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Clinical characteristics of synthetic cannabinoid-induced psychotic disorders: a single-center analysis of hospitalized patients

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ABSTRACT

This study was designed to evaluate synthetic cannabinoid (SC)-induced psychotic disorders in terms of their structure and clinical characteristics among hospitalized patients in Russia. It was a longitudinal, observational cohort study which included a total of 46 male patients who underwent the inpatient treatment in the intensive care unit or emergency department due to the SC-induced psychoses. Data on sociodemographic and disease-related characteristics, psychometric assessment scales obtained in face-to-face interviews, were recorded in all patients. The duration of catamnestic follow-up period was 2 years, with the major focus on manifestation of the schizophrenic process. Mean (SD) age of the patients with psychotic disorders induced by the SC use was 23.2 (3.5) years. Among 46 patients, 29 (63%) were SC-dependent and 17 (37%) were diagnosed with SC abuse. Average age at onset was 16.4 for psychoactive substances and 19.7 years for SC use. Marijuana was the most common first used substance. Based on our observations, we identified four clinical variants of the SC-induced psychoses. Our findings revealed that psychotic disorders are typical for the SC intoxication and most commonly influence young adults. Based on our observations, we identified four clinical variants of the SC-induced psychoses and revealed the signs which may indicate them. This study emphasizes the role of appropriate psychiatric management of SC-induced psychoses, since often only catamnestic long-term follow-up enables clinicians to determine the correct diagnosis and reveal the manifestation of the schizophrenic process.

KEYWORDS

Synthetic cannabinoid; psychosis; substance-induced psychosis; cannabinoid use disorder; withdrawal; addiction; differential diagnosis; psychopathology; patients

Introduction

Since the mid-2000s, herbal mixtures (generic name: Spice, K2) laced with new psychoactive substances (NPS), known as synthetic cannabinoids (SCs) appeared in the recreational drug scene[1]. SCs were first marketed as legal alternatives to natural cannabis products, but in many ways they are different. SCs are potent cannabinoid receptor agonists, which produce effects similar to those of delta-9-tetrahydrocannabinol and play a predominant role in the rapidly evolving "legal highs" market. SCs are 2–100 times more potent than THC and can induce severe side effects and even death, but are often chosen over illegal cannabis as they do not turn up in traditional urine drug screenings[1]. SCs continue to be the largest group of new substances monitored by the European Monitoring Centre for Drugs and Drug Addiction (MCDDA) and are becoming increasingly chemically diverse, with 179 detected since 2008—including 10 reported in 2017[2]. In Russia, first cases of SC abuse were registered in 2011, with a subsequent exponential growth in SC use reaching epidemic proportions[3].

Cannabis intoxication is associated with anxiety[4] and transient psychosis-like or psychotomimetic effects that include depersonalization, de-realization, ideas of reference, grandiose and paranoid delusions, flight of ideas, disorganized thinking, and auditory and visual hallucinations[5]. Such effects have been increasingly reported with high THC-containing strains of cannabis and SCs[6]. SCs, sold as "spice," "K2," and "kush," have a mixture of constituents that are generally CB1R and CB2R full agonists[7]. Furthermore, it may be the case that some SCs might exhibit pharmacologically relevant affinity for psychosis-associated receptors, including D2, 5-HT2A, or NMDA[8].

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Given the biotransformation of many SCs to active metabolites[9], even if the parent drugs themselves do not interact with these receptors, it may be the case that a generated metabolite would do so. This pharmacologic profile of SCs confers their much higher risk of inducing acute psychosis, disorganized behavior, and even catatonic-like reactions[10]. A thorough differential diagnosis of possible causes of psychosis is necessary to avoid the mistaken attribution of psychosis to a primary endogenous psychotic episode. In this regard, catamnestic long-term follow-up would be useful to establish the correct diagnosis.

Despite the high prevalence rates of SC-induced psychotic disorders, limited data are available on their clinical characteristics, and classification of such disorders is still a controversial issue. This study was therefore designed to evaluate SC-induced psychotic disorders in terms of their structure and clinical characteristics among hospitalized patients in Russia.

Material and methods

Study population

A total of 46 male patients diagnosed with psychotic disorder induced by the use of SCs according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5), diagnosis criteria who were hospitalized at the intensive care unit or emergency department of the Moscow Research and Practical Centre on Addictions of the Moscow Department of Healthcare, were included in this longitudinal, observational cohort study. Age 16–60 years, being literate, a diagnosis of SC dependence (F12.2, according to The International Classification of Diseases, 10th revision (ICD-10), or 304.30, Cannabis Use Disorder, Moderate to Severe, according to DSM-5) or SC abuse (F12.1, according to ICD-10, or 305.20, Cannabis Use Disorder, Mild, according to DSM-5), positive urine test for SC at time of entry to the clinic and lack of previous diagnosis of any psychiatric disorder were the inclusion criteria. Subjects were excluded if they had significant physical illnesses, such as cerebrovascular disease, cardiovascular disease, or stroke which had been previously diagnosed by physicians. The participants who declined to participate or otherwise did not participate were not disadvantaged in any way.

Written informed consent was obtained from each subject following a detailed explanation of the objectives and protocol of the study, which was conducted in accordance with the ethical principles stated in the Declaration of Helsinki and approved by the Ethics Committee of the Moscow Research and Practical Centre on Addictions of the Moscow Department of Healthcare.

Assessments

A self-designed structured questionnaire that collected information on sociodemographic and disease-related characteristics was administered in face-to-face interviews by the qualified and well-trained research psychiatrists. Sociodemographic variables included age, ethnicity, education, employment, and marital status. Disease-related characteristics included: family history, age at onset, detailed history of substance use (type, usage pattern, main route, source, cause, sites of administration, dosage) with special attention to SC, disease duration, number and history of hospitalizations. Urinalysis for SC metabolites was performed in all patients at day 1. Laboratory analysis to confirm the use of SC included SC screening of urine samples with gas chromatography and mass spectrometry. Psychometric assessments including Brief Psychiatric Rating Scale (BPRS), Positive and Negative Syndrome Scale (PANSS) and Hamilton Anxiety Rating Scale (HAM-A) were recorded in all patients.

Brief psychiatric rating scale

This scale was developed by Overall and Gorham to assess the severity and change of psychotic and some depressive symptoms in schizophrenia and other psychotic disorders. The BPRS assesses the level of 18 symptom constructs, each being rated for severity ranging from 1 (not present) to 7 (extremely severe). It is based on the clinician's interview with the patient and observations of the patient's behavior. The patient's family can also provide the behavior report. Factor analysis results signal different symptom clusters in this

scale: the set of negative symptoms (emotional withdrawal, blunted affect, and motor retardation) and the set of positive symptoms (conceptual disorganization, hallucinations, and unusual though content). Scores obtained from the BPRS rating do not separate negative schizophrenia cases from positive schizophrenia cases; rather they are used to establish both negative and positive symptoms seen in a given case.

Positive and negative syndrome scale

Based on two established psychiatric rating systems, the 30-item PANSS was conceived as an operationalized, drug-sensitive instrument that provides balanced representation of positive and negative symptoms and gauges their relationship to one another and to global psychopathology. Of the 30 items, 7 are positive symptoms, 7 are negative symptoms, and 16 are general psychopathology symptoms. Symptom severity for each item is rated according to which anchoring points in the 7-point scale (1 = absent; 7 = extreme) best describe the presentation of the symptom.

Hamilton anxiety rating scale

The HAM-A is a widely used and well-validated tool for measuring the severity of a patient's anxiety. This scale consists of 14 items designed to establish anxiety states and distribution of symptoms, and to measure change in severity.

Follow-up

The duration of catamnestic follow-up period was 2 years. The major focus of the follow-up study was manifestation of the schizophrenic process. The research psychiatrists with at least 10-year experience in a psychiatric unit who performed the initial screenings conducted the face-to-face interviews and collected all diagnostic and medication information at every follow-up visit. All of the patients had been told that they could contact the research psychiatrists anytime for questions and to provide progress reports on their medical conditions during the subsequent 2 years.

Statistical analysis

Descriptive analysis was conducted for the sociodemographic and disease-related characteristics, psychotic symptoms, depressive symptoms, and anxiety symptoms of the study participants with the estimated means and proportions. Data were expressed as "mean" and "percent (%)" where appropriate. $P < 0.05$ was considered statistically significant.

Results

Data on sociodemographic and disease-related characteristics are presented in Table 1. Mean (SD) age of the patients with psychotic disorders induced by the SC use was 23.2 (3.5) years. The majority (63%) of patients had secondary or upper-secondary education, 32.6% of them were university students and only 4.4% had higher education. Only 10.9% of patients held jobs, whereas 89.1% were unemployed. The majority of patients were single and living with their family. Among 46 patients, 29 (63%) were SC-dependent (F12.2, according to ICD-10, or 304.30, according to DSM-5) and 17 (37%) were diagnosed with SC abuse (F12.1, according to ICD-10, or 305.20, according to DSM-5).

Average age at onset was 16.4 years for psychoactive substances and 19.7 years for SC use. Marijuana was the most common substance first

Table 1. Sociodemographic and disease-related characteristics

Characteristics	Patients (n = 46)
Age (years)	
Mean (SD)	23.2 (3.5)
Education, n (%)	
Secondary or Upper-secondary	29 (63.0)
University student	15 (32.6)
Higher education	2 (4.4)
Employment status, n (%)	
Hold a job	5 (10.9)
Unemployed	41 (89.1)
Marital status n (%)	
Married	3 (6.5)
Single	42 (91.3)
Cohabiting with, n (%)	
Family	40 (87)
Alone	6 (13)
Diagnosis, n (%)	
SC dependence	29 (63)
SC abuse	17 (37)
Age at disease onset (years), mean	
Psychoactive substances	16.4
SCs	19.7
Substance first used, n (%)	
Marijuana	27 (58.7)
Alcohol	16 (34.8)
SC	3 (6.5)

used (in 27 cases), whereas 16 patients started their experimenting with psychoactive substances with alcohol and only 3 started with SC. There was no evidence to suggest that patients were dependent from any other psychoactive substances except SC (cannabinoids, alcohol, psychostimulants, opioids, etc.). None of 46 patients was previously followed up by the psychiatrist and none of them was diagnosed with a psychiatric disorder.

Since it was an inclusion criterion, all 46 patients were diagnosed with psychotic disorder induced by the use of SCs by the research psychiatrists. Data on BPRS, PANSS, and HAM-A scores are presented in Table 2.

SC dependence development and disease course followed the established patterns relevant to the dependence syndrome. Duration of SC use in the targeted cohort of patients ranged from 5 months to 2 years. An increase in tolerance level was evident in all patients and manifested both in the increased frequency of drug use (from episodic drug consumption to daily SC consumption followed by repeated use of SC per day) and in the increased drug dosage (from a certain part of pack to several packs per day). Duration of the withdrawal syndrome development ranged from 6 to 18 months of systematic SC use.

The withdrawal syndrome development was progressive and started with an obsessive sensation as if something is lacking, which was accompanied with general discomfort and growing internal stress. In 1.5–2 days vegetative symptoms appeared: nausea (often with vomiting), sweating, episodes of increases in cardiac rhythm, and increased blood pressure. Against this background, patients experienced the growing anxiety and, commonly, muscle twitches in the extremities. The behavior of patients was aimed at fulfilling their growing desire and at drug search. The withdrawal syndrome duration ranged from 5 to 9 days.

Table 2. BPRS, PANSS and HAM-A scores.

Psychometric scale	Patients (n = 46)
BPRS score, mean	38.7
PANSS overall, mean	99.8
PANSS positive, mean	29.5
PANSS negative, mean	16.8
HAM-A score, mean	19.7

Overall, four (8.7%) patients had a psychotic disorder in the structure of withdrawal syndrome: at the height of the growing anxiety, by day 3 of abstinence, against the backdrop of insomnia, patients experienced visual hallucinations (most commonly terrifying).[a] Psychopathologically this disorder followed the structure of delirium. Due to the small number of cases it was impossible to exclude other exogenous factors as possible reasons for the development of delirium symptoms. These cases were not included in the psychopathological analysis.

Thus, it is possible to make a preliminary assumption that delirium may occur as the SC withdrawal syndrome complication, but its development mechanism remains unclear and requires further study.

Four clinical variants of SC-induced psychoses were identified (see Table 3).

1. *Psychosis with predominant delirium symptoms* (11 patients—27%). Against the backdrop of specific classical triad of delirium (includes disorientation to date and place with orientation to person, psychomotor agitation or anxiety and vivid hallucinations, most commonly—visual), the structure of the psychotic disorder included tactile hallucinations and auditory verbal hallucinations. Specific feature of the psychosis is the appearance of the elements of Kandinsky–Clerambault's syndrome: delusion of influence and automatisms. In most cases delusional ideas of influence were interwoven with persecutory delusion. The average duration of the psychosis was about 10–14 days,

[a]One patient told: "I've seen an unknown man who came to me. He said that he had searched me a lot to kill me. Then he said that he wanted to put me in prison and instantly transformed into the police officer. He interrogated me and bound my wrists. I ran away as I was real scared that he could kill me. I ran, shouted, and called for help. Nonetheless he always caught and handcuffed me …"

Another patient recounts: "I've seen cockroaches coming out of the woodwork. At first I got scared, but then I began to look at them. I wondered where they were crawling to. Then blue mice appeared. Mice were angry and tried to bite me. I realized that something bad was going on and felt the intense fear. I saw that I was not at my home and tried to understand where I was, but I was afraid to move anywhere. I began to shout and call for help. I heard my voice inside my head, it sounded hollow, much as it passed through the tube. I realized that no one will hear me, the history is finished, that it's all over. Blue mice will eat me…"

For ethical reasons slang was substituted by literary language.

Table 3. Clinical variants of SC-induced psychoses identified and their description

Variant of SC-induced psychosis	Description
Psychosis with predominant delirium symptoms (n =11)	Against the backdrop of specific classical triad of delirium, the psychotic disorder included tactile hallucinations and auditory verbal hallucinations. Key specific feature is the appearance of the elements of Kandinsky-Clerambault's syndrome: delusion of influence and automatisms. Patients presented delusional ideas that they were deprived of their will, their actions were imposed from outside, someone was wiretapping them through special equipment (as a rule, it were various intelligence agencies); some of the patients exhibited thought broadcasting. Subsequently, the delusional structure expanded in some patients: they told that someone was hunting or persecuting them.
Psychosis with predominant hallucinatory symptoms (n =8)	After a short prodromal period filled with anxiety, irrational fear and psychic hyperaesthesia, patients experienced acute verbal hallucinosis. Hallucinations were scenic; usually patients heard threatening monologues or dialogues from somewhere behind the wall or behind the back. The plot of hallucinations was generally narrow and was usually associated with the patient's fear of coming in view of the law enforcement agencies due to the illicit use of psychoactive substances or their search. Hallucinations were accompanied by the sensual delusion with the same plot. Patients presented specific behavior: they responded to voices, tried to enter into dialogue with them, escape or hide from voices and in some cases showed the aggression toward the perceived enemies.
Psychosis with predominant affective-delusional symptoms (n =9)	Against the backdrop of acutely developed sensation of fear, patients presented the delusional ideas of interpretation and reference followed by persecutory delusion. At manifestation, delusion became multi-thematic: persecutory delusion was interwoven with the delusional ideas of philosophical and esoteric nature. For instance, patients told that their consciousness expanded, its boundaries blurred and they understood how the world was created. Most of the patients began to associate themselves with the centre of the Universe, said that they explored all the mysteries of creation. Some of the patients expressed manioform statements. A patient said: " … suddenly I understood everything, so immediately. And everything became clear: I am navel … " Another patient recounts: " … I can become the president of any country", "there are lots (an entire army) of people working for me, they don't even know about that … , but they enrich me and provide me with all the benefits: women, money, food … ", "I'm a very rich person; I could buy every physician a car. Or a house … Do you want a house?" * For ethical reasons slang was substituted by literary language.
Psychosis with predominant mental automatism (n =14)	Against the backdrop of emotional tension, severe anxiety and confusion, patients shortly presented the delusional mood, agitation and delusional persecutory ideas, with subsequent mental, motor and, less frequently, senestopathic automatisms. In most cases it was thought broadcasting, thought insertion or thought withdrawal, "made emotions" and speech automatisms. Then the Kandinsky-Clerambault's syndrome developed with verbal hallucinations, delusion of influence and persecutory delusion, as well as automatisms.

whereas some elements of automatisms remained up to 4–6 weeks.

2. *Psychosis with predominant hallucinatory symptoms* (8 patients—19%). After a short (from several hours to 1 day) prodromal period filled with anxiety, irrational fear and psychic hyperesthesia, patients experienced acute verbal hallucinosis. Hallucinations were scenic; usually patients heard threatening monologues or dialogs from somewhere behind the wall or behind the back. The plot of hallucinations was generally narrow and was usually associated with the patient's fear of coming in view of the law enforcement agencies due to the illicit use of psychoactive substances or their search. Hallucinations were accompanied by the sensual delusion with the same plot. Patients presented specific behavior: they responded to voices, tried to enter into dialog with them, escape or hide from voices and in some cases showed aggression towards the perceived enemies.
3. *Psychosis with predominant affective-delusional symptoms* (9 patients—21%). Against the backdrop of acutely developed sensation of fear, patients presented the delusional ideas of interpretation and reference followed by persecutory delusion. However, in the beginning of psychosis patients showed motor retardation (they described it as "getting stuck"), very commonly with the elements of catatonia, which had drastically changed to motor agitation. At manifestation, delusion became multi-thematic: persecutory delusion was interwoven with the delusional ideas of philosophical and esoteric nature. For instance, patients told that their consciousness expanded, its boundaries blurred and they understood how the world was created. Most of the patients began to associate themselves with the center of the Universe, said that they explored all the mysteries of creation. These "insights" were accompanied calm feelings and even euphoria. However, it was impossible to gain a coherent explanation from any of the patients. The narrative was mainly uncertain, with lengthy reasoning and sharp transitions from one topic to another.
4. *Psychosis with predominant mental automatism* (14 patients—33%). Against the backdrop of emotional tension, severe anxiety and confusion, patients shortly presented the delusional mood, agitation and delusional persecutory ideas, with

subsequent mental, motor and, less frequently, senestopathic automatisms. In most cases it was thought broadcasting, thought insertion or thought withdrawal, "made emotions" and speech automatisms. Then the Kandinsky–Clerambault's syndrome developed with verbal hallucinations, delusion of influence and persecutory delusion, as well as automatisms.

After a gradual onset the average duration of the psychosis ranged from 1 to 1.5 months. There were fluctuations in the emotional sphere from mild hypomania to anxious–depressive symptoms. In addition, during the next 3–4 months patients experienced short term psychotic symptoms which required medical intervention.

Catamnestic follow-up revealed that manifestation of the schizophrenic process was present in 17% of cases (8 patients of 46). This is confirmed mainly by the patient's condition after the psychosis. These patients presented a loss of interest to communication with the environment, loss of energetic potential (as described by Conrad[11]), loss of desires and interests, unwillingness or even inability to work. For instance, one patient who had a psychosis had changed after he had returned home. He became silent, stayed at bed for the long time, disregarded the daily morning procedures (teeth cleaning, combing), stopped caring about the cleanliness of clothes, and stopped his education. Another patient stopped talking to his parents, began to show irritation when someone asked him about something, avoided his friends, slept a lot, complained of severe fatigue and unwillingness to do anything. However, he was physically healthy. At that period patients revealed no severe specific schizophrenic thought disorders. All patients presented the symptoms of poor concentration, short attention and memory problems, reflecting the cognitive functions disorder. As a whole, we considered such conditions to be the negative symptoms of schizophrenia.

Discussion

Our findings revealed that SC-induced psychoses influence young adults. Consistent with the statement that the majority of first-time SC users are experienced marijuana smokers, SC was used following other transitional substances rather than as a first substance in majority of our patients, with cannabis being the most popular antecedent substance. SC was not the first substance used in the majority of our patients, and it had been preceded by use of other transitional substances, such as cannabis in most cases.

Despite the exogenous nature, structurally SC-induced psychoses are often endoformic, even the delirium is atypical and includes the elements of Kandinsky-Clerambault's syndrome. Psychopathologically hallucinations and delusions dominate in the clinical presentation of the psychoses (with predominant hallucinatory symptoms or affective paranoid symptoms—up to 40% cumulatively). It is important to point out that the proportion of psychoses with Kandinsky–Clerambault's syndrome is also high at about 33%. Substance-induced psychoses are often associated with the manifestation of schizophrenic process (in our study it was revealed in 17% of cases). It is extremely difficult to create a differential diagnosis between such psychotic disorders and primary endogenous psychotic episode. In such cases the appearance of deficit symptoms specific for schizophrenia becomes crucial.

Based on our observations, psychoses developing in the structure of SC intoxication have the following nonspecific characteristics: (1) structurally such psychoses are often endoformic (for instance, verbal hallucinations, kinesthetic automatisms, delusion of grandeur or influence can be present); (2) these psychoses are usually long-term and last from 10–14 days to 4–6 weeks, depending on the psychosis' structure; (3) such psychoses usually end gradually with the persistence of astheno-depressive symptoms and cognitive disorders for 4–8 weeks and more.

The substance-induced psychoses can be diagnosed in the following cases: (1) the plot of psychosis is closely associated with the illicit drugs (i.e., it is primitive, simple, and understandable, with no fantasies, pretentiousness and absurdity of psychotic experiences specific for schizophrenic psychoses); (2) patients become critical to these conditions and show no signs of

emotional and volitional reduction or other specific signs of schizophrenia.

Conclusion

Our findings revealed that psychotic disorders are typical for the SC intoxication and most commonly influence young adults. Based on our observations, we identified four clinical variants of the SC-induced psychoses and revealed the signs which may indicate them. Our study emphasizes the role of appropriate psychiatric management of SC-induced psychoses, since often only catamnestic long-term follow-up enables clinicians to determine the correct diagnosis and reveal the manifestation of the schizophrenic process. Hence, in such cases cooperation between the psychiatrists and addiction psychiatrists would be the optimal tactic. Our findings also highlight the need to develop prevention and treatment strategies for psychiatric symptoms, and psychotic symptoms in particular, across the SC users.

Declaration of interest statement

The authors declare that there is no conflict of interest regarding the publication of this article.

Ethics approval and consent to participate

Written informed consent was obtained from each subject following a detailed explanation of the objectives and protocol of the study, which was conducted in accordance with the ethical principles stated in the Declaration of Helsinki and approved by the Ethics Committee of the Moscow Research and Practical Centre on Addictions of the Moscow Department of Healthcare.

Authors' contributions

All authors made substantial contributions to conception and design, acquisition of data, and analysis and interpretation of data; all authors participated in drafting the article and revising it critically for important intellectual content; and all authors gave final approval of the version to be submitted.

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