.201]	d = 0.847	Big impact, statistically significant improvement
PANSS+ (positive symptoms)	Paired t-test	41	28.3 ± 7.60 → 22.1 ± 8.98	t = 4.63, p = 0.001, [0.375–1.065]	d = 0.724	Moderate to large effect, partial clinical improvement
PANSS– (negative symptoms)	Wilcoxon signed-rank	41	16.1 ± 9.32 → 13.6 ± 6.13	W = 366, p = 0.021	r = 0.474	Moderate effect, statistically significant, but moderate improvement
PANSS (total)	Paired t-test	41	98.0 ± 19.24 → 80.7 ± 18.02	t = 5.19, p = 0.001, [0.453–1.161]	d = 0.811	Large effect, statistically significant improvement

In patients who used psychoactive substances, a statistically significant decrease in the scores on all three PANSS scales is established between the first and second period. Mean value of general psychopathology decreases from 53.9 (SD = 10.18) during first period to 45.2 (SD = 10.89) during second period, with the difference being significant according to paired samples t-test (t (40) = 5.42, p = 0.001) with medium effect size (Cohen's d = 0.847, 95% CI [0.485; 1.201]). For the positive scale, a decrease from 28.3 (SD = 7.60) during the first period, and up to 22.1 (SD = 8.98) during the second period is recorded. This is also statistically significant (t (40) = 4.63, p = 0.001) with effect size Cohen's d = 0.724 and 95% CI [0.375; 1.065]. For the negative scale, mean value decreases from 16.1 (SD = 9.32) during the first period to 13.6 (SD = 6.13) during the second period. The difference is confirmed with the Wilcoxon signed-rank test (W = 366, p = 0.021), with effect size assessed through biserial correlation (r_bis = 0.474). In the PAS group, the total score by PANSS total decreases from a mean value of 98.0 (SD = 19.24) during the first period to 80.7 (SD = 18.02) during the second period. This difference is statistically significant (t (40) = 5.19, p = 0.001) with a medium effect size (Cohen's d = 0.811, 95% CI [0.453; 1.161]), which shows substantial improvement in overall symptomatology between the two periods.

5.1.1. Effect size and clinical improvement in the PAS group

Medium effect size (Cohen's d) reveals a medium-sized difference between the two periods. Values around 0.2 are considered a small effect, around 0.5 — moderate, and over 0.8 — a large effect. In this analysis, effects for general psychopathology and positive scale are large, which means that symptom reduction is not only statistically significant but also clinically relevant.

For the negative subscale, assessed through biserial correlation/Wilcoxon test, the difference between initial and outcome values is statistically significant and with a medium effect size, which also supports real but moderate clinical change.

The presented graphs in Appendix 4 (Figures 30 – 33) of the thesis visualise statistically significant but clinically moderate improvement after therapy, with the most substantial reduction of positive symptoms and general psychopathology by PANSS.

Table 16 presents results from PANSS 1 and 2, with the degree of statistical and clinical improvement in the PAS group calculated and interpreted according to the following criteria:

Criteria for clinical improvement by PANSS [Kay et al., Leucht et al.]

Criterion for clinical improvement according to PANSS	Interpretation
< 20 %	No clinically significant improvement
20–49 %	Partial improvement
≥ 50 %	Significant clinical improvement
≥ 75 %	Remission/stabilisation

Table 16. Interpretation of the degree of clinical improvement in the PAS group

Subscale	PANSS1 (Mean ± SD)	PANSS2 (Mean ± SD)	Difference (Δ)	% improvement	t/W, p-value (95% CI)	Effect size	Interpretation
PANSSG (General Symptoms)	53.9 ± 10.18	45.2 ± 10.89	8.7	16.1 %	t = 5.42, p = 0.001 [0.485; 1.201]	0.847	Significant statistical, moderate clinical improvement
PANSS + (Positive symptoms)	28.3 ± 7.60	22.1 ± 8.98	6.2	21.9 %	t = 4.63, p = 0.001 [0.375; 1.065]	0.724	Partial clinical improvement
PANSS − (Negative symptoms)	16.1 ± 9.32	13.6 ± 6.13	2.5	15.5 %	W = 366, p = 0.021	0.474	Minimal but statistically significant improvement
PANSS (total)	98.0 ± 19.24	80.7 ± 18.02	17.3	17.7 %	t = 5.19, p = 0.001 [0.453; 1.161]	0.811	Statistically significant, but below the clinical threshold

Results show that in the studied group (n = 41), substantial statistical improvement occurred in overall and all PANSS subscales between the initial and outcome period, a decrease of 17.7%, and although this decline does not reach the threshold for clinically significant improvement (≥ 20%), it reflects real dynamics of psychopathological severity reduction.

Positive symptomatology decreases by 21.9% – a partial improvement, which is statistically significant (t = 4.63, p = 0.001) and partial clinical improvement, accompanied by a large treatment effect (d = 0.72).

Negative and general psychopathological symptomatology decreases by ~15–16%, which is a statistically significant improvement but a clinically insignificant improvement.

Despite the presented moderate decrease in percentages, the treatment effect is large (Cohen's d = 0.81), which confirms real therapeutic benefit and reduction

of general psychopathology. Clinically, this can be interpreted as a manifestation of good treatment response in positive symptomatology, weaker influence over time on negative manifestations and moderate overall improvement, reflecting the initial stage of stabilisation but not complete remission. These results overlap with those already established by other statistical methods in the study group (see Fig. 18).

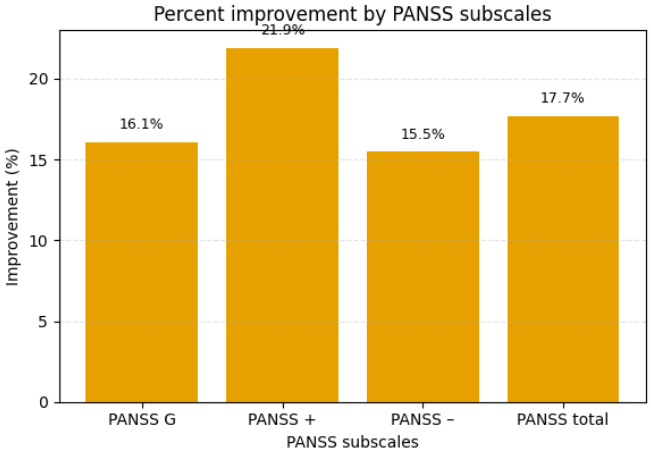


Figure 18

5.2 Initial and outcome values (by PANSS) of the control group

In the control group, a significant decrease in scores on all three PANSS scales is observed between the first and second period (see Table 17).

Table 17. Change in PANSS indicators (n = 40)

Indicator	N	Mean	SD	Paired t-test, 95% CI	Effect size (Cohen's d)
PANSS1 G	40	56.1	11.52	t=4.82, p=0.001,	0.762
PANSS2 G	40	40.6	17.09		
PANSS1 +	40	29.4	7.61	t=8.70, p=0.001, [0.937;1.806]	1.376
PANSS2 +	40	14.4	6.45		
PANSS1 -	40	16.0	6.75	t=2.37, p=0.023, [0.051;0.693]	0.374
PANSS2 -	40	13.3	6.66		
PANSS1 total	40	101.5	17.86	t=9.02, p=0.001, [0.979;1.863]	1.426
PANSS2 total	40	64.5	21.51		

Mean value of general psychopathology decreases from 56.1 (SD = 11.52) to 40.6 (SD = 17.09), with the difference being statistically significant (t (39) = 4.82, p = 0.001) with medium effect size (Cohen's d = 0.762). Positive scale shows a strongly significant decline from 29.4 (SD = 7.61) to 14.4 (SD = 6.45) (t (39) = 8.70, p = 0.001, d = 1.376). Negative scale decreases from 16.0 (SD = 6.75) to 13.3 (SD = 6.66) (t (39) = 2.37, p = 0.023, d = 0.374). Total score PANSS total decreases from 101.5 (SD = 17.86) to 64.5 (SD = 21.51) (t (39) = 9.02, p = 0.001, d = 1.426), which shows significant improvement in overall symptomatology. This difference is with strong statistical significance (t (39) = 9.02, p = 0.001) and shows a large effect size (Cohen's d = 1.426, 95%), which suggests significant improvement in overall symptomatology (see Appendix 4, Figures 32 – 33).

5.2.1. Effect size and clinical improvement in the control group

Clinically significant improvement in the control group is expressed mainly in the reduction of positive symptoms and general psychopathology. The observed larger effects by PANSS + and PANSS total show a high degree of therapeutic response and significant restoration of functioning. Mean reduction of general psychopathology shows a medium to large statistical effect according to Cohen's criteria (1988). According to Kay et al. (1987), a reduction of over 20% in total PANSS score reflects clinically significant improvement. In this case, reduction reaches approximately 28%, which confirms a significant clinical decrease of general psychopathology in the control group.

Positive symptoms show the most substantial decline, and according to Leucht et al. (2005), a reduction of ≥40% on the positive subscale corresponds to marked clinical improvement, which is also confirmed in the present data. This result manifests effective management of productive symptomatology (delusions, hallucinations, and disorganisation) after treatment.

Negative symptomatology shows more limited but statistically significant improvement. Regardless that the effect is moderate, this corresponds to expected trends for weaker and slower influence on primary negative symptoms, unlike secondary ones (e.g., social withdrawal), which are often a consequence of positive symptoms.

Total score – PANSS total decreases significantly, which represents a reduction of approximately 36.4%. This is above the threshold for "moderate clinical improvement" according to Leucht et al. (2005).

Summary for the control group:

Reductions in the range of 28–36% of values in the first and second PANSS measurements are established, corresponding to moderate to significant clinical improvement. The obtained results correspond to international data for the degree of influence on positive, negative symptomatology and assessment of general psychopathology in early treatment stages [Kay et al., 1987; Leucht et al., 2005].

5.3. Comparison of psychosis severity by PANSS between the two groups

To compare mean values between the two independent groups (patients with PAS use and the control group), an independent samples t-test was used when data met normality and homogeneity of variance. When these prerequisites were violated, the non-parametric Mann-Whitney U test was applied. Effect size was assessed with Cohen's d coefficient for the t-test and r coefficient for the Wilcoxon test. Statistical significance was determined at $p < 0.05$. The following table presents an analysis of inter-group differences by PANSS (see Table 18).

Table 18. PANSS comparison between the two groups

Indicator	Group	N	Mean	SD	Тест (t/U, CI)	Effect size
PANSS1 G	with PAS	41	53.9	10.18	t=-0.900, p=0.371, [-0.636; 0.237]	-0.200
PANSS1 G	controls	40	56.1	11.52		
PANSS1 +	with PAS	41	28.3	7.60	t=-0.655, p=0.514, [-0.581; 0.291]	-0.145
PANSS1 +	controls	40	29.4	7.61		
PANSS1 -	**with PAS**	41	16.1	9.32	U=750, p=0.511	0.085
PANSS1 -	controls	40	16.0	6.75		
PANSS1 total	with PAS	41	98.0	19.24	U=718, p=0.337	0.124
PANSS1 total	controls	40	101.5	17.86		
PANSS2 G	with PAS	41	45.2	10.89	U=549, p=0.010	0.331
PANSS2 G	controls	40	40.6	17.09		
PANSS2 +	with PAS	41	22.1	8.98	U=396, p=0.001	0.517
PANSS2 +	controls	40	14.4	6.45		
PANSS2 -	with PAS	41	13.6	6.13	U=760, p=0.599	0.073
PANSS2 -	controls	40	13.3	6.66		
PANSS2 total	with PAS	41	80.7	18.02	t=3.66, p=0.001, [0.358;1.265]	0.814
PANSS2 total	controls	40	64.5	21.51		

Clinically interpreted, these statistical data show the following trends:

• At initial measurement (PANSS1), no statistically significant differences in symptom severity are established between the PAS use group and control group on any of the PANSS1 + / - / G / total indicators.

• At the end of the study, PANSS2 reveals clear statistical differences between the PAS group and the control group, especially regarding positive symptoms and general psychopathology.

• Patients with PAS show higher levels of general psychopathology at the end of treatment. The difference is statistically significant with a small to moderate effect (PANSS2 G: $U = 549$, $p = 0.010$, $d = 0.331$).

• Positive symptomatology remains significantly higher in the PAS group (weaker therapeutic influence and reduction of psychotic production) (PANSS2 +: $U = 396$, $p = 0.001$, $d = 0.517$).

• In the control group, greater reduction is observed in all PANSS subscales and more pronounced clinical improvement - reduction of total PANSS score by ~36%, which corresponds to partial to significant clinical improvement.

• In the PAS group, reduction is smaller (~18–20%), which falls within the boundaries of minimal clinical improvement.

• Total PANSS score remains significantly higher in patients with PAS, with a large effect size (Cohen's $d = 0.814$), which means more severe symptom course and more pronounced residual psychotic symptomatology even after treatment (PANSS 2 total: $t = 3.66$, $p = 0.001$, $d = 0.814$).

• Difference in negative symptomatology is not established, remaining resistant in both groups (PANSS2 −: $U = 760$, $p = 0.599$).

The obtained results confirm that PAS use is associated with a slower and more incomplete reduction of productive psychopathology and is a more unfavourable prognostic factor for achieving remission and restoration of mental functioning. (In Appendix 5 of the thesis, results are presented graphically with Figs. 35–42)

5.4. Comparison of psychosis severity by PANSS total in both groups and its correlation with socio-demographic and clinical factors

The present subsection aims to investigate differences in the overall severity of psychotic symptomatology, measured through total PANSS scale score, between patient groups with PAS use and the control group, and correlations between the severity of psychopathology and main socio-demographic and clinical factors. ANOVA (one-way analysis of variance) was used, which is a statistical test applied for comparing mean values between more than two independent groups. If the ANOVA result is statistically significant ($p < 0.05$), this means that at least one of the groups differs in mean value from the others

5.4.1. Results in the PAS group

Education

Results from one-way analysis of variance (ANOVA) show that there is no statistically significant difference in the psychopathology severity by PANSS total depending on educational level, both at first (F=0.667, p=0.578) and second measurement (F=0.190, p=0.903). Despite the lack of statistical significance, a tendency is observed for people with secondary education to have higher mean PANSS1 total values (M=101.8, SD=23.84) compared to lower educated groups. After therapy, however, PANSS2 total values decrease in all subgroups, with differences evening out. This may suggest that educational level is not a decisive predictor of psychotic symptomatology severity, but may influence indirectly through cognitive and social resources for adaptation and adherence to treatment and future remission.

The interrelationships of PANSS total in both measurements and the education level are presented below (see Figs. 19, 20).

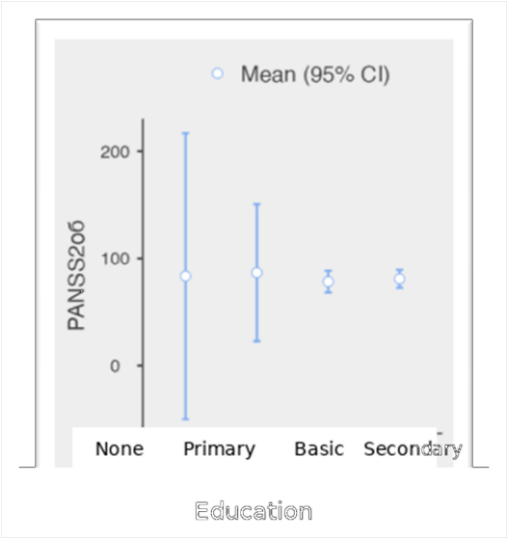


Figure 19

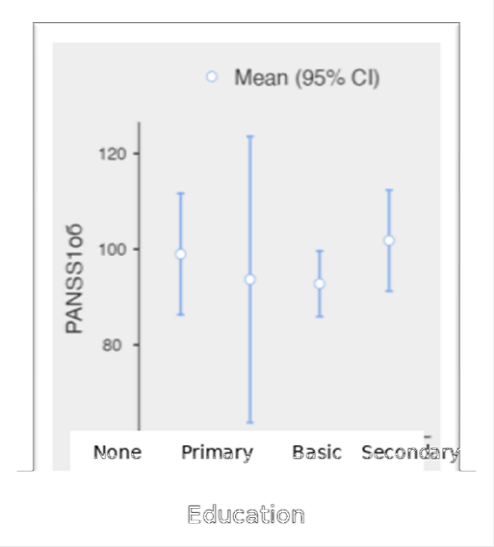
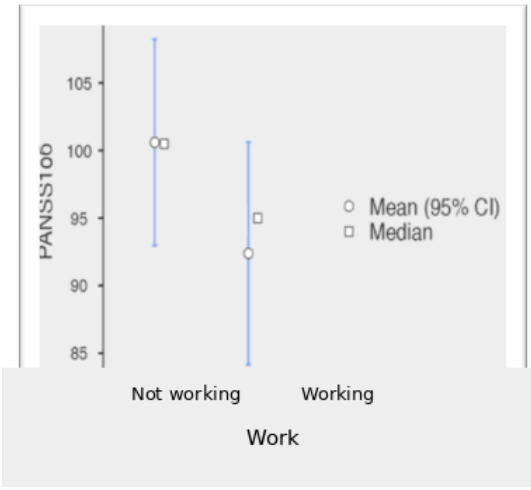


Figure 20

Professional employment

The results from the non-parametric Mann–Whitney test do not show statistically significant differences in the overall severity of psychopathological symptoms between employed and unemployed in the PAS group, both at first (U=142, p=0.262) and second measurement (U=126, p=0.116). Nevertheless, a tendency toward lower mean PANSS total values is observed in employed participants (M=92.4 at first and M=73.8 at the second measurement), which may reflect faster and more effective recovery and better social functioning in

this subgroup. As clinically significant, we can interpret these differences according to which employed patients, regardless of PAS use, show lower levels of overall symptomatology after treatment, which may be due to higher motivation, better adherence to therapy and social support. Although the difference does not reach statistical significance, the clinical tendency shows better recovery in socially active participants. Graphically, below are presented the interrelationships of PANSS total in both measurements and employment (see Figures 21 – 22).



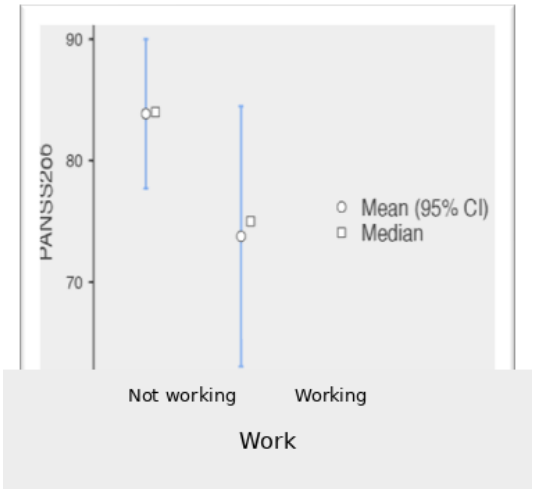


Figure 21 **Figure 22**

Marital status

The results from the Mann-Whitney U test show no statistically significant differences in the severity of psychopathological symptoms between married and unmarried patients. However, mean PANSS total values point to a tendency for lower symptomatology levels in married patients, both initially (M = 89.3 versus 99.5) and after treatment (M = 77.7 versus 81.2). This can be interpreted as clinical, though not statistically significant, as it shows a possible supportive effect of family environment on mental recovery.

In line with literature data and our clinical experience, families play a decisive role in mental health care, and family interventions lead to a moderate reduction in hospitalisation frequency in patients with early psychosis compared to standard medical care - fig.23 [Gleeson et al., 2009].

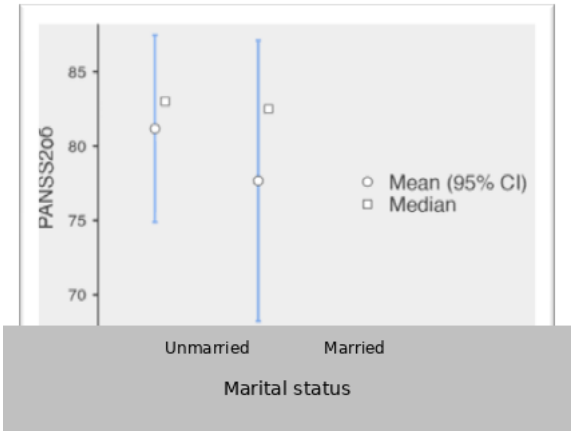


Figure 23

Family burden

In the present study, a comparison between PANSS total results cannot be made because in the studied group, there are no patients with data for family burden with mental illnesses.

Comorbid diseases

The comparison between results from both PANSS total measurements has no statistical significance in the PAS group due to the lack of established change in this indicator at the second measurement. Nevertheless, we derived this comparison due to its clinical significance, especially psychiatric comorbidity (see Table 19).

Table 19. Comorbid disease and PANSS1 and PANSS2 assessment

Comorbid disease	N1 (PANSS1)	Arithmetic mean 1	Standard deviation 1	Min 1	Max 1	N2 (PANSS2)	Arithmetic mean 2	Standard deviation 2	Min 2	Max2
Absence		100.9	20.26	68	71	9	82.9	19.28	33	114
Somatic	1	83.0	—	83	83	1	68.0	—	68	68
Comorbid psychotic disorders	8	88.4	16.10	71	105	8	77.5	16.29	58	106
Comorbid alcohol use	3	100.3	11.68	90	113	3	72.0	7.55	6	79

Note: *SD – standard deviation; Min./Max. – minimum and maximum value*

The results show that patients without comorbid diseases have the highest PANSS values both at first (M = 100.9) and second measurement (M = 82.9),

which may reflect a more severe baseline condition but also a more pronounced treatment response.

In patients with comorbid mental disorders, in this case – the highest frequency of OCD, mean values are lower (PANSS1 total = 88.4; PANSS2 total = 77.5), which can be interpreted as more moderate baseline severity but slower improvement over time.

Comorbid alcohol use is associated with lowered PANSS values in the second period (M = 72.0), which probably reflects short-term symptom reduction after abstinence, but given the combined effects with PAS intake (alcohol and drugs) in the future, stable remission cannot be guaranteed.

Somatic conditions (n = 1) do not allow statistical conclusion, but available data suggest lower overall physical symptomatology, probably due to a lack of sufficiently good self-assessment and predominance of young adult age.

In clinical aspect, we can outline the tendency that accompanying mental disorders substantially change the dynamics of recovery in this group, especially when it concerns mental disorders similar in clinical picture – as in dual diagnosis (psychosis with PAS and mental illness), symptoms are more resistant and their reduction is slower, which requires more intensive and complicated therapeutic strategies [Buckley et al. (2009].

5.4.2. Results in the control group

Education

The educational status indicators in the control group show a tendency for patients with secondary and higher education to have higher PANSS total values at first measurement. This may reflect better history and symptom description, and subsequent diagnostic precision in these groups. At the second measurement, after treatment, all groups show a substantial lowering of mean values. Lowest values are recorded in patients with primary education (26.0), but due to the minimal number of cases, these results cannot be generalised. Overall tendency indicates that educational level does not exert a statistically significant influence on the degree of symptomatology reduction. However, patients with higher education express better engagement in the therapeutic process, which is also described in other studies [Leucht et al., 2006; Kay et al., 1987] (see Figures 24, 25).

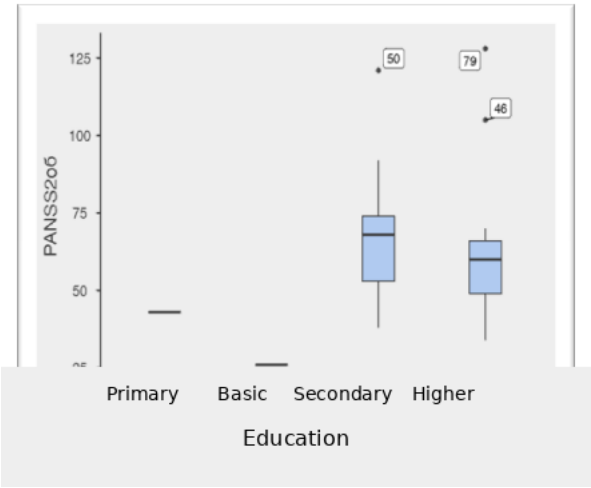


Figure 24

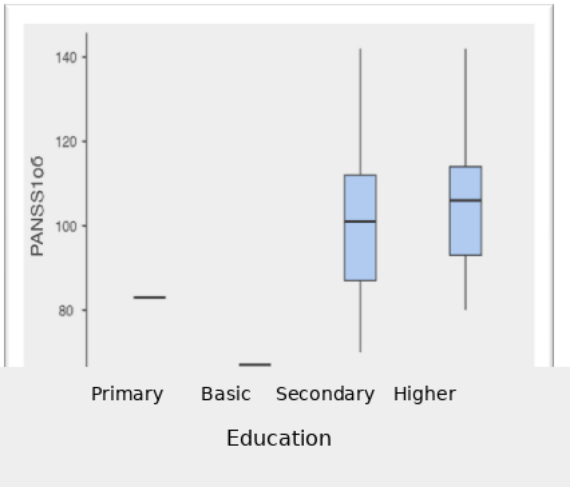


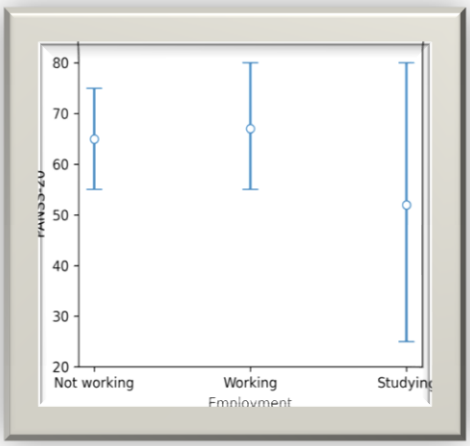
Figure 25

Professional employment

ANOVA results analysis shows that statistically significant differences do not exist in the total PANSS score relative to patients' professional employment, both at first and second measurement. At the first measurement (PANSS1 total), mean values are similar: 101.0 (SD=19.3) for patients who do not work, 102.3 (SD=16.1) for employed and 100.0 (SD=22.6) for students, with differences between groups being insignificant (F=0.032, p=0.968). The conclusion is that psychotic symptomatology severity is not influenced by employment status.

At the second measurement (PANSS2 total), despite a decrease in the mean values in all groups, mean results are 64.6 (SD=19.5) for unemployed, 67.2 (SD=24.6) for employed and 52.8 (SD=16.9) for students, with no statistically significant difference here either (F=0.959, p=0.417). Working patients maintain slightly higher values (67.2), which may be due to greater social activity and more frequent stress factors. Student patients show the lowest values (52.8), which may suggest better therapeutic engagement and cognitive recovery.

Despite the absence of statistical significance, the clinical interpretation of results suggests that social functioning and work integration represent a longer and more difficult process after initial reduction of psychotic symptomatology (see Figures 26, 27).



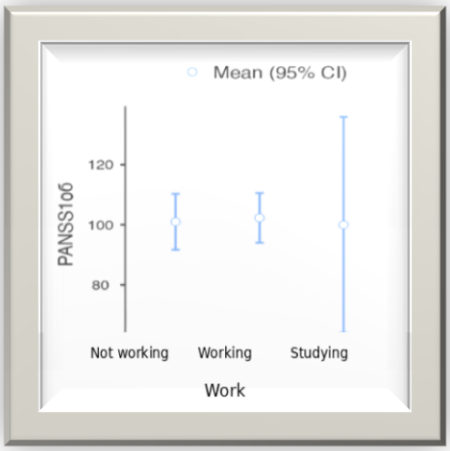


Figure 26 **Figure 27**

Marital status

In the analysis of marital status and PANSS total results, no statistically significant differences were established. Unmarried patients (N = 25) have a mean PANSS1 total score of 98.0 (SD = 15.6), while married patients (N = 15) have a mean score of 107.1 (SD = 20.4), with the difference not being statistically significant (U = 146, p = 0.246). At the second measurement, mean results also do not show significant differences — unmarried have a mean PANSS2 total score of 64.1 (SD = 22.1), and married 65.2 (SD = 21.2) (U = 184, p = 0.922), (see Table 20).

Table 20. PANSS results and marital status

PANSS1 total

Group	N	Arithmetic mean	Standard deviation	Mann–Whitney U
single	25	98.0	15.6	U = 146, p = 0.246
family	15	107.1	20.4	

PANSS2 total

Group	N	Arithmetic mean	Standard deviation	Mann–Whitney U
single	25	64.1	2.1	U = 184, p = 0.922
family	15	65.2	21.2	

The correlation between marital status and total PANSS score in the control group shows that marital status has no statistically significant influence on

psychotic symptomatology severity, neither at first nor second measurement. Unmarried patients have similar mean PANSS values compared to married patients, both initially (98.0 versus 107.1) and after a two-year period and treatment (64.1 versus 65.2). This suggests that family support by itself is not a determining factor for clinical improvement in a shorter-term plan, despite its significance for long-term remission and social reintegration.

Family burden

In the control group, family burden with mental illness was established in only two patients. In both cases, the initial diagnosis is from section F23 – Acute and transient psychotic disorders, and the final diagnosis is F20.0 – Paranoid schizophrenia. These observations represent single cases relative to the overall control sample and have no statistical significance, but have clinical and theoretical significance as they support theories of hereditary predisposition as a substantial factor in the pathogenesis of chronic psychotic disorders. From a clinical perspective, these data emphasise the need for early assessment of family history in the first psychotic episode, as well as more intensive follow-up of patients with hereditary risk.

Comorbid diseases

The following table presents mean PANSS total 1–2 values and their correlation with different comorbid diseases in the control group (Table 20).

Table 20. Correlation between comorbid diseases and total PANSS score

PANSS1 total

Comorbid disease	N	Arithmetic mean	Standard deviation	Minimum	Maximum
Absence	26	98.3	15.36	67	123
Somatic	5	109.4	18.20	83	129
Comorbid psychotic disorders	7	100.3	21.89	1	142
Comorbid alcohol use	1	112.0	–	112	112
Hepatitis B/C	1	142.0	–	142	142

PANSS2 total

Comorbid disease	N	Arithmetic mean	Standard deviation	Minimum	Maximum
Absence	26	61.3	22.06	6	121
Somatic	5	74.2	33.03	43	128

Comorbid psychotic disorders	7	65.9	5.81	57	74
Comorbid alcohol use	1	88.0	–	88	88
Hepatitis B/C	1	67.0	–	67	67

The results show that comorbid diseases do not exert a substantial influence on psychotic symptomatology reduction, measured by PANSS, between the first and second examination, but some clinically interesting tendencies are observed. Patients without comorbid diseases have a mean PANSS1 total score of 98.3, which decreases significantly to 61.3 at the second measurement, showing good therapeutic response and clinical improvement. In individuals with somatic diseases, initial values are higher (109.4), and the reduction to 74.2 is less pronounced. This suggests that the presence of physical illness may aggravate the course of psychosis or delay recovery processes. The group with comorbid mental disorders shows moderate initial values (100.3), with a limited decrease to 65.9, which may reflect more resistant symptoms and slower clinical recovery. In single cases with alcohol dependence and hepatitis B/C, PANSS values remain higher than average, which, although without statistical significance, confirms the negative effect of somatic comorbidity and comorbidity of substance use on the course of psychosis.

These results correspond to literature data [Buckley et al., 2009; Leucht et al., 2005], according to which accompanying somatic and mental illnesses are associated with lower therapeutic response and more prolonged disease course, even with adequate treatment (see Figs. 28, 29).

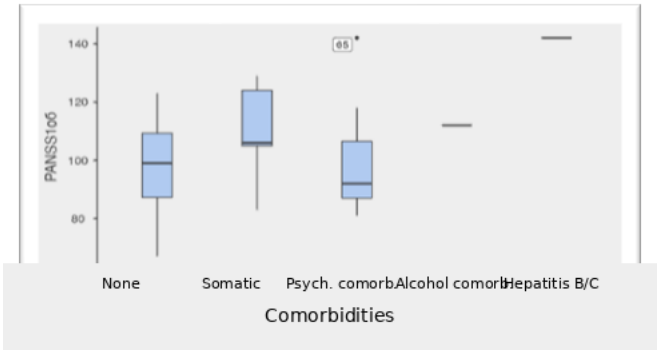


Figure 28

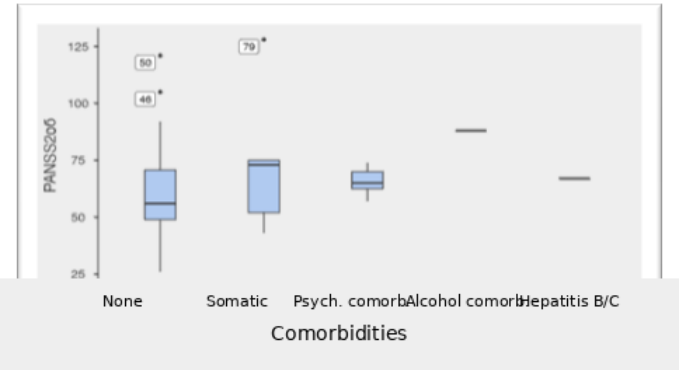


Figure 29

6. Analysis of GAF results – degree of functional improvement in both groups

The GAF scale assesses mental illness severity through the degree of psychological, social and occupational functioning. The scale ranges from 0 (severe symptoms and lack of functioning) to 100 (absence of symptoms and exceptionally high level of functioning). The final score is the lowest in the two subscales: symptoms and functioning, with GAF results ≥81 considered an indicator of recovery (DSM-IV-TR, 2000). Degree of clinical recovery is interpreted through low scores on key PANSS subscales and a high GAF score, with the combination of both scales giving a more objective assessment of recovery. In the present study, two main t-test types were used: the paired t-test and the independent t-test for assessing the degree of functional improvement in both groups by GAF.

6.1. Results in the PAS group

The results show a significant improvement in the functional status in patients with PAS between GAF1 and the second GAF2. Mean GAF value increases from 28.7 (SD = 11.8) to 38.9 (SD = 16.5). Paired t-test shows that this difference is statistically significant (t = -4.68, p = 0.001), with a 95% confidence interval for the difference between [-1.07; -0.381]. The effect of change is medium-sized (-0.730), which speaks of moderate improvement in the overall functional state of patients over time (see Table 21).

Table 21. Changes in global functioning (GAF) in the PAS group

Indicator	N	Arithmetic mean	Standard deviation	t-test for paired samples (95% CI)	Effect size (Cohen's d)

GAF1	41	28.7	11.8	t = -4.68, p = 0.001, [-1.07; -0.381]	-0.730
GAF2	41	38.9	16.5		

Although mean scale values remain in the range of moderately impaired functioning (GAF < 50), there is a tendency towards positive dynamics and partial recovery. Due to continuing PAS use in a large percentage of the group during the observation period, global assessment is still in the range of impaired functioning (see Figure 30).

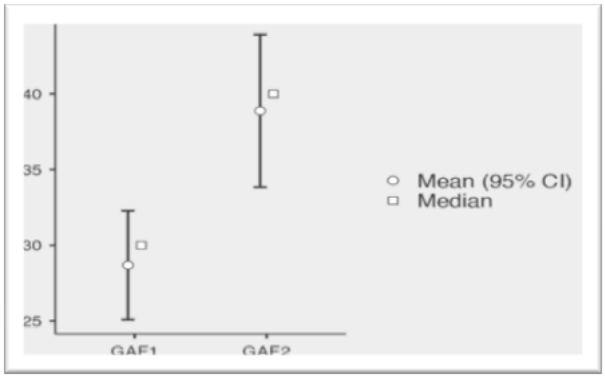


Figure 30

6.2. Results in the control group

In the control group, the mean GAF scale score significantly increases from 26.3 (SD = 10.2) at the first measurement to 55.4 (SD = 17.3) at the second measurement. Paired t-test shows a significant difference between the two measurement points (t = -9.67, p = 0.001), with 95% confidence interval (-1.98; -1.07). The effect is large (Cohen's d = -1.53), which shows substantial improvement in functioning over time (see Table 22).

Table 22. Changes in global functioning (GAF) in the control group

Indicator	N	Arithmetic mean	Standard deviation	t-test for paired samples (95% CI)	Effect size (Cohen’s d)
GAF1	40	26.3	10.2	t=-9.67, p=0.001, [-1.98;-1.07]	-1.53
GAF2	40	55.4	17.3		

In the control group, an exceptionally significant improvement in global functioning is observed between the first and second GAF measurements. Mean value increases from 26.3 to 55.4 points, representing an increase of over 100% relative to the baseline level. T-test result (t = -9.67, p = 0.001) shows a statistically highly significant difference, and the effect size is large (Cohen's d = 1.53), which testifies to strong clinical improvement. The latter can be interpreted as a reduction of psychotic symptomatology and restoration of social and occupational functioning, better adaptation and better quality of life after treatment. GAF2 values (mean 55.4) now fall within the boundaries of moderate to mild functional impairment, which suggests the occurrence of stable remission in a significant part of participants. Similar dynamics are reported in studies by Kay et al. (1987) and Leucht et al. (2006), who note that significant GAF increase in response to medication therapy correlates with reduction of positive symptoms. The following figure presents a graphical expression of change (see Figure 31).

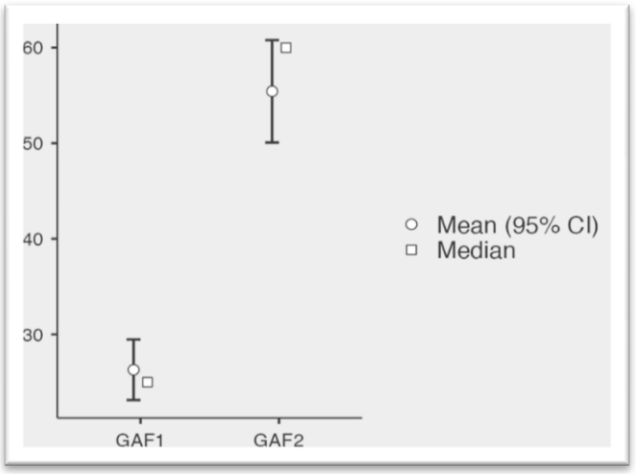


Figure 31

The distinct improvement in functioning in patients with PAS use between GAF1 and GAF2 is statistically significant but remains in the range of moderately impaired functioning (GAF < 50). The result in the control group shows significant improvement between GAF 2 > 50, which is a statistically significant difference with effect size (Cohen's d = 1.53), as pronounced clinical improvement and remission.

7. Discussion

In the present study, a total of 41 patients with FPE associated with PAS use and a control group of 40 patients with FPE without PAS use were included. The sample size is sufficient for statistical processing of results and can be accepted as clinically representative of the studied population.

Demographic characteristics of the sample show that in the study group with PAS, males dominate (90.2%) compared to females (9.8%), while in the control group, the ratio is males (40%) compared to females (60.0%).

Age distribution in the groups establishes that the highest disease frequency in the PAS group is observed in young and young adult age, almost half of those studied are in the 18–29-year age category (48.8%) and in the 30–44-year range (43.9%). The mean age of the PAS group is 31.3 years, with 3 to 4 years earlier FPE onset compared to the control group (mean age 35.4 years). Our results correspond to other studies that identify the age of psychosis onset in cannabis users and combined PAS use as 2.0 to 2.7 years younger than in non-users [Murrie et al., 2020].

Distribution by educational level in the PAS group outlines dominance of patients with lower education levels, 87.8% (secondary and primary education), compared to the control group, 95% (with secondary and higher education). Literature data confirms that lower educational level and poor premorbid functioning carry a greater risk for psychosis onset at a younger age [Koparal, 2025; Queirazza, 2014].

Professional employment. Educational status can be linked with a lower degree of professional employment – 68.3% unemployed in the PAS group, compared to 47.5% in the control group. Similar results are seen regarding marital status, with the majority of PAS users defining themselves as unmarried (85.4%) compared to the control group (62.5%), which is an indicator of higher social vulnerability and lack of family support.

Family history of mental illness is absent in all patients in the PAS group, which points toward predominant exogenous provoking factors. Compared to them, in the control group, there is, although small, a percentage of hereditary burden with psychosis (7.5% – three patients). Low percentages in both groups can be explained by the small sample size.

Psychiatric comorbidity is approximately equal in both groups (17–18%) and is clinically significant, with OCD diagnosis predominating, followed by alcohol abuse (7.3%). The results do not establish statistical significance due to small sample volume, but there is clinical significance regarding diagnosis, treatment and prognosis.

Our clinical data show that in the study group with PAS use, the individuals with prolonged drug substance use predominate, nearly half (46.3%) report over five years of exposure, and another 36.6%, between two and five years. This outlines a clearly expressed tendency toward chronic and sustained use, which is probably among the leading factors for the development of psychotic symptomatology. Relatively low is the percentage of use up to two years – 17.1%, which can be linked with rarer and later seeking of psychiatric help. Data show that early onset of starting PAS use and prolonged intake carry a greater risk of triggering FPE.

The urine test results show the largest number positive for combined PAS use (22% to 34.1%), with THC (cannabis) being the most commonly detected substance – 17.1% of samples are positive only for cannabis. In combined use, cannabinoids and methamphetamines predominate. The obtained data correspond to published international observations according to which combined PAS use, including cannabis, is associated with increased risk of developing psychotic disorders [Murrie, 2020].

The number of hospitalisations emphasises the chronic character of psychosis with PAS intake – 34.1% of patients are hospitalised up to three times, and 26.8% have more than five hospitalisations, with a statistically significant correlation between duration of PAS use and number of hospitalisations present. Compared to them, in the control group cases without hospitalisations predominate – outpatient treatment (22.2%) or with only one (17.3%), and the share of patients with over 5 hospitalisations is much lower (1.2%). In the control group, cases in remission are present (10%), a sign of more favourable development and recovery.

Results from the DAST-10 questionnaire show that 41.5% of the individuals have no indications for problematic use, 36.6% with low to medium risk, and 22.0% with high to very high risk, which shows that nearly 60% of the group have some degree of dependence risk. Our data confirms that early detection of

psychotic symptoms in people with PAS use requires application of brief and reliable screening instruments, such as self-assessment questionnaires of the DAST-10 type. Their application is possible with the stabilisation of the patient's condition and the presence of insight [Kim et al., 2011].

In initial diagnoses in the study group, F19 – "Psychotic disorders related to combined psychoactive substance use" dominates (65.9%), followed by F12 (cannabinoids) and F23 (acute and transient psychotic disorders) – 14.6% each, and F11 (opioids) – 4.9%. In final diagnoses, transformation toward chronic manifestations is observed: F19 remains leading (43.9%), followed by paranoid schizophrenia (F20.0) – 34.1%. This testifies to persisting combined intake in this group as a provocative factor and confirms the high risk of transition from PAS-induced to chronic psychoses, which corresponds to data presented in the literature review [Weiden et al., 2007].

In the control group, acute and transient psychotic disorders F23 (75%) initially predominate, which are subsequently specified as schizophrenia (37.5%) or schizoaffective disorders (27.5%), reflecting the more frequent diagnostic transition from acute to chronic psychoses, probably due to more frequent family burden, which also corresponds to literature data [Queirazza, 2014; Provenzani, 2021].

Results from the statistical processing can be summarised as follows:

- At initial measurement (PANSS1), no statistically significant differences in symptom severity are established between the PAS use group and and the control group on any PANSS indicators.
- At the end of the study, PANSS2 reveals clear statistical differences between the PAS group and the control group, especially regarding positive symptoms and general psychopathology.
- In the PAS group, psychopathology reduction at the end of treatment by PANSS2 +/G is around (~18–20%), which falls within the boundaries of minimal clinical improvement. The difference is statistically significant with a small to moderate effect. Positive symptomatology remains significantly higher, probably due to weaker therapeutic influence and/or non-cooperation with treatment.
- In the control group, a more pronounced change is observed in all PANSS subscales and a more noticeable clinical improvement – reduction of total

PANSS score by ~36%, which corresponds to partial towards significant clinical improvement.

- Total PANSS score remains significantly higher in patients with PAS use, with a large effect size, which means a more severe psychosis course and more pronounced residual psychotic symptomatology even after treatment.
- Differences in negative symptomatology are not established, which remains relatively resistant in both groups during the studied period.
- Fisher's exact test result ($p = 0.049$) shows statistically significant correlation between initial and final diagnosis in the PAS group, with tendencies for transition to chronic psychoses from the spectrum of schizophrenia and affective disorders (51.2% of cases), leading diagnosis being paranoid schizophrenia (34.1%).
- In the control sample, statistically significant change is not established ($p = 0.089$), but a clearly expressed tendency is clinically observed – for clarification of initial acute and transient psychoses toward chronic psychotic disorders (mainly schizophrenia and BAD). Our results correspond to models of evolution after the first psychotic episode described in the literature [Inchausti et al., 2023]. Presence of remission in controls testifies to possibly more favourable development and functional recovery, also linked with better treatment adherence.
- Correlation analysis reveals substantial differences in the dynamics between psychopathological symptomatology in both groups – stable internal consistency of PANSS is established, with positive correlations between subscales and negative dependence with GAF, which confirms the reliability of psychometric measurements.
- In the PAS group, strong and consistent negative correlations are observed between general and positive symptomatology by PANSS and GAF, with positive symptom reduction being the main factor associated with functioning improvement. In contrast, negative symptomatology remains relatively stable and weakly influenced, a sign of resistance and persisting character of negative and cognitive deficits in this group.
- Data show that PAS influence on the functioning level and the quality of life is not clearly manifested in the initial stage, but probably becomes prominent later, at the second measurement (GAF2), when the difference in therapeutic response and degree of recovery occurs.

- The distinct functioning improvement in patients with PAS between GAF1 and GAF2 is statistically significant but remains in the range of moderately impaired functioning (GAF < 50). The result in the control group shows significant improvement between GAF 2 > 50, which is a statistically significant difference, as pronounced clinical improvement and remission.

V. Conclusions and summary, limitations and recommendations

1. Conclusions

- In patients with FPE after PAS use, the following sociodemographic characteristics predominate – males, in young and young adult age groups, with low or medium education level, unemployed and unmarried.
- The mean age at FPE onset in the PAS group is 3–4 years earlier than in the control group.
- The demographic and clinical characteristics show that male sex and early onset of PAS use carry a greater risk of FPE triggering and a greater probability of pronounced clinical picture severity.
- In patients with PAS use, long-term abuse over five years predominates, with a statistically significant correlation between duration of use, psychosis severity and number of hospitalisations present.
- Combined PAS intake, followed by cannabis and its derivatives, represents the most common use pattern in patients with substance-induced FPE.
- In the group with PAS use, dominance of psychoses with F19 is observed at the beginning (65.9%) and at the end of the period (36.6%).
- Diagnostic dynamics reveal a statistically significant correlation between initial and final diagnosis in the PAS group, with a tendency for transition from induced psychoses with F19 (17.1%) to chronic schizophrenic disorders, with the leading diagnosis being paranoid schizophrenia (34.1%).
- In the control group, acute and transient psychotic disorders initially predominate (75%), which are subsequently specified as schizophrenia (37.5%) or schizoaffective disorders (27.5%).
- In both groups, statistically significant reduction of psychotic symptomatology is established between the first and second PANSS measurements, with clinical improvement being more pronounced in the control group.
- Patients with PAS use show slower recovery and lower levels of global functioning compared to the control group.
- Positive symptomatology is the main predictor of therapeutic influence and functional recovery. Its reduction is proportional to the increase in GAF scores and the achievement of remission.

- Negative and cognitive symptoms are distinguished by weaker dynamics over time, confirming their therapeutic resistance and lasting influence on social maladaptation.
- The obtained results correspond to available literature data, emphasising the leading role of positive symptoms for short-term prognosis and remission in FPE, as well as the resistance of negative and cognitive deficits over time.
- Use of standardised assessment scales and questionnaires (PANSS, GAF, DAST-10) are reliable instrument for objective clinical assessment in patients with a first psychotic episode.

2. Conclusion

In conclusion, the results of our study confirm that PAS use is a substantial modifying factor in the development and course of psychotic disorders. This exerts unfavourable influence on psychosis severity, number of relapses and hospitalisations, degree of recovery and the quality of life. In patients with PAS use, slower and partial improvement is observed, as well as a tendency towards chronification of the process of psychopathological manifestations. The decrease in positive symptomatology remains the leading prognostic marker for early remission, while negative and cognitive impairments determine poorer long-term prognosis and degree of social maladaptation.

All main hypotheses set at the beginning of the study are fully or partially confirmed. The study demonstrates the applicability of standardised psychometric instruments (PANSS, GAF, and DAST-10) in Bulgarian clinical practice and outlines the need for inclusion of neuropsychological assessments in future studies.

3. Limitations and recommendations for the clinical practice

Main limitations established in the course of the study:

1. Relatively small sample size ($n \approx 80$), which limits the possibility for generalising results and requires additional statistical processing.

2. Follow-up is limited to a two-year period, which does not provide information about long-term remission stability and relapse risk. Most literature data report a lack of stable diagnosis within two to three years of FPE.

3. Limitations regarding the lack of social support for individuals with FPE and PAS use and their early inclusion in specialised programs obstruct the possibility of treatment adherence and their complete recovery.

4. In future studies, inclusion of larger and more diverse samples is recommended, as well as long-term follow-up of clinical dynamics, especially in patients with combined substance use.

5. Limitations related to poor cooperation and communication difficulties with the respondents, predominantly in the study group with PAS use, due to a lack of adequate support from social services. The results confirm the necessity of integrated early therapeutic programs combining medication treatment with psychosocial interventions and rehabilitation, especially in patients with PAS use and comorbid mental disorders.

6. The lack of specialised assessment of cognitive functions in the studied groups can also be highlighted as a limitation, which reduces the possibility for complete interpretation of psychosis severity and the degree of recovery.

VI. Scientific and clinical contribution

The present study confirms the existence of statistically and clinically significant differences in the first episode of psychosis with and without PAS use regarding symptom dynamics, number of hospitalisations and degree of functional recovery.

The study presents empirical evidence for diagnostic transition from PAS-induced and acute primary psychoses to chronic disorders from the schizophrenia and affective spectrum.

The study confirms the role of positive symptoms as a key predictor for early remission and negative symptoms as a factor for long-term disability.

The results from the study have direct clinical applicability, outlining patient groups with a higher risk of psychotic disorder chronification, which aids early diagnosis, timely interventions and improvement of treatment outcome.

The study has both theoretical and practical contributions for improving the diagnostic-therapeutic approach in patients with a first psychotic episode after PAS use in clinical practice.

VII. Thesis-related publications

Author's publications on the subject

1. Avramov D., Kozhuharov H. Psychoactive substance-induced psychosis and comorbidity with obsessive-compulsive disorder – diagnostic and therapeutic problems in a clinical case. Bulgarian Journal of Psychiatry. 2025; 10 (1).

2. Avramov D. A clinical case of transition from acute psychotic substance abuse disorder to schizophrenia. International Bulletin of Otorhinolaryngology. 2024; 20(4).

ABSTRACT

The first psychotic episode marks a critical moment in the development of chronic psychotic disorders and carries substantial diagnostic and prognostic significance. In recent decades, a steady increase in the number of registered psychotic disorders induced by psychoactive substance use has been documented. The dynamics of diagnosis in these patients is a relevant and insufficiently researched issue, thereby requiring investigation into the subject matter.

The thesis aims to track the variability (dynamics) of diagnosis in patients with a first psychotic episode after psychoactive substance use within a two-year period.

The study is designed as a longitudinal, prospective study, including a total sample of 81 patients aged 18 to 65 years, divided into two groups: the study group of 41 individuals with a diagnosis of first psychotic episode after psychoactive substance use and the control group of 40 individuals. To achieve the objectives, sociodemographic and clinical characteristics, severity of psychotic symptomatology, frequency of hospitalisations, level of functional recovery and dynamics of initial diagnosis were studied. Applied research methods included clinical psychiatric examination, standardised assessment instruments (PANSS, GAF scales and DAST 10 questionnaire), clinical laboratory tests and combined urine tests for psychoactive substances. Data were processed with modern statistical methods, ensuring reliability and statistical significance of the obtained results.

The analysis of results and conclusions confirm that psychoactive substance use is a substantial modifying factor in the development and course of psychotic disorders and exerts unfavourable influence on psychosis severity, number of hospitalisations, degree of recovery and the quality of life. In patients in the study group, slower and partial improvement is observed, as well as a tendency toward chronification of psychosis, mainly with transition to diagnosis in the schizophrenia spectrum. Decrease in positive symptomatology remains the leading prognostic marker for early remission, while negative and cognitive impairments determine poorer long-term prognosis and social maladaptation. The study demonstrates the applicability of standardised psychometric instruments (PANSS, GAF, and DAST-10) in Bulgarian clinical practice and outlines the need for inclusion of neuropsychological assessments in future studies. The main limitations in the course of the study were the relatively small sample size ($n \approx 80$) and an insufficiently prolonged follow-up period.

Keywords: first-episode psychosis; psychoactive substances; dynamics of diagnosis; PANSS; GAF;