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Psychiatric Comorbidity and Synthetic Cannabinoid (Spice) Abuse Syndrome

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Abstract. The clinical presentation of psychiatric comorbidity in substance use disorders resulting from the consumption of synthetic cannabinoids (Spice) differs from the traditional pattern of cannabinoid use. This divergence can potentially lead to diagnostic errors by psychiatrists. *Aim*: to describe the psychiatric comorbidity of substance use disorders due to the use of synthetic cannabinoids (Spice). *Research Methods:* clinical-psychopathological, psychometric (SANS, CGI, MMPI), follow-up, statistical. *Results:* 291 men were included in this study. The authors differentiated synthetic cannabinoid use-related conditions, personality disorders, negative and psycho-positive pathological symptoms of schizophrenia in synthetic cannabinoids users. The paper also describes options for pharmacotherapy and rehabilitation. *Conclusion:* Intoxication resulting from synthetic cannabinoids can trigger psychotic episodes according to endogenous schizophreniform type and potentially initiate schizophrenia. The misuse of synthetic cannabinoids can lead to the development of various types of narcotic intoxication, including delirious, schizophrenic, pseudohallucinatory, and delirious states. Individuals dependent on synthetic cannabinoids tend to exhibit personality traits characterized by a mix of antisocial, schizoid, and paranoid tendencies. Prolonged abuse of synthetic cannabinoids can lead to symptoms of schizophrenia among users. In comparison to typical drug addicts, individuals with personality disorders and synthetic cannabinoid dependence exhibit distinct behavioral patterns, such as disorganization, conflict, unpredictability, impulsivity, thoughtlessness in actions, and non-conformity. These traits may contribute to difficulties in social adaptation and pose a risk to society. Stigmatizing signs of endogenous mental disorders are often observed in schizophrenic patients who regularly use drugs. These signs may include mild apathy (abulia) and the "hood" catatonic symptom. Notably, schizophrenic patients who use drugs may exhibit

paradoxical and expressive emotions, maintain visual and speech contact, seek interpersonal relationships, and experience anxiety and anticipation. Treatment for exogenous psychoses typically involves combinations of typical antipsychotic medications and tranquilizers. Negative symptoms may necessitate a combination of typical and atypical antipsychotics, along with efforts to integrate patients into socially acceptable groups for individuals with addictive behavior.

Keywords: comorbidity, schizophrenia, personality disorders synthetic cannabinoids, SANS, CGI, MMPI.

Introduction

The current situation concerning substance abuse remains problematic, characterized by a rise in comorbid conditions, shifting consumption patterns, and an expanding spectrum of psychoactive substances (Bokhan & Semke, 2009; Bokhan et al., 2021). Mental health issues among individuals who use "designer" drugs, particularly synthetic cannabinoids (SC) or "Spice," which gained popularity in Russia and Europe around 2008, are drawing increasing attention from psychiatry and addiction psychiatry specialists (Shagiakhmetov & Shamakina et al., 2015). This heightened attention is due to the growing number of reported cases of SC abuse and dependence syndrome in Russia since 2009 (Little et al., 1989; Wiley et al., 1998; Huffman et al., 2008; Justinova et al., 2009; Van der Veer & Friday, 2011; Bokhan et al., 2012; Bokhan et al., 2014).

SC-based smoking mixtures remained legal for an extended period, resulting in frequent changes in their chemical composition (Fernandez-Ruiz et al., 2011). Initially marketed as a legal alternative to marijuana, they were readily available as they were not classified as narcotic substances. There was a widespread belief among young people that they were both legal and harmless, despite being significantly more dangerous than cannabis (Bokhan et al., 2014).

It was already evident that the use of plant-based cannabinoids could trigger transient psychotic episodes and serve as a predisposing factor for the development of paranoid schizophrenia (PS) (Mechoulam et al., 1988; Muller et al., 2010). Synthetic cannabinoids, it seemed, could lead to these outcomes in an even shorter timeframe (Bokhan et al., 2014, 2015; Klimova & Ovchinnikov, 2019). For individuals who systematically consumed cannabinoids from various sources, researchers observed notable memory impairment, the development of amotivation syndrome (characterized by indifference toward family, health, and work), increased lethargy, and reduced concentration. It has also been proposed that prolonged use over two to three years could lead to a decline in cognitive function, potentially influencing personality development (Chukhlovina, 2015). This is just one facet of this complex issue.

Until recently, individuals who abused Spice did not draw the attention of addiction specialists. Only in the past decade have they started

to be hospitalized with atypical psychotic conditions. According to a study conducted by Russian researchers, several dozen synthetic cannabinoids (SCs) were initially identified in global drug trafficking between 2011 and 2015 (Sofronov et al., 2012; Golovko et al., 2013; Golovko et al., 2015).

According to a report from the UN Office on Drugs for 2021, approximately 271 million people used drugs in 2017, which accounts for roughly 5.5% of the global population aged 15 to 64. While these figures were similar to estimates for 2016, a more extended analysis revealed that this number had increased by 30% since 2009. Cannabinoids, both synthetic and nonsynthetic, remained the most commonly used drugs worldwide, with an estimated 188 million people using them in 2017, alongside opioids (Bokhan & Selivanov, 2015; Mustonen et al., 2018; World Drug Report 2021).

The other aspect of this issue was the increase in schizophrenic patients with an addiction to Spice within the psychiatric healthcare system. Simultaneously, efforts toward preventing addiction (Korolenko, 1990) and providing psychiatric rehabilitation for these patients (Bokhan & Selivanov, 2015; Freeman et al., 2018; Fridell et al., 2019) started to receive reduced attention from specialists. This shift was due to attempts to implement treatment standards emphasizing pharmacotherapy for positive psychopathological symptoms, resulting in a one-sided perspective on the problem (Mustonen et al., 2018; Fastovtsov & Oskolkova, 2018; Klimova & Ovchinnikov, 2019; Forti et al. and the EU-GEI WP2 Group, 2019). The uniqueness of psycho-positive symptoms could be assessed by any doctor, whether a psychiatrist or addiction specialist. However, it's worth noting that after resolving positive psychopathological symptoms, negative psychopathological symptoms didn't receive adequate attention due to rigid guidelines for patient treatment (including the number of hospital days and timely discharges) (Murray et al., 2016; Freeman et al., 2018; Jongsma et al. and EU-GEI WP2 Group, 2018; Bokhan et al., 2019; Curran et al., 2019; Fridell et al., 2019). In other words, this rigid framework distorted a doctor's clinical thinking and consequently diminished the rehabilitation potential of schizophrenia patients. Negative symptoms significantly impact patients' employability, their range of needs, hospitalization frequency, and socialization (Kornetova & Semke, 2014; Kornetova et al., 2016; Bokhan et al., 2022).

Previously, both we and other researchers have highlighted the significant impact of grouping patients with similar mental disorders, such as drug-addicted patients with schizophrenia, on patient adaptation (Bokhan et al., 2018, 2022; Klimova & Ovchinnikov, 2019; Selivanov & Bokhan, 2021; Selivanov et al., 2022). The transition from addictive behavior to behavior acceptable in society has also been shown to reduce hospitalization rates. However, there remains a question about achieving the highest quality remissions, characterized by longer periods of stability outside the hospital with fewer pronounced psychotic reactions and deficit symptoms.

Furthermore, we and other researchers have observed that adaptation mechanisms significantly influence the addictive behavior of patients with paranoid schizophrenia (PS) who were previously addicted to synthetic cannabinoids (SC) (Bokhan et al., 2016; Bokhan et al., 2018; Fastovtsov & Oskolkova, 2018; Klimova & Ovchinnikov, 2019; Bokhan et al., 2019). Transforming addictive behavior into a socially acceptable form has also been linked to reduced hospitalization rates (Dubatova et al., 2018; Klimova & Ovchinnikov, 2019).

However, the question of how to help these patients adapt to life outside the hospital still remains. This question arises due to a lack of research on the specific features of deficit symptoms among PS patients with a history of SC addiction. Often, when supervising these patients, inadequate attention has been paid to their potential for rehabilitation, largely due to insufficient awareness of this issue (Bokhan et al., 2016; Klimova & Ovchinnikov, 2019; Bokhan et al., 2019).

Another aspect of the problem related to endogenous psychopathology involved variable stigmatizing symptoms, often referred to as "chimeras." These symptoms exhibited significant differences from the typical presentation of paranoid schizophrenia. Consequently, even highly skilled specialists occasionally encountered challenges in accurately diagnosing the condition, occasionally leading to misdiagnoses (Bokhan et al., 2016; Klimova & Ovchinnikov, 2019; Bokhan et al., 2019).

An analysis of the literature and available data suggests that the causes of comorbidity with Spice addiction have not been fully elucidated. The current literature contains limited information on this topic, and some of the existing data are contradictory.

The primary national statistical indicator for assessing the social and occupational adaptation of individuals with mental illness is their disability status, which entails receiving social and financial assistance from the government. When there is a sustained reduction or loss of work capacity, the Medical and Social Examination Bureau determines the patient's disability group based on the following criteria:

Disability group I is defined by the presence of social insufficiency requiring social protection and assistance. These are provided in Russia for people with health disorders that cause persistent and significantly pronounced disorders of body function leading to limitations on their ability to live independently (i.e., self-care, movement, orientation, communication, control over their behaviour).

Disability group II is defined by a persistently expressed disorder of bodily functions, leading to the limitation of one or several abilities of life, but to a lesser degree. This includes the ability to work and learn.

Disability group III is defined by similar manifestations of social insufficiency due to persistent, minor, and moderately pronounced disorders of the body's functions, accompanied by mild and moderately pronounced limitations in one category of the body's vital activity or their combination.

Aim

To classify and describe psychiatric comorbidity of synthetic cannabinoids (Spice) related substance use disorders.

Materials and Methods

This study was conducted in collaboration with several institutions including the Siberian Federal Scientific-Clinical Center of the Federal Medical and Biological Agency of Russia in Seversk, Tomsk Clinical Psychiatric Hospital in Tomsk, Mental Health Research Institute at Tomsk National Research Medical Center, Russian Academy of Sciences in Tomsk, and the Emergency Medicine Station in Tomsk. It also involved the "Nizhnevartovsk psycho-neurological hospital" in Nizhnevartovsk, "Psycho-neurological dispensary No. 5" in St. Petersburg, and the Psychiatric Hospital of St. Nicholas the Wonderworker in St. Petersburg. The data collection spanned from 2013 to 2021 and then from 2021 to March 2022, all in Russia.

All patients provided informed consent for examination and hospitalization upon admission to the hospital. The study included 291 men. Within this group, 34.7% (101) of the patients were diagnosed with a personality disorder associated with synthetic cannabinoids (F60.xx-F62.xx + F12.2), with an average age of 27.8 ± 7.6 years. These patients were registered by an addiction specialist with a diagnosis of SC dependence syndrome (F12.2). In terms of marital status, 58.42% (59) were single, 34.65% (35) were married, and 6.93% (7) were divorced. Regarding education, 47.52% (48) had completed secondary education, 37.62% (38) had specialized vocational education, 7.92% (8) had incomplete higher education, and 6.94% (7) had obtained a higher education. In terms of employment, 39.60% (40) were unemployed, 35.64% (36) had temporary or seasonal employment, and 24.76% (25) held permanent jobs.

The primary group of patients with endogenous mental disorders consisted of 140 individuals diagnosed with paranoid schizophrenia (PS) and concurrent addiction to synthetic cannabinoids (F20.xx+F12.2). Their average age was 30.2 ± 0.54 years, with 43 of them experiencing the onset of the endogenous disease following SC use. In terms of marital status, 69.29% (97) were single, 16.43% (23) were married, and 14.28% (20) were divorced. Regarding education, 43.57% (61) held a secondary education, 38.57% (54) had completed secondary specialized education, 12.86% (18) had incomplete higher education, and 5% (7) had a higher education. Disability status included 84.28% of patients (118) in disability group II and 15.72% (22) in disability group III. In terms of employment, 39.58% (91) were unemployed, 35.61% (37) had temporary or seasonal employment, and 24.80% (12) held permanent jobs.

The control group comprised individuals with endogenous mental disorders, specifically 50 men diagnosed with paranoid schizophrenia (PS) but without substance addiction. In this group, 56% (28) were single, 34% (17) were married, and 10% (5) were divorced in terms of marital status.

Regarding education, 50% (25) of these patients had completed comprehensive specialized education, while 32% (16) held a secondary education, and 18% (9) had incomplete higher education. In terms of disability status, 90% (45) were in disability group II, and 10% (5) were in disability group III. Professional employment was distributed as follows: 80% (40) were unemployed, and 20% (10) had temporary or seasonal earnings (see Table 1).

Table 1. Socio-demographic indicators of patient's dependent on synthetic cannabinoids

Disease / **Sociodemographic indicators**	**F60.xx-F62.xx+F12.2 (n=101)**	**F20.00x+F12.2 (n=140)**	**F20.00x (n=50)**
Age, years (M±m)	27.7±7.5	30.1±0.53	29.5±0.49
Family status %			
Unmarried	58.41 %	69.28%	56%
Married	34.64 %	16.45%	34%
Divorced	6.95 %	14.27%	10%
Education level %			
School education	47.51 %	43.55%	32%
Secondary specialized education	37.61 %	38.57%	50%
Incomplete higher education	7.91 %	12.89%	18%
Higher education	6.97	4.9%	0%
Professional employment%			
Non-working	39.58 %	65.1%	80%
Temporary (seasonal) earnings	35.61 %	26.68%	20%
Permanent place of work	24.80 %	8.31%	0%
Disability group%			
I group	0%	0%	0%
II group	0%	84.25%	97.5%
III group	0%	15.75%	2.5%

The study employed various methods, including clinical-psychopathological assessment (which involved evaluating symptoms, syndromes, and the condition of patients during disease remission and periods of abstinence from drug use in both inpatient and outpatient settings). Psychometric evaluations were conducted using the Minnesota Multiphasic Personality Inventory (MMPI), and the results were subsequently interpreted using a standardized multifactorial method for

studying personality (SMPT) developed by Sobchik in 2009. Additionally, the Scale for the Assessment of Negative Symptoms (SANS) was used for evaluating patients with schizophrenia, based on the criteria established by Andreasen in 1982 and Mosolov in 2001. The Clinical Global Impressions Scale (CGI), as outlined by Busner and Targum in 2007, was also employed.

It's worth noting that the SANS was preferred over the Positive and Negative Syndrome Scale (PANSS), as it has a greater ability to distinguish negative symptoms and can detect approximately four times more symptoms than the PANSS. This choice was made, in part, due to the identification of patients with schizophrenia in incomplete remission "B" (as per Sereisky, 1939) who exhibited either the absence or mild severity of residual symptoms.

The data were organized and systematized by creating a database, and subsequent processing was carried out using the R programming language for Windows (R version 3.2.4). Descriptive statistics and correlation analysis (Spearman Rank Order) were applied in the data analysis. To assess the normality of result distribution, the Kolmogorov-Smirnov criterion ($\alpha = 0.05$) was employed. Significance of differences between the samples was determined using Student's t-test ($\alpha = 0.05$). Data were presented as the arithmetic mean (M) and the standard error of the mean (m).

Results and Discussion

According to the results of the study, all respondents of the main group (n = 241) were divided into diagnostic categories with specification of the corresponding diagnostic group of patients with mental disorders due to the use of SC (F12), combined with mental illness, the first group consisted of 101 patients with personality disorders (F60.xx-F62.xx): 1) 34 had SC acute intoxication with delirium (F12.03), 2) 31 had a withdrawal state with delirium due to the use of SC (F12.4), 3) 27 had a psychotic state (mainly hallucinatory) due to the use of SC (F12.52), 4) 9 had residual and delayed psychotic states of the "flashback" type due to the use of SC (F12.70).

The second group consisted of 140 patients with paranoid schizophrenia (F20.00x): 1) 30 had SC acute intoxication with delirium (F12.03), 2) 26 had SC acute intoxication, uncomplicated (F12.00), 3) 25 had a psychotic state (mainly delusional) due to the use of SC (F12.51), 4) 23 had a psychotic state (mainly hallucinatory) due to the use of SC (F12.52), 5) 19 had uncomplicated withdrawal state due to the use of SC (depressive-asthenic variant) (F12.30), and 6) 17 had a withdrawal state with delirium due to the use of SC (F12.4x) (Table 2).

Table 2. Percentage of patients with respect to the diagnostic group of diseases caused by the use of synthetic cannabinoids (F12)

Mental illness / **Drug addiction disease**	**F60.xx-F62.xx+F12.2 (n=101) %**	**F20.00+F12.2x (n=140) %**
F12.00	0%	18.56%
F12.03	33.67%	21.47%
F12.30	0%	13.57%
F12.4x	30.69%	12.14%
F12.51	0%	17.85%
F12.52	26.73%	16.41%
F12.70	8.91%	0%

By the character of SC intoxication, we divided patients into the following groups: 123 had delirium-like intoxication, 87 had schizophrenia-like intoxication, 53 had a predominance of auditory pseudo-hallucinations, and 28 had a predominance of delusional symptoms. The study detected distinctive features of each diagnostic category.

Acute intoxication uncomplicated due to the use of SC (F12.00)
This condition typically occurs 5-10 minutes after drug use and is characterized by several features, including:

Heart Rate Fluctuations: There's variability in heart rate.
Scleral Hyperemia: The whites of the eyes become red or bloodshot.
"Glassy" Appearance: The eyes may have a glossy or unfocused look.
Sensations of Warmth and Cold: Individuals experience alternating sensations of warmth and cold.
Muscle Relaxation: A sense of muscle relaxation is felt, accompanied by lightness and smoothness in movements.
Emotional Elevation: Euphoria and heightened emotions are common.
Altered Time Perception: Perception of time varies, moving from accelerated to slowed pace.
Coordination Issues: Patients may experience coordination problems such as ataxia (lack of muscle coordination) and difficulties in executing actions.
Absent-Mindedness and Inattention: Individuals become absent-minded and inattentive.
Accelerated Thinking: Thought processes are dominated by an accelerated tempo and excessive rapid thinking, with occasional mental slippage.
Physical Sensations: There's a subjective feeling of dry mouth, increased appetite, and thirst.

This condition typically resolves on its own within 0.5-1 hour after drug use.

Acute intoxication with delirium due to the use of SC (F12.03)

It develops 5-10 minutes after drug use. For these patients, derealization, metamorphopsias, and various visual hallucinations (usually of a threatening nature) were typical, against the background upon which unstructured delusional constructions of a persecutory nature formed. For all this, the patients oriented on the calendar date and situation, but although they could accurately report where they were, at the same time they doubted themselves. Their attention was scattered and unstable, and there were thought disorders in the form of tachyphrenia, mentisms, and slippages, though very rarely reaching the elements of schizophasia.

Their symptoms were stopped after intramuscular administration of an antipsychotic and tranquilizer (haloperidol 7.52 ± 0.91 mg, bromdihydrochlorphenylbenzodiazepine 1.53 ± 0.91 mg) after 1-2 hours. Subsequently, patients underwent detoxification therapy with tranquilizers (bromdihydrochlorphenylbenzodiazepine 1.52 ± 0.92 mg).

Withdrawal syndrome uncomplicated (depressive-asthenic) due to the use of SC (F12.30)

It develops 3.5 days after stopping the SC intake. The façade were somatic symptoms of withdrawal syndrome, which initiated sleep disorders (including daytime dyssomnia), there was a decrease in motor activity, subjective feeling of weakness, lethargy; slowness of thinking, decreased mood, painful ide's of "reference, impairment". The condition was stopped after a week, after prescribing a combination of anxiolytic and conventional antipsychotic (haloperidol 7.52 ± 0.93 mg, bromdihydrochlorphenylbenzodiazepine 1.5 ± 0.93 mg), then detoxification therapy with anxiolytics (bromdihydrochlorphenylbenzodiazepine 1.52 ± 0.92 mg) was carried out.

Withdrawal state with delirium due to the use of SC (F12.4)

For these patients symptoms occurred on the third or fourth day after stopping the SC use. The leading symptom was withdrawal syndrome and insomnia joined it (including daytime dyssomnia). Further, there was an increase in protopathic and epicritic anxiety with absent-mindedness and distraction, which were realized in delirious clouding of consciousness (arising regardless of the time of day, in contrast to alcoholic). The phenomenon of allopsychic disorientation was observed. The clouding of consciousness included optical and auditory hallucinations with an entire galaxy of classic thought disorders that cumulate haphazard ideas of persecution. The peak of the state was the development of psychotic agitation.

The condition was stopped for four to six days after one parenteral administration of antipsychotics and tranquilizers (haloperidol 7.5 ± 0.94 mg, bromdihydrochlorphenylbenzodiazepine1.5 ± 0.94 mg), followed by detoxification therapy with tranquilizers bromdihydrochlorphenylbenzodiazepine 1.5 ± 0 94 mg).

Residual and delayed psychotic conditions of the "flashback" type due to the use of SC (F12.70)

For these patients, these symptoms typically occurred following the spontaneous cessation of SC use, usually after a period ranging from one and a half to two months of abstinence from narcotization. These states were marked by both nonverbal and verbal pseudo-hallucinations. Delusional constructs, though unstructured, often revolved around themes of reference and persecution (such as feeling persecuted by drug traffickers). Formal thought disorders, including inconsistencies, philosophizing, paralogy, and mentism with slippage elements, were less pronounced. Additionally, partial disturbances in orientation were observed regarding the calendar date and time.

The condition was stopped after intramuscular administration of an antipsychotic and tranquilizer (haloperidol 7.5 ± 0.94 mg, bromdihydrochlorphenylbenzodiazepine 1.5 ± 0.94 mg), after 1.5 hours. Subsequently, the patients underwent detoxification therapy with anxiolytics and oral administration of typical antipsychotics (chlorprothixene 75 ± 9.33 mg), all pathological symptoms were finally reduced within 3.5 days.

Psychotic state (mainly delusional) due to the use of SC (F12.51)

It developed after 3.5 days of abstinence from the use of SC (without withdrawal syndrome) or against the background of continuous use for up to 4 days. At any time of the day, disturbances in nighttime and daytime sleep were primary, followed by an increase in situational anxiety. Subsequently, haphazard ideas arose (persecution by participants in drug trafficking, surveillance), accompanied by slow thinking.

The condition was stopped after intramuscular injection of anxiolytic and neuroleptic (bromdihydrochlorphenylbenzodiazepine 1.5 ± 0.93 mg, haloperidol 7.5 ± 0.92 mg), after 2.5 days. Subsequently, the patients underwent oral therapy with typical neuroleptics (chlorprothixene 75 ± 9.33 mg), all pathological symptoms were finally reduced within 2.5 days.

Psychotic state, predominantly hallucinatory, due to the use of SC (F12.52)

Similarly, these patients experienced symptoms after three to four days of abstinence from the SC use (without signs of withdrawal) or against the background of continuous use for up to four days. Regardless of the time of day, insomnia initially arose, then anxiety developed. This later turned into verbal hallucinations of various nature, against a background from which unstructured delusional constructions of reference, persecutorial character and mental disorders in the form of bradyphrenia arose. The conditions were stopped after similar administrations, within three to four days.

Paranoid schizophrenia associated with dependence on SC (F20.0x+F12.2xx)

For this group, the stage of manifestation of schizophrenia was determined by Kandinsky-Clérambault syndrome (with subjective resistance to automatism) with a predominance of auditory and visual true and pseudo-delirious hallucinations of a harassing or threatening nature, in 37 cases with Fregoli's symptom and paraphrenic interpretation of morbid experiences. The above symptoms were likely a manifestation of the combination of two morbid processes: paranoid schizophrenia and the condition due to SC use, the catalyst for the severity of which was SC intoxication. The course of the disease was continuous and progressive in nature. Remissions were short-term (one to two months), which was indirectly associated with narcotization. Continuous SC use for up to seven days provoked atypical psycho-positive symptoms with the presence of visual hallucinations.

Patients of the first group (F60.xx-F62.xx, F12.2) can be characterized as asocial, schizo-paranoid personalities. Their behavior can be described as disorganized, unpredictable, spontaneous, thoughtless, impulsive, nonconformal. The formation of social interactions was catalyzed by morbid judgments, a paradoxical interpretation of the actions of the milieu. Violation of adaptation in society is due to: friendliness, interspersed with conflict; intolerance of discipline; easily forming relationship ideas; inability to distinguish between normative and asocial behavior (Table 3).

Table 3. Indices of MMPI in SC-addicted patients

MMPI scales	Study groups (Diagnoses according to ICD-10)		
	F60.xx-F62.xx+F12.2 (n=101)	F20.0xx+F12.2 (n=140)	F20.0xx (n=50)
	Indices of MMPI scales (T-scores) M±m		
1.Hs	58.04±3.34	62.15±1.41	52.03±0.33
2.De	61.43±4.42	65.44±1.48	70.43±2.01
3.Hy	54.12±2.13	55.21±1.11	50.49±0.42
4.Pd	76.52±2.98	69.92±0.99	58.96±3.33
5.Mf	49.89±2.31	59.13±1.49	48.87±1.69
6.Pa	73.95±4.32	65.27±0.95	58.12±0.93
7.Pt	56.79±6.25	63.27±0.79	59.78±1.96
8.Sch	78.15±3.79	74.49±2.13	51.38±0.89
9.Ma	57.58±3.73	68.87±2.01	69.96±4.31
0.Si	56.97±2.95	56.15±0.74	55.11±0.98

When examined on the CGI scale, the mental state of patients in the main group was more severe than in the control group. We assumed this was associated with both exacerbation of endogenous disease and deformation of the psychotic state due to the SC use. Equal therapy was provided to patients (during periods of hospitalization and transfer to maintenance therapy), as we present below. Nevertheless, in patients from the main group, a paradoxical improvement in the state and level of functioning was observed, in contrast to the control group (Table 4).

Table 4. CGI indices in schizophrenic patients

CGI scale	**Control group F20.0xx (psh) (n=50) M±m**	**Main group F20.0xx, F12.2xx (psh+sc) (n=140) M±m**
CGI-S subscale (Severity of the state)	4.7±0.11	6.21±0.07
CGI-I subscale (improvement of the state)	2.44±0.13	1.7±0.06

Paranoid schizophrenia remission had a nonclassical pattern of morbid manifestations, that combined the picture of two diseases: (1) Withdrawal syndrome due to SC use, which usually proceeded in depressive asthenic and other variants (dysphoric without sleep disorders, dysphoric with predominant sleep disorders, paranoiac [anxious-phobic], hallucinatory-paranoid [delirium-like], polymorphic [mixed]), which we described earlier (Bokhan et al., 2016; Bokhan et al., 2019), and (2) atypical negative (deficit) symptoms as a manifestation of mental endogenous process, which we describe below.

Table 4. SANS indices in schizophrenic patients

No.	**Indicator of the SANS scale**	**Control group F20.0xx psh (n=50) M±m**	**Main group F20.0xx, F12.2xx psh+sc (n=140) M±m**
1	Unchanging Facial Expression	3.57±1.82	1.55±1.62
2	Decreased Spontaneous Movements	2.61±1.76	0.24±1.70
3	Paucity of Expressive Gestures	3.65±1.62	0.25±0.52
4	Poor Eye Contact	2.01±1.34	0.27±0.82
5	Affective Nonresponsivity	3.21±1.54	0.23±0.72

6	Inappropriate Affect	2.05±1.48	3.43±1.43
7	Lack of Vocal Inflections	2.08±1.62	0.22±1.70
8	Global Rating of Affective Flattening	3.21±1.60	1.58±1.62
9	Poverty of Speech	3.78±1.54	1.67±1.49
10	Poverty of Content of Speech	3.34±1.38	1.73±1.36
11	Blocking	2.57±1.32	0.35±1.30
12	Increased Latency Response	3.67±1.26	2.11±1.28
13	Global Rating of Alogia	3.67±1.24	1.62±1.23
14	Grooming and Hygiene	3.45±0.78	2.28±0.35
15	Impersistence at Work or School	2.55±0.66	3.25±0.42
16	Physical Anergia	3.21±0.72	3.5±0.41
17	Global Rating of Abulia - Apathy	2.55±0.74	3.25±0.36
18	Recreational Interests and Activities	4.25±1.35	1.25±0.52
19	Sexual Interest and Activity	3.46±1.29	0.45±0.49
20	Ability to Feel Intimacy and Closeness	3.75±1.28	0.33±0.57
21	Relationships with Friends and Peers	4.38±1.89	1.54±0.72
22	Global Rating of Anhedonia-Asociality	3.75±1.25	1.64±1.72
23	Social Inattentiveness	2.78±0.45	0.12±0.12
24	Inattentiveness During Mental Status Testing	2.44±0.35	0.21±0.15
25	Global Rating of Attention	2.44±0.37	0.19±0.24

Let us consider in detail the manifestations of negative symptoms in patients with PS who are addicted to SC (significantly different from the typical picture of PS): affective flattening or blunting, alogia (poor speech production), abulia-apathy, and anhedonia-asociality, and attention deficit.

A comparison of the indices of negative symptoms in patients of the main group and the control group are presented in Table 4 and in Figures 1 and 2.

It should be noted that at the time of evaluating the negative symptoms, patients with PS addicted to SC were in a state of incomplete medically induced remission "B" (Sereisky, 1939) of endogenous mental disease (i.e., at the stage of transition from inpatient to an outpatient observation network). Pathological psycho-positive symptoms were manifested in them in the form of a trail loop or transient, weakly persistent thought disorders by the type of philosophizing, symbolism, paradox of judgment, slippage, and floridity. Patients in the control group showed a tendency to form unstable, unstructured, and grandiose ideas that could be corrected from the outside. They differed from the main group of patients by a pronounced increase in social and occupational functioning.

Figure 1. Compare SANS total score of basic parameters in patients with schizophrenia

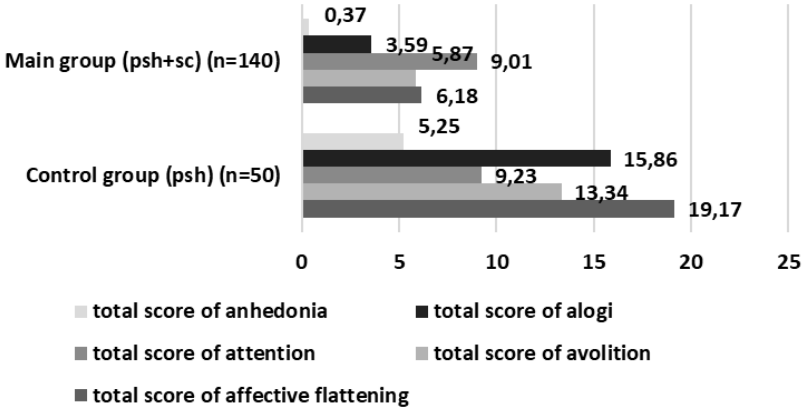
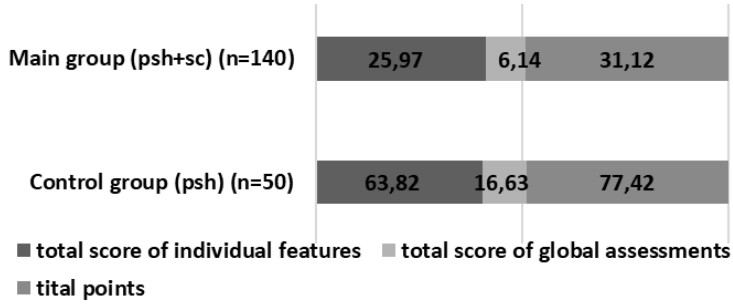


Figure 2. Comparison of the sum of the total SANS scores in schizophrenic patients



Distinctive features in the manifestations of negative syndromes

Pathological psycho-productive symptoms manifested in them as transient, mildly persistent thinking disorders. There was a tendency towards the formation of unsystematic and easily corrected overvalued ideas, which actually led to an increase in their social and occupational functioning.

When comparing individual manifestations of negative syndromes among the different study groups, several differences became apparent. Patients in the main group displayed vivid and expressive motor and facial reactions, and they either lacked or showed only mild affective flattening. This could potentially mislead specialists, leading to these patients being initially excluded from the endogenous nosological cluster in the early stages of their illness. It might also lead to debates regarding the final diagnosis and the withdrawal of patients from psychiatric supervision in a drug network.

A distinctive micro sign of affective flattening in the main group, as compared to the control group, was the catatonic symptom known as the "hood." These patients tended to cover their heads with items like blankets, caps, scarves, bathrobes, hospital robes, or t-shirts. The depth of their experiences could only be estimated through eye contact, which provided insight into the patients' moods and the richness of their emotional experiences, particularly considering their paradoxical emotional reactions to stimuli.

These differences were apparently associated with the previously described grouping of patients, primarily those who were drug addicts and did not suffer from endogenous mental diseases (Bokhan et al., 2018-2022). In contrast to the control group, the main group exhibited pronounced speech productivity due to enhanced associative mobility and flexibility. They quickly formed unifying topics for communication, often centered around Spice, new methods of use and product forms, commercial names, discussions of intoxication episodes, boasting about drug experiences, and feelings of impunity due to the difficulties in diagnosis through urine tests.

Patients of the main group (PS+SC) also tended to have increased communication needs and desire for social activity, which gave them pleasure. They focused on widening the circle of contact with theologically oriented people who were former or current drug addicts, in search of and formation of groups of people who used legal psychostimulating substances (all of these groups were characterized by passivity of leisure). Patients in the main group were characterized by a pronounced desire for coitus and masturbation, which they reported reduced their levels of protopathic and epicritical anxiety. Features distinguishing them from the total population of patients included illegibility, impartiality in choosing a sexual partner, and locations of sexual activity. In addition, they were characterized by organization and attention, which was probably due to the stereotype of addictive behavior and environment and other components that affect attention.

Patients of the second group (F20.0xx, F12.2xx) can be characterized as mixed personalities, mainly schizo-unstable, with hypomanic and paranoid inclusions. Individuals of this category experience an all-encompassing feeling of discomfort due to subjective internal tension, difficulties in forming and maintaining stable social ties, active decision-making and subsequent action, prompted by morbid ideas, with the phenomena of conflict along with friendliness, loss of contact with reality, which determines the ideas of the overvalued and delusional character (Table 3).

The predominant syndrome that was common among patients in both groups, those suffering from PS, was avolition-apathy. This syndrome did not exhibit significant progression, which could potentially lead specialists unfamiliar with this patient category to suspect an endogenous mental illness. The behavioral motives of these patients were oriented towards addictive, theological, and mystifying drives. They often induced those in their close circles and involved them in morbid ideation.

Themes that were conditionally socially acceptable included religious missions, providing comprehensive assistance and guardianship to strangers, recruitment into theological and other groups, mysticism, and a paradoxical passion for tea and coffee. Smoking, especially electronic cigarettes or devices that generated nicotine vapor, was also common. On the flip side, there was an antisocial orientation that included the pursuit of drug addiction, the formation of drug-addicted groups, and engagement in offensive actions.

When assessing negative symptoms, it was noted that these symptoms were less pronounced in schizophrenic patients dependent on spices than in the control group (Fig. 2).

The atypical picture of the negative symptoms of patients with PS addicted to SC reflects the fact that in both groups we used a similar therapy, which equally affected the deficit symptoms. To relieve psychotic symptoms, patients of both groups received combinations of injection forms of conventional antipsychotics (haloperidol 7.5 ± 0.94 mg and chlorpromazine 37.5 ± 4.73 mg, haloperidol 7.5 ± 0.89 mg and droperidol 10 ± 0.91 mg). With long-term therapy, there were combinations of prolonged typical antipsychotics (haloperidol 75 ± 9.45 mg, fluphenazine 37.5 ± 4.70 mg, zuclopenthixol 300 ± 37.80 mg) and atypical (clozapine in doses of 450 ± 56.70 and 300 ± 37,72 mg, risperidone in dosages of 3 ± 0.38 mg and 5 ± 0.38 mg). The prescribed dosages did not exceed the highest therapeutic ones.

This study found that in the treatment of negative symptoms of respondents and the prevention of hospitalism, the method of managing patients with the above-described pharmacotherapy, as well as the involvement of patients into antidrug groups (community of anonymous drug addicts or anonymous alcoholics, religious groups of various kinds, “vape” smoking clubs, tea lovers’ clubs), proved effective.

Conclusion

Intoxication induced by synthetic cannabinoids can trigger psychotic episodes and serve as a catalyst for the onset of schizophrenia. The misuse of synthetic cannabinoids initiates the development of schizophrenic psychotic states, which can manifest in four different ways: delirious, schizophrenic, schizophrenic with pseudohallucinatory, and schizophrenic with delirium.

The personality traits of individuals addicted to synthetic cannabinoids often exhibit a prevalence of antisocial, schizoid, and paranoid characteristics. The abuse of synthetic cannabinoids tends to alter the personality of the user towards a more schizophrenic profile. These patients, who have personality disorders and are dependent on synthetic cannabinoids, display distinctive behavioral patterns that distinguish them from typical drug addicts. These patterns include disorganization, conflict, unpredictability, spontaneity, thoughtless actions, impulsivity, and non-conformity. These traits can lead to social maladaptation and pose a social danger.

In schizophrenic patients who regularly use drugs, there are stigmatizing signs of endogenous mental disorders, such as mild avolition-apathy and the catatonic symptom known as the "hood." Unique characteristics include paradoxical and expressive emotions, visual and speech engagement, a desire to establish interpersonal relationships, satisfaction of desires, and anxiety related to expectations.

In the treatment of exogenous psychoses, combining typical antipsychotics and tranquilizers has been effective. For managing negative symptoms, a combination of typical and atypical antipsychotics, along with patient involvement in socially acceptable groups for addictive behavior, has shown promise.

Conflict of Interest

The authors declare that there are no potential conflicts of interest in connection with the publication of this article.

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Ethics

The work complies with the ethical standards of the Helsinki Declaration of the WMA (protocol of the meeting of the Ethics Committee of Mental Health Research Institute no. 114 of October 22, 2018; protocol of the meeting of the Ethics Committee of Mental Health Research Institute no. 133 of June 19, 2020 (no. 133/4. 2020)).

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