CASE REPORT

Recurrent Psychotic Episodes Induced by Synthetic Cathinones in a Monozygotic Twin with Drug Addiction: A Case Report

Рекуррентные психотические эпизоды вследствие употребления синтетических катинонов: клинический случай монозиготных близнецов

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Case report

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ABSTRACT

We have described a clinical case of psychotic disorder induced by synthetic cathinones in one drug-addicted monozygotic twin. This clinical case is unique, because it offers the opportunity to observe many features of the singularity of the dependence syndrome in twin brothers: drug choice; motivation to use drugs; and the development of multiple, long-lasting psychoses in one of the brothers. We pursued a twelve-month follow-up of this case. The case substantiates the paucity of a fundamental understanding of mental disorders and highlights the importance of further research into the clinical features of drug-induced psychoses, especially those induced by novel psychoactive substances such as synthetic cathinones.

АННОТАЦИЯ

В статье описан случай развития психотического расстройства у одного из монозиготных близнецов, оба из которых имеют сформированный синдром зависимости от нескольких психоактивных веществ. Этот случай предоставляет редкую возможность наблюдать индивидуальные особенности в процессе параллельного формирования синдрома зависимости у близнецов (наркотик выбора, мотивация к употреблению) и дальнейшее развитие двух затяжных психозов только у одного из братьев. В статье описаны и проанализированы результаты 12-месячного наблюдения. Данный случай демонстрирует нехватку фундаментального понимания механизмов развития психических расстройств и подчеркивает важность дальнейшего изучения психозов, связанных с употреблением психоактивных веществ, в частности синтетических катинонов.

Keywords: *synthetic cathinones; "bath salts"; psychotic disorders; twins; case report*

Ключевые слова: *синтетические катиноны; «соли для ванн»; психотические расстройства; близнецы; история болезни*

INTRODUCTION

Synthetic cathinones (Scaths) are modern psychoactive substances which are synthetic analogues of cathinone. Cathinone is an alkaloid found in the leaves of *Catha edulis* (Khat). Scaths have psychostimulant, euphorigenic, and empathogenic action. The actions spectrum is similar to that of "traditional" drugs, such as methamphetamine, amphetamine, and methylenedioxymethamphetamine [1–3]. In Russia, α-pyrrolidinopentiophenone (α-PVP) and 4-methylenemethcathinone (mephedrone) are the most prevalent Scaths [4, 5]. In comparison with traditional stimulants, they (a) cause a stronger reinforcement system activation, which leads to severe craving and higher overdose risk, and (b) are capable of inducing psychoses, including those with schizophreniform clinical presentation.

Accordingly, Scath-induced psychoses are often hard to diagnose, as they are similar to schizophrenia manifestations and sometimes may trigger mental disorders. In the case of comorbidity between dependence syndrome and schizophrenia both disorders have an altered clinical picture. Clinical presentation and the course of the disease in comorbid schizophrenia with modern psychoactive substances addiction are currently the object of rigorous research [6–9].

Schizophrenia is known to show an inheritance rate of up to 50%; in monozygotic twins, the heritability rate of schizophrenia can attain 79% [10]. A meta-analysis by Murrie et al. (2020) arrived at a 25% rate of schizophrenia development (CI 18%–35%) during a four-year follow-up period after drug-associated psychosis manifestation [11]. The study found that the highest risk of schizophrenia development was associated with cannabinoid-associated psychoses (34%; CI 25%–46%), while hallucinogens and amphetamine constitute a slightly lower risk, 26% (CI 14%–43%) and 22% (CI 14%–34%), respectively [11]. Thus, schizophrenia and drug-induced psychoses can no longer be considered antithetical conditions. Today, their concepts are frequently seen as overlapping, providing opportunities for research into the etiology and pathophysiology of mental disorders. Not with standing the aforesaid differential diagnosis of psychoses in psychoactive substance users remains relevant for us.

We present a clinical case of a psychotic disorder induced by synthetic cathinones in a drug-addicted monozygotic twin. This clinical case is unique, because it offers the opportunity to observe many of the features that constitute the singularity of the dependence syndrome in twin brothers, from the first experience to the development of multiple, long-lasting psychoses in one of the brothers that we followed-up for 12 months.

Written informed consent was obtained from both brothers after 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 I.M. Sechenov First Moscow State Medical University (Sechenovskiy University).

PATIENT INFORMATION AND CLINICAL FINDINGS

Patient M, 26 years old, presented himself at the private addiction clinic in Moscow accompanied by his parents and brother B.

Patient M and his monozygotic brother B had used alpha-PVP and mephedrone for 4 months without interruption before the admission of M. Ten days before admission, M became aloof and irritable, professed to be "tired of drugs", and stopped using them. On the admission date, he started scrutinizing cars for special signs on license plates and "realized" that he had to depart for the USA in order to become a senator. He was found in such a condition in front of the roof door at his office building, where he was trying to "catch a helicopter to reach the USA".

During the interview, M was well oriented in time, place, and his own personality, although alert, strained, suspicious, and taciturn. According to the information from his relatives, during the day M behaved excitedly, was talkative, and claimed to have special abilities for which he could be persecuted. M did not argue with his parents when they reported on his condition, but he seemed tense and upset. The patient himself answered questions in a monosyllabic manner, sitting with his fists clenched. He kept his ruminations secret and said nothing about his supposed persecutors. Despite the apparent psychic tension, M easily agreed to stay in the hospital. He was admitted with the primary diagnosis F15.5 "Mental and behavioral disorders due to use of other stimulants, including caffeine: psychotic disorder".

Meanwhile B seemed anxious during the entirety of M's interview. At first B declined to answer when asked about his worries, but shortly afterwards he confessed to having consumed the same drugs as M in the last months and was now afraid to develop psychosis too. At that moment, B had been abstinent for a week and displayed no signs of developing psychosis. Therefore, B agreed with his parents

to submit to blood testing for drugs weekly for the next month and that if he tested positive, he would be placed in the rehabilitation center.

Life history

Family history was related by both brothers during two parallel interviews. The paternal grandmother and paternal grandfather of the patient had suffered from alcohol use and the second female cousin had an opioid dependence. The parents did not suffer from any psychiatric disorders or substance misuse. There is no family history of mental disorders.

Since childhood, M and B had lived together and been always active and physical. The brothers were brought up by their grandparents on the mother's side, while the parents were busy with their jobs. The development of M and B was simultaneous and in line with their age. At the age of five, the brothers started to show a divergence in character: while M started to turn into a shy and introverted individual, B began to develop sociability and gregariousness. In 2000, at the age of seven, the brothers began school. At school, M kept his distance from peers and stuck to his brother; M made efforts in his studies. On the contrary, B became livelier and leaned towards copying off from M rather than studying himself. At the age of 13, the brothers' behavior changed. M became more aggressive, having turned into a frequent participant in school fights. Although B's behavior was far from perfect, B got into trouble less frequently because he was more careful and slyer.

At the age of 13, the brothers tried beer and cannabinoids (bulk weed) for the first time. The effect of cannabinoid use did not appeal to the brothers: hence, they never again used these substances until their first year at university. Alcohol intake did not appeal to the brothers after the first try either. However, their attitude changed later. By the age of 14, the brothers were systematic alcohol consumers. Both drank up to 0.5 liter of hard liquor (vodka) every week. Both brothers graduated from school (full 11-grade course) with poor marks, but M having higher marks than B, and entered university having chosen the same major. On the first university year, M and B got closer to rich peers and began to attend parties at which substance use was common. In this company, the brothers felt embarrassed of their inferior financial status. To blend into the group, the brothers started consuming drugs as well. Accordingly, from the age of 18, M has complemented alcohol with hashish and, by graduation from university, amphetamine. B, however, chose stimulants initially. M liked the feeling of being aloof, indifferent, and relaxed, while B gained the feeling of his own might, overcame his fear and shyness in social interactions, and found it easier to complete academic and work tasks under the influence of amphetamine.

After a year of drug use, the brothers found out that it became harder to stay sober even for a few days. During the sober days, they experienced deep melancholy, mixed with anxiety or agitation and a desperate need for drugs. To avoid feeling that way, the brothers began taking drugs daily. Three years later, at the age of 21, patient M's tolerance for cannabinoids had increased by up to 4–5 grams of hashish and 2 grams of amphetamine per day. Meanwhile B preferred to use amphetamine only, and his tolerance stayed at a similar level of 2 grams per day. M became more aloof, spending time in solitary reading and playing guitar. At the age of 23 (in 2017), the brothers tried Scath (mephedrone) for the first time. The effect of mephedrone highly appealed to M; he experienced euphoria that was stronger than that caused by amphetamine. During the following year, M's drug use turned severe, his craving for mephedrone became irresistible: the patient sniffed mephedrone every 30 minutes and began to experience difficulties with nasal breathing, which led to M's transition to smoking. B traveled a similar course, with acute craving, and constant mephedrone consumption at high doses, but he quit amphetamines. During this period, the brothers kept smoking cannabinoids a few days a week to "slowdown" after stimulants use.

At the age of 24 (in 2019), M's mental condition changed dramatically. He became taciturn and detached and was telling his brother about his constant fear of persecution by special services and criminal organizations. M was also complaining of racing thoughts and difficulties thinking. Despite such a dramatic turn in his condition, M continued his substance use (either did B). Three months later, M developed visual, tactile, and verbal hallucinations: he could visualize his former teachers demanding that he confess to having committed a murder. Concurrently, M started hearing threatening voices that were "dropping into his head directly". Experiencing extreme fear, M began to bang his head against the wall, which led to the loss of consciousness. M was found unconscious by his girlfriend, who lived with him. He was taken to the neurology unit of a city hospital by ambulance. In the city hospital, M did not tell the doctors about his fears. After having been

discharged from the city hospital, M was sent by his parents to the rehabilitation center for patients with addictive disorders. One week later, M escaped from the center, having taken no warm clothing despite the winter weather. After having wandered in the city for several hours, M froze up and came back to the rehabilitation center. Upon coming back, M stated that he had seen a "dream" in which "the real owners of the drugs that he had lost had come to him and explained everything that had been going on". He described that condition as a journey to the parallel universe, where he had been shown "the truth". M told the staff of the rehabilitation center that he was "the chosen one" as he had "special" blood flowing in his veins. According to the patient, "anything" could be made of his "special" blood. He also talked about his fear of being killed by unknown powers and feeling that someone is manipulating his thoughts. M claimed to see around him special signs that were passing him messages. Seeing that, M's parents committed him to a psychiatrist, who initiated a treatment with second-generation antipsychotics. Upon treatment, M's condition improved and psychosis retreated. M adhered to maintenance therapy and abstained from recreational drugs. During the same period, B also ceased drug use without professional assistance. On the third month of sobriety M found a job as a sales manager in an airline company, lived alone in a rental apartment, and was socially active. After seven months of maintenance therapy M decided to give up treatment, as he "felt fine and got overweight because of therapy". Afterwards, M experienced intense craving for Scaths and during the New Year's holidays (in 2020) resumed consumption. B did as well. The brothers had been using Scaths four months straight before M's admission. They reported that daily consumption was approaching upward of 10 grams of mephedrone or 7 grams of alpha-PVP. Table 1 provides a summarized timeline of events.

DIAGNOSTIC ASSESSMENT

During neurological examination hands tremor was observed, and during physical examination tachycardia (96 beats per minute) was discovered.

A series of routine tests were administered upon the patient's admission: in blood tests, ECG and EEG were normal. Toxicological blood test (gas chromatography-mass spectrometry) did not show the presence of any substances (since it had been 10 days since the last drug intake according to patient report).

In terms of psychiatric assessment, we performed a psychopathological differentiation between substance-induced psychosis and schizophrenia spectrum disorder using the facts from the patients` history and their present mental state.

Based on our clinical judgment, the psychotic episodes had delusional manifestation, with a trend towards increasing complexity: hallucinations combined with pseudohallucinations and psychic automatism (thought broadcasting and insertion) and oneiroid syndrome (dream-like statement at the peak of the first psychotic episode) were observed. Furthermore, during the first psychotic episode M believed in his own might, special possibilities, and adopted risky behavior, which can be considered as mania symptoms. The first psychotic episode lasted around six months; such duration is atypical for substance-induced psychosis, as novel psychoactive drugs usually

Table 1. Timeline summary of patients events

Age (year)	Event
13 years old (2006)	First alcohol and cannabinoids intake (M and B).
from 14 to 18 years old (2007–2010)	Regular alcohol consumption (M and B).
from 18 to 23 years old (2010–2016)	M is using cannabinoids and amphetamine regularly. B is using amphetamine regularly.
23 years old (2017)	First mephedrone intake (M and B).
24 years old (2018)	M and B are using Scath regularly. M has developed a first episode of psychosis. Treatment in the rehabilitation center for addictions, then outpatient psychiatric treatment with antipsychotics during 7 months that patient discontinued himself.
the New Year holidays (2019–2020)	M and B resumed consumption of Scaths at the same day. After this point they continued using Scaths for 4 months.
26 years old (2020)	M's second psychosis and current admission. B quits drugs without professional help.

cause psychotic episodes that last 5–7 days. Nevertheless, by the time the psychotic episode ended, M had fully recovered, got a job, and showed no signs of negative symptoms for seven months.

In the absence of negative symptoms, such a condition could be interpreted as schizoaffective disorder. But a few counter-arguments exist:

a. there was no signs of affective disorders (neither mania, nor depression) beyond the peak of the first psychotic episode;
b. on the current admission, delusion with self-aggrandizing ideas was also observed, but euphoria, elevated or irritable mood, psychomotor agitation and impulsivity were not present;
c. the patient kept formal insight into his condition and was able to conceal his condition, which is not typical for severe affective disorders; and
d. a large dose of substances and long period of their consumption led to the development of psychosis, whereas exacerbation of a primary psychiatric disorder usually happens after a moderate substance consumption.

The current episode began approximately 10 days after the last Scath intake and cannot be explained by intoxication or withdrawal syndrome. Therefore, the patient meets ICD-10 diagnostic criteria for F15.5 "Mental and behavioral disorders due to use of other stimulants, including caffeine: psychotic disorder".

THERAPEUTIC INTERVENTION

The patient received the following round of therapy in the addiction treatment unit of the psychiatric hospital: fluid therapy up to 1 liter per day, haloperidol up to 20 mg/day, and valproic acid up to 1200 mg/day. During the treatment course, M remained taciturn and aloof, spending most of the day in bed with closed eyes. Nevertheless, the patient would easily wake up and join a conversation with a doctor. From the first days of the therapy, M denied having psychotic symptoms, including fear of persecution, referring to the therapy effects. However, he remained detached and distrustful, tried to limit any kind of verbal contact, and all his answers were monosyllabic. So doctors concluded that M is still experiencing psychosis. A felt burdened by staying in hospital, was curious about discharge date, and often asked for a call to his parents.

Fluid therapy lasted for 3 days in order to prevent possible electrolytic and rheological disorders. Antipsychotics and anticonvulsants were used throughout the period of the stay in the addiction treatment unit. Psychosis was in retreat by the second week of treatment, M's condition improved. He became more communicative and active and reported no complaints. On the third week of therapy, M was referred to the rehabilitation unit.

TWELVE-MONTH FOLLOW-UP

M remained under the supervision of the psychiatrist. In general, therapy with haloperidol and valproic acid was well tolerated. However, the patient was sedated and after three weeks of treatment developed akathisia. His therapy was modified: haloperidol and valproic acid were discontinued, carbamazepine 600 mg/day and olanzapine 15 mg/day were prescribed. This course remained unchanged until the end of the follow-up period. The patient endured blood testing every month and a physical examination every week to monitor adverse effects. No side-effects were noticed.

M was active and coopereative from the first day in the rehabilitation unit. Psychotherapy consisted of a twelve-step program and individual therapy with a gestalt therapist. Concurrently, B stayed sober. He started individual sessions with a therapist in the cognitive-behavioral approach and joined the Narcotics Anonymous community.

During his first month in the rehabilitation unit, M did not reveal his worries. Instead, M was telling his psychiatrist that he felt well and was willing to recover. However, his speech consisted of clichéd "right" phrases. After three months in the rehabilitation unit, M's condition improved. He became less guarded and confessed that his recent condition was almost identical to his first psychosis: M reported seeing signs that imparted him various pieces of information, to have thought of others speaking of him in secret, and to have thought to have "special" blood coursing through his veins.

Upon improvement, M became an active participant in every event, started asking staff for help, and was amicable and genuinely interested in advice given by the psychiatrist and the psychologist.

Despite noticeable improvement, the possibility of a schizophrenia spectrum disorder could not be excluded. On the 11th month of the follow-up, a cognitive evaluation by psychologist was performed. M's thinking was concrete. Abstraction and generalization were somewhat impaired. There were isolated generalization distortions and derailments. M's emotional status was remarkable for its

vivid emotionality and immaturity of emotional reactions. Short-term and long-term memory were intact. Working efficiency, warming-up extent, and mental stability were normal. Attention span was normal, but attention fluctuations were observed. Thus, no signs of organic-type or schizophrenic-type disorders were detected in M.

The psychiatrist did not detect any negative symptoms during the year of follow-up. No specific thought or emotional-volitional disorders (power potential decrease, blunted affect, and schizophrenia-type thought disorder) were observed during the psychological examination. Therefore, the diagnosis of schizophrenia was excluded.

After a year of follow-up, M was discharged from the rehabilitation unit of the private clinic with an ICD-10 diagnosis F19.202 "Dependence syndrome due to multiple drug use, currently in remission, stage 2" based on the main criteria for the dependence syndrome: presence of craving, lack of control over consumption, high tolerability for a drug, and withdrawal syndrome.

Concurrently, B remained sober and has landed a job as a manager. B now rarely experiences a craving for drugs and the craving is easy to overcome. In addition, he attends open city groups of the Narcotics Anonymous community. B never experienced psychotic symptoms.

DISCUSSION

This case demonstrates the paucity of a fundamental understanding of mental disorders and highlights the importance of further research into the clinical features of psychoactive drug-induced psychoses, especially those induced by novel psychoactive drugs such as Scaths.

The case is unique for several of its development features and the course of the dependence syndrome in the twin brothers: the choice of a recreational drug, motivation for consumption, and, undoubtedly remarkably, psychosis development. Genetic predisposition would be suggested not only by the hereditary load, but also by a concurrent development of addiction syndrome in the brothers. The age of drug abuse onset, consumption frequency, the development of regular consumption, and the progressive disorder course are identical in both brothers. Following in the steps of the community, in which it was customary to use psychoactive drugs, consequent expansion of the consumed psychoactive drugs range and fast development of regular use generally reflect the effects of the environmental factor. The different motivation for psychoactive drug use is remarkable: while M wanted to stand out in a crowd and isolate himself from society, B desired to overcome his shyness and fear to achieve a higher social status. Hence, personality traits have determined in this case the vector of psychoactive drug choice. M, having schizoid personality traits, preferred alcohol and cannabinoids at the initial stage of his addiction and started using Scath only after full development of the addiction, when his tolerance level had risen and there was a need for a stronger effect. B, being more inclined towards hysteroid personality traits, chose stimulants initially. Remarkably, B did not develop any psychotic episode throughout the whole observation period despite the severity of his dependence and his drug consumption being as intense as that M himself. Another remarkable aspect of our case is the so-called "twin telepathy": B's periods of not professionally assisted sobriety were concurrent with M's periods of abstinence, as well as B's relapses.

The case has some key findings. Firstly, there are several factors that affect the risk of psychosis development, and that risk is not identical even for monozygotic twins. Secondly, schizophrenia-like psychosis induced by novel substances have to be differentiated from schizophrenia spectrum disorders even when repetitive psychotic episodes are being observed. And thirdly, prolonged supervision under a qualified psychiatrist is necessary for patients with substance-induced psychoses.

The challenge that comes with differentiating a diagnosis of substance-induced psychotic disorder (SIPD) from that of schizophrenia spectrum disorders (SSD) is significant. The Diagnostic and Statistical Manual (DSM-5) emphasizes that patients with SIPD demonstrate different social and demographic features compared to patients with schizophrenia [12]. The risk of developing schizophrenia is higher in families with a history of any psychotic disorders [13]. Yang et al. (2020) found that the methamphetamine use initiation age correlates negatively with the Brief Psychiatric Rating Scale total score and the Activation subscale score, and that the duration of methamphetamine use correlates positively with the duration of psychosis [14]. Despite the fact that the positive symptoms of stimulant-induced psychoses (SIP) and SSD are generally similar, research confirms the absence of negative symptoms in SIP. [15]. On the other hand, there is evidence of a global and domain-specific cognitive dysfunction in SIP with a similar magnitude as schizophrenia compared to healthy controls [16]. We consider it safe to state that our case corresponds to the mentioned features as well: a family history of an

addictive disease with no psychiatric history; a socially active and well-adapted patient despite the reality of severe addiction; no signs of primary psychiatric disorder before the psychosis; long-lasting psychosis after a long episode of consumption; and severe, positive symptoms with no negative symptoms. Nevertheless, based on current data, stimulant-induced psychosis morphs into schizophrenia in approximately 20% of cases during a five-year period and patients with repetitive prolonged psychosis face the highest risk of schizophrenia [9, 11].

Our case has practical value for the treatment of comorbid psychotic and addictive disorders. We obtained a sufficiently result of the therapeutic combinations in multiple ways: (a) a parallel approach to psychosis and addiction treatment was performed, which appeared the best in this situation; (b) a combination of individual and group therapy for addiction was performed; (c) and a combination of psychotherapy and pharmacotherapy was utilized. This combined, comprehensive approach to the treatment of comorbid disorders appears optimal due to the need to develop strong motivation for sobriety and compliance with medical professionals to prevent further deterioration of a patient's condition.

Limitations

This case report has limitations that should be acknowledged. Unfortunately, this case description is based primarily on the patients' retelling of their life history and other information obtained from their relatives, which mostly could not be verified by any medical documentation. That makes disputable the equality of the consumed amounts of drugs and the periods of sobriety stated by the brothers during the interview, as well as the accuracy of the description of the first psychotic episode. Moreover, negative symptoms of schizophrenia may appear minor at this stage or concealed by antipsychotics.

PATIENT PERSPECTIVE

After a year of treatment, the brothers have developed a strong motivation for sobriety based on their own internal values. M said the following during the interview: "Rehab showed me that I really have a choice, but on the other hand I met people who fell deeper in this abyss and don't have a chance to return. I'm about to live a fulfilling life and I've realized how lucky I am for not being disabled forever or forever hallucinating." Nevertheless, he had a controversial view on medication: "I agree that it's necessary to take pills, but I'd like to stop it someday. I don't have some serious side effects like I've had before with my first psychiatrist, such as weight gain, but I would like to be more active and feel less sleepy".

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