

ИНДУЦИРОВАННЫЕ НАРКОТИЧЕСКИМИ ВЕЩЕСТВАМИ ПСИХОЗЫ И ШИЗОФРЕНИЯ: ТОЧКИ СОПРИКОСНОВЕНИЯ

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Одним из наиболее тяжелых осложнений злоупотребления наркотическими вещества являются индуцированные психотические расстройства. Частота их встречаемости варьирует от 5,2 до 100% и зависит от типа наркотического вещества. В настоящем обзоре приведены актуальные данные и дискуссия о сходствах и различиях индуцированных психозов и шизофрении. Обсуждаются возможные общие патогенетические пути возникновения, возможности дифференциации на клиническом уровне и основные затруднения при этом. Также рассматривается проблема трансформации индуцированных психозов в шизофрению и значимость дифференцированной тактики лечения.

Ключевые слова: индуцированные психозы; шизофрения; наркомании.

SUBSTANCE-INDUCED PSYCHOSIS AND SCHIZOPHRENIA: THE INTERACTION POINT

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One of the most severe complications of narcotic drugs misuse are induced psychotic disorders. Their frequency is varies from 5.2 to 100% and depends on the type of drug. This review provides current data and discussion on the similarities and differences between induced psychosis and schizophrenia. Possible interaction of pathogenic pathways, the possibility of differentiation at the clinical level and the main difficulties in clear diagnostic are discussed. The problem of transformation of induced psychoses into schizophrenia and the significance of differentiated treatment are also considered.

Keywords: substance induced psychoses; schizophrenia; substance-related disorders.

World Health Organization (WHO) reported that the number of drug users in the world is steadily growing [1]. According to the report of European Monitoring Center for Drugs and Drug Addictions, the type of most used drug in our region is represented

by cannabinoids (about 70%), cocaine (10%), heroin (5%), amphetamine (6%) and other psychoactive substances – PAS (9%). Besides, about 50 new PAS are annually identified, most of them being synthetic cathinones and synthetic cannabinoids [2].

Russian tendencies is similar to the rest of the world [3]. The global COVID-19 pandemic and associated restrictive measures produced a negative effect on the vulnerable group of drug users, causing an increase in both the use of psychoactive substances and the incidence of complications [4].

One of the most threatening complications of misuse of narcotic PAS is induced psychotic disorder (IPD). In a sample of

5,529 individuals recruited in 10 European countries, it was estimated that IPD occurred in 6.3% of all acute intoxications with narcotic PAS, requiring hospitalization to the emergency department [5]. At the same time, the incidence of IPD in the general population of narcotic PAS users may reach 100% for certain substances (risks of development of IPD due to the use of different PAS are summarized in Table 1) [6].

Table 1

Risk of Development of Induced Psychotic Disorders due to Use of Different PAS

Type of Narcotic PAS	Source	Analysis	Risk of Development of IPD
Methamphetamine	Lecomte T., et al. (2018) [7]	Meta-analysis (17 research works included)	36.5%
Amphetamine	Smith M.J., et al. (2009) [6]	Prospective study (467 individuals, 19 years of observation)	5.2% in episodic use, 100% in severe addiction syndrome
Opiates	Smith M.J., et al. (2009) [6]	Prospective study (467 individuals, 19 years of observation)	6.7% in episodic use, 58.2% in severe addiction syndrome
Synthetic cannabinoids	Hobbs M., et al. (2018) [8]	Systematic review	40 % (15% turn for help)
Natural cannabinoids	Ragazzi T.C.C., et al. (2018) [9]	Systematic review	0.5-5.0%
Cocaine	Roncero C. (2017) [10]	Retrospective analysis	48.4% (6.6% – tactile hallucinosis)

By the clinical manifestations, PAS-induced psychoses are to the largest extent schizophrenia-like that was first described in the mid-20th century [11,12]. Besides, the use of narcotic PAS increases the risk of the onset of schizophrenia. This clinical peculiarity brings up a question of probable similar mechanisms of development of PAS-induced and schizophrenic psychoses, and on the other hand it raises a discussion about the possibilities and reasonability of differential diagnosis. The given issue is currently under active discussion [13-15]. This article is a continuation of the opened discussion and is devoted to consideration of current evidence-based theoretical common points of PAS-induced and schizophrenic psychoses.

Common Points at the Level of Neurobiology

Schizophrenia-like psychotic disorders

may be induced by PAS that increase release of dopamine in the striatum [16,17]. Thus, cocaine reduces reuptake of dopamine, amphetamine and methamphetamine directly increase release of dopamine. Other substances act indirectly: cannabinoids – through endocannabinoid system, hallucinogens (MDMA) – through agonism to 5-HT_{2A} serotonin receptors and inhibition of serotonin transporter, and dissociative substances (ketamine and phencyclidine) also increase release of dopamine through antagonism to NMDA receptors [18] (Table 2). Besides, study of psychoses induced by dissociative substances and associated with alterations of glutamate brain transmission, opened a new direction in a study of the pathogenesis of schizophrenia – the glutamate theory [19].

All models of schizophrenia obtained on animals, including those used for clinical

Table 2

Criteria of IPD in ICD-10, ICD-11 and DSM-V

	ICD-10 F1x.5 Psychotic disorder	ICD-10 F1x.7 Residual psychotic disorder or psychotic disorder with late (delayed) onset	ICD-11	DSM-V
Time of onset	Within 2 weeks after use of PAS	Later than in 2 weeks	During or immediately after use of PAS*. Here, intensity and duration of use of PAS should correspond to a probability of causing psychosis	Within 1 month after use of PAS
Duration of symptoms	More than 10 days, but less than 6 months	Indefinitely long	A short time*	Not more than 1 month
Main symptoms	Delusion, hallucinations, affective symptoms, psychomotor agitation	Reduction of cognitive functions, of reminiscence, affective disorders, disorders in personality and behavior	Delusion, hallucinations, disorganization of thinking, coarse disorganization of behavior	Most evident are delusion and hallucinations. No awareness of one's own diseased condition
Additions	-	Cause-and-effect relationship between use of PAS and development of the disorder in future should be proven	<i>* at present only preliminary version of ICD-11 is available, in further elaboration time criteria should be clarified</i>	PAS should be etiologically related to the developed psychosis
Bordeline with schizophrenia	Diagnosis of the group of schizophrenia, schizotypal and delusional disorders is more preferable if: -psychotic symptoms precede use of PAS -psychotic symptoms last more than 6 months	-	Diagnosis of the group of schizophrenia and other primary psychotic disorders is more preferable if: -psychotic symptoms precede the current use of PAS -there are psychotic episodes in history not associated with use of PAS -symptoms of psychosis persist and build up without repeated use of PAS	-

trials of new medical drugs, are conditions induced by narcotic PAS. Here, administration of amphetamine leads to deficit of latent inhibition, reduction of the volume of working memory, but does not cause social withdrawal or other negative symptoms, while introduction of phencyclidine and ketamine, besides pronounced psychomotor

agitation, also leads to reduction of prosocial activity and to other negative symptoms [20]. This emphasizes the fact that dopamine-active PAS to a larger extent influence the appearance of positive psychotic symptoms, while glutamate-active ones – the appearance of productive, as well as negative and cognitive symptoms.

Common neurobiological mechanisms of induced psychosis and schizophrenia were also shown in the experiments with prenatal damage to the ventral hippocampus [21]. At the same time, there is insufficient amount of works that would prove the existence of neurobiological differential diagnostic markers. Diagnosis and differentiation of these conditions are carried out exclusively at the clinical level.

Common Points at the Clinical Level

Common symptoms of disorders of schizophrenia spectrum and induced psychotic disorders are delusion, hallucinations, psychomotor agitation, and other positive symptoms. Modern diagnostic systems suggest use of two main criteria for differential diagnosis (Table 2):

- 1) existence of cause-and-effect relationship between the disorder and use of PAS possessing a potential psychotic effect,
- 2) duration of psychotic symptoms.

In the ICD-10, two main categories are given describing IPD:

1. F1x.5 Psychotic disorder (with the onset within two weeks and duration not more than 6 months),
2. F1x.7 Residual psychotic disorder, or psychotic disorder with the late (delayed) onset (it starts later, mostly manifests with cognitive and affective disorders and always requires special attention in establishment of cause-and-effect relationship).

The time criteria in ICD-10 were taken from large samples obtained on the basis of the population data. The second diagnostic category presents a very wide group of different conditions with vague boundaries, therefore it is rarely used in practice and was not included into the new revision of ICD.

ICD-11 suggests use of one diagnostic category – Psychotic disorder, which, besides limitation of time criteria that are to be clarified, also contains clear parameters of differential diagnosis with schizophrenia and with other primary psychotic disorders. The idea of ICD-11 is that in any doubts the more

preferable diagnosis is schizophrenia. This recommendation rests on the fact of multiple use of PAS before the first admission to hospital with the onset of a psychotic disorder (according to Brunnete M.F., et al. (2018) [22], this parameter reaches 50%).

In the light of diagnostic difficulties, the introduction of separate clinical entity (substance related exogenous psychosis) is discussed. Substance related exogenous psychosis is conceived as a distinct psychotic disorder with psychopathological specificities that clearly differentiate it from schizophrenia. This psychosis is characterized by altered states of consciousness, persecutory delusions, visual and cenesthetic hallucinations, impulsivity and psychomotor agitation, affective and negative symptoms, a pervasive feeling of unreality and intact insight. Delusions are typically secondary to abnormal perception resulting from a characteristic «sensorialization» of the world [23].

Several attempts were also undertaken to find other psychopathological and socio-demographic differences that could help differentiate between IPD and schizophrenic disorders at the stage of the first turning for medical assistance (Table 3).

In general, socio-demographic «portrait» of patients with IPD is in most cases represented by men with a relatively late onset of a psychotic episode, with a lower premorbid educational level and a more common existence of a comorbid antisocial disorder of personality with characteristic behavioral patterns in history (mostly traumas and infringement of the law). Psychopathological peculiarities of a subgroup of patients with the primary psychotic disorder include a lower level of criticism to their own disorders, more evident positive and negative symptoms of psychosis with more evident underlying positive heredity for schizophrenia.

In a detailed discussion of the topic of clinical pathomorphism of presentation of IPD, V.D. Mendelevich (2014) stated that in the early XX century IPD were associated

Table 3

***Study of Socio-Demographic and Psychopathological Differences
between IPD and Schizophrenia***

Source	Research Type	Data in Favor of Diagnosis of IPD	Data in Favor of Diagnosis of Schizophrenia
Caton C.L.M., et al. (2005) [24]	3-year longitude study on a sample of 400 patients, the USA	1. Existence of addictions in patients' relatives 2. Existence of any chemical addictions in patients 3. Existence of visual hallucinations	1. High results on the scale of negative and positive disorders
Caton C.L.M., et al. (2007) [25]	1-year prospect study, 319 patients, the USA	-	1. More evident hereditary burden for schizophrenic disorders 2. Lower criticism to one's own condition 3. Lower premorbid functioning
Mauri M., et al. (2017) [26]	5-year longitude study, 48 patients, Italy	-	1. Higher results on pre-tentiousness of thinking scale (BNPS)
Weibell M.A., et al. (2013) [27]	One stage study of 141 patients, Norway	1. Patients are commonly men with low educational level 2. More expressed positive symptoms on PANNS	1. A longer period of untreated psychosis 2. Higher parameters of expressiveness of symptoms in patients with comorbid schizophrenia with addictions
Crebbin R., et al. (2009) [28]	Population study (all patients with primary psychotic episode in North England from 1998 to 2005)	1. These patients more often discontinued outpatient treatment	-
Fraser S., et al. (2012) [29]	One stage study of 61 young patients (16-24 years of age) with a primary psychotic episode, Australia	1. Higher level of criticism to one's own state 2. More traumas and problems with law in history 3. More evident symptoms of anxiety	-
Piataeva I.V., et al. (2015) [30]	One stage study of 21 men under 25 with a primary psychotic episode, Russia	Reduction of generalization processes by «organic» type and actualization of «latent» signs	-
Dubatova I., et al. (2018) [31]	One stage study of 158 men with psychosis, Russia	45% of patients had IPD with exogenous-organic clinical symptoms (delirium, visual hallucinosis) 55% - with endogenous clinical symptoms	-
Quattrone D., et al. (2020) [32]	Retrospective study of 905 patents with first episode psychosis and 1235 controls	There was a linear relationship between the positive symptom dimension and the extent of lifetime exposure to cannabis, with daily users of high-potency cannabis having the highest score	Negative symptoms were more common among patients who never used cannabis compared with those with any pattern of use

with use of traditional natural PAS (morphine, cocaine, natural cannabinoids, etc.), which determined a more moderate character of psychotic disorders and permitted a more precise differentiation between schizophrenia and IPD (for example, using hexogen model of Karl Bonhoeffer [33]). In XXI century the problem of IPD changed due to heavy use of highly potent synthetic PAS, which made the clinical picture of IPD more acute and complicated the problem of clinic-psychopathological differential diagnosis [34].

Besides, of importance in clinical aspect is singling out of Hallucinogen Persisting Perception Disorder (HPPD) in DSM-V, which is a particular kind of IPD associated with use of hallucinogens. Its clinical peculiarities are existence of psychosensory visual disorders (such as geometric hallucinations, false perception of movements on the periphery of the field of vision, «halos» around objects, macro- and micropsia, «visual snow», etc.), which differ from hallucinations and are not reduced by intake of antipsychotics [35]. This is probably due to the fact that HPPD results from dysregulation of serotonergic neurotransmitter system [36]. There exist some works showing that a combination of HPPD and schizophrenia reduces the intensity of negative symptoms of schizophrenia [37].

Transformation of IPD to Schizophrenia

The clinical construct of the diagnosis of IPD is unstable, and in the long-term prospective study of the given category of patients, there may be observed transition of the primary diagnosis of IPD to schizophrenia and other chronic mental disorders. Reverse transition is impossible, because schizophrenia is considered to be a primarily chronic mental disorder, and any exacerbation of clinical symptoms in a patient with the established diagnosis of schizophrenia will be unambiguously interpreted as exacerbation of schizophrenia even if it was provoked by intake of PAS.

The statistical aspect of transition of IPD to schizophrenia was addressed in some studies. Thus, in one of the first studies by P.L.M. Caton, et al. (2007) in 1-year prospective observation of a sample of 319 patients with past IPD it was found that after 1 year in 25 % of patients the diagnosis was changed to schizophrenia. In most cases the diagnosis had to be changed in patients with low premorbid functioning, high heredity for schizophrenia and low criticism to their state. Important conclusions on this issue were also obtained after analysis of national cohorts of some Scandinavian countries (Denmark [38], Sweden [39] and Finland [40]), which have digitized databases of all patients in their medical networks and may draw conclusions on large population samples. For example, on the results of study of Danish national cohort (6 788 patients, observation from 1994 to 2014) the 5-year risk of transition of IPD into schizophrenia was 30% for cannabinoids, 20% for hallucinogens and 15% for amphetamines [38].

It was also shown that the existence of comorbid viral hepatitis increases both the risk of development of IPD and the risk of its transition to schizophrenia [41].

In the latest meta-analysis it was found that the average proportion of transition of IPD to schizophrenia is 25% (95% CI 18%-35%). Under the highest risk of transition are IPD associated with use of cannabinoids (34%), hallucinogens (26%) and amphetamines (22%). The risk of transition of IPS associated with use of opioids (12%), ethanol (10%) and sedatives (9%) is lower probably due to the low influence of these substances on the dopamine neurotransmitter system [42].

Common Points at the Level of Therapeutic Approaches

The most effective chemical drugs to correct symptoms of both schizophrenia and IPD, are antipsychotics. Their symptom-reducing effect is associated with block of postsynaptic D2 receptors in the striatum.

In the existing studies and meta-analyses of therapy of IPD, as well as of schizophrenia, no therapeutic advantage of the second-generation antipsychotics over the first-generation ones was found even despite better toleration of the second-generation antipsychotics [43-45]. Recommendations on therapy of IPD, in contrast to therapy of schizophrenia, suggest a shorter duration of use of antipsychotics with a higher probability for stabilization of remission after refusal from repeated use of PAS [46]. Secondary prevention also should focus on harm reduction strategies for IPD. For example, continuing using cannabis after psychosis onset is asso-

ciated with more chances to relapse and a worse outcome [47].

Conclusion

Thus, IPD and schizophrenia are disorders that are very close in the pathogenetic mechanisms of development and clinical manifestations. The existing diagnostic methods only partially permit their differentiation admitting transition of IPD to schizophrenia. Unfortunately, classic psychopathological approaches lose their significance with new PAS that come into use and more often cause IPD with schizophrenia-like symptoms. The task of future studies is to find clear paraclinical methods for differentiation of these conditions.

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