

Schizophrenia: a Narrative Review of Etiological and Diagnostic Issues

Шизофрения: нарративный обзор этиологических и диагностических проблем

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Review

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ABSTRACT

BACKGROUND: Despite the fact that schizophrenia has already been described historically and researched for a long time, this disorder remains unclear and controversial in many respects, including its etiology, pathogenesis, classification, diagnosis, and therapy.

METHODS: Literature from the selected sources (elibrary.ru, Russian Science Citation Index and the Russian branch of the Cochrane Library) were searched and analyzed using the diachronic method. Priority was given to reviews, guidelines, and original research on schizophrenia written during the past 10 years.

RESULTS: Historically, scientists have described schizophrenia as a single disorder, a group of disorders, or even as a combination of certain syndromes. The polymorphic symptoms and the most typical dynamics of various forms of schizophrenia have been systematized, but neither in Russia nor in other countries have the etiology and pathogenesis been proven. The reasons for the under- and overdiagnosis of schizophrenia cannot cover all possible objective and subjective difficulties arising in the diagnostic process.

CONCLUSION: The existing literature shows that the problem of schizophrenia may not be regarded as settled for a long time. This largely depends on the position of society, the development of biological sciences, and the pathomorphosis of the disorder itself. Many aspects of schizophrenia can become clearer and less controversial with systematic studies based on previous data, as well as data obtained using new research methods.

АННОТАЦИЯ

ВВЕДЕНИЕ: Несмотря на описание шизофрении еще в древней истории, многолетние исследования, данное расстройство во многих аспектах остается неясным и спорным. Это касается этиологии, патогенеза, классификации, диагностики, оптимизации терапии.

МЕТОДЫ: Литература (выборочные релевантные открытые источники — из системы elibrary.ru и РИНЦ, а также базы Российского отделения Кокрановской библиотеки (<https://www.cochrane.org/ru/evidence>)) анализировалась диахроническим методом, что позволило выявить важные переменные в воззрениях на шизофрению на протяжении 100 лет до настоящего времени. Приоритет отдавался обзорам и руководствам, оригинальным исследованиям по проблеме шизофрении последних 10 лет.

РЕЗУЛЬТАТЫ: Согласно литературе, проанализированной по концепционной схеме (основные направления и факты в изучении этиологии, динамики, критериев диагностики шизофрении, спорные аспекты указанных

направлений и фактов; основные перспективы в изучении шизофрении), были получены представленные результаты. У психиатров всегда были основания различных воззрений на данное расстройство, варианты его динамики и критерии динамических этапов, включая ремиссию. В разные годы ученые находят аргументы для взгляда на шизофрению и как на одно расстройство, так и на два и даже на группу расстройств, а также как на синдромы. Систематизирована полиморфная симптоматика и наиболее типичная динамика многообразных форм шизофрении, однако ни в России, ни в других странах по-прежнему не доказана этиология и не сформирована концепция патогенеза даже в рамках отдельных типов расстройства. Приведенные в доступной литературе причины гипо- и гипердиагностики шизофрении не могут охватить все вероятные объективные и субъективные трудности, возникающие при диагностическом процессе.

ЗАКЛЮЧЕНИЕ: В целом же, как следует из отечественной и зарубежной литературы, проблему шизофрении еще долго нельзя будет относить к исчерпанным. Во многом это зависит от позиций общества, развития биологических наук и патоморфоза самого расстройства. Многие аспекты шизофрении могут стать более ясными и менее спорными при систематических системных исследованиях, основанных на полученных ранее и дальнейших данных, на новом этапе методических возможностей. Обзор литературных данных по указанным выше аспектам шизофрении может способствовать вниманию ученых к тем или иным результатам исследований, при ином анализе и синтезе информации.

Keywords: *schizophrenia; biological psychiatry; etiology; diagnostic approaches; diagnostic errors*

Ключевые слова: *шизофрения; биологическая психиатрия; этиология; диагностические подходы; диагностические ошибки*

INTRODUCTION

It has long been known that schizophrenia is a severe mental disorder distorting the life of the sufferer and their loved ones. Almost all outstanding psychiatrists of both the past and present have made the attempt to comprehend the condition [1–19]. In the Canon of Medical Science, *Avicenna* [20] mentioned a condition called “severe insanity”, which by description resembles schizophrenia. The first descriptions of the manifestations of a mental disorder, which was named “ideophrenia” in 19th century, and “schizophrenia” in 1908, refer to the 17th century BC: the Book of Hearts, Egyptian papyrus of Ebers, mentioned “phrenitis” [20, 21].

E. Kraepelin, in the 19th century [2], called a similar mental disorder “dementia praecox”. At the beginning of the 20th century, E. Bleuler introduced the term “schizophrenia” [1], noting its characteristic feature as “violation of the unity of psyche.” In addition, the disease is characterized by productive and negative symptoms, neurocognitive disorders, and impaired social adaptation. In the 1930s, K. Schneider developed a nosological concept of schizophrenia and formulated “symptoms of the 1-st rank” [7].

Currently, about 24 million people in the world are affected by schizophrenia [22–24]. All existing research on schizophrenia is difficult to describe. Although

the existing literature on the etiology of the disease is diverse and contradictory, the role of the hereditary nature of schizophrenia is the most proven. However, in the hereditary theory there is no consensus regarding which link the genetics “activates”. Furthermore, scientists are relatively unanimous in their opinion about the role of the dopamine system in the etiology and pathogenesis of the disease. At the same time, opinions about the dynamics of schizophrenia and views on its remission remain controversial. Finally, there is no common opinion as to whether the term “schizophrenia” refers to a single disease or to a group of diseases with different etiologies [23–28]. It is not only the disease itself but also clinical syndromes [25–28] that combine both mental and behavioral phenomena that are referred to as “schizophrenia”. Also, errors in the differential diagnosis of schizophrenia are the most common ones encountered in psychiatry and entail (in addition to medical) social, economic, and legal consequences; however, relatively little research has been devoted to this aspect of the disorder. Given the changes in psychiatric classifications, the pathomorphosis of schizophrenia and attention to the issues of its diagnostic criteria are still relevant. Based on the research gaps described above, the present review aims to explore the existing etiological and diagnostic issues of schizophrenia.

METHODS

The following electronic databases were searched: elibrary.ru, the RSCI (Russian Science Citation Index), and the Russian branch of the Cochrane Library (www.cochrane.org/ru/evidence) using search terms such as “schizophrenia”, “etiology of schizophrenia”, “diagnosis of schizophrenia”, and “diagnostic errors”. Priority was given to reviews, guidelines, and original research on schizophrenia written during the past 10 years. Records published in Russian, English, German, and Dutch were included in the review. When a reference to an earlier source of data was identified, the strategy of referring to the original source was adopted.

Included records were analyzed using the comparative phenomenological method and the diachronic method of information analysis in order to clarify the changes in certain views on the etiology and diagnosis of schizophrenia during certain periods of time (after 20 years, 50 years, before the introduction of antipsychotics into therapy, and after that).

RESULTS

According to the data reported in different years, schizophrenia is the main area of research in psychiatry [10, 11, 19, 24]. However, its diagnosis often comes 5–10 years after the actual onset of disease [10, 11, 19, 24, 27–33]. At the same time, considering its socio-economic significance, the issue of the timely diagnosis, correct therapy, and rehabilitation can be considered one of the priorities in the psychiatric practice [19, 27–33]. The results of the current review will be presented to highlight the following aspects of schizophrenia research:

1. Etiology of schizophrenia.
2. Course of schizophrenia.
3. Diagnosis of schizophrenia.
4. Errors in diagnostics of schizophrenia.

1. Etiology of schizophrenia

Scientists around the world were occupied with the issues of schizophrenia's etiology for a long time. There are several theories of the etiology of this disease, with different ones prevailing during different periods of time. It seems significant that scientists returned to some of these theories after decades. In this section, different etiological theories of schizophrenia that was or remain relevant during the period about 100 years will be discussed.

Genetic theory

In the late 20th to early 21st century, heredity began to be studied at the chromosomal level, which confirmed the scientific opinion about the great prospects of this direction in terms of understanding the etiology of schizophrenia. Several scientists note that the interpretation of genetic data in psychopathology is hampered by the complexity of their reproduction under identical methodological conditions and non-Mendelian mechanisms of inheritance [34, 35]. However, the same scientists cite important data [36] on the establishment of a relationship between mutations and the quantitative level of expression of the C4A and C4B genes and the clinical picture of schizophrenia. In addition, it is indicated [37] that knockout mice were created for the above genes using gene knockout technology. In these animals, a statistically significant decrease in neural connections between brain structures was found. This made it possible to convincingly prove the association between a separate genetic mutation with the pathophysiology of schizophrenia. According to A.Yu. Morozova et al. [36], disclosing the biology of the gene and the mechanism of occurrence of the risk of schizophrenia allows the potential genetic variations that are most significant in the etiology of this disease to be determined. These authors believe that advances in genetics already indicate a key role of gene networks in the development of disease complemented by likely biochemical pathways [34, 36, 37]. It was recently concluded that “there is no definitive genetic cause of schizophrenia” [38]. However, the authors further point out that “a new and promising direction in the study of the etiology of schizophrenia is in the search for associations between genetic polymorphisms and particular clinical and psychopathological manifestations of mental pathology, as well as with the identified neurochemical disorders” [34, 36, 38–40].

Neuromediator theory

In the second half of the 20th century, biological research had become more important. For about 40 years, the so-called “dopamine” hypothesis of schizophrenia was one of the most popular. It was largely confirmed by the discovery of antipsychotics that suppress dopamine, as mentioned in the works of various years [31, 41–43]. According to this hypothesis, productive symptoms of schizophrenia are associated with long-term elevation

of levels of dopamine in the brain striatum and negative symptoms are associated with long-term decreases in levels of dopamine in the brain cortex (compared to healthy people) [44–45]. But even among the supporters of the dopamine theory of schizophrenia and other psychoses, two main trends could be distinguished from the last 10 years. Some researchers consider this phenomenon to be congenital, whilst others believe it to be acquired [41–42]. Scientists proved that antipsychotics block dopamine D2 receptors, which suppresses positive symptoms. However, since the action of antipsychotics is selective and affects such receptors outside the mesolimbic system, their use may be accompanied by extrapyramidal side effects [43]. The second part of classical dopamine hypothesis connects the hypoactivity of dopamine receptors in the cortex with negative symptoms, including the formation of severe cognitive deficit. Neurochemical correlates of glucose metabolism in central neurons with changes in thinking, attention, speech have been established [46].

Neurodegenerative theory

According to existing data [47, 48], intravital visualization of brain structures (using functional MRI, positron emission tomography (PET), and magnetic encephalography) came to represent a new era in the study of the etiology and pathogenesis of schizophrenia. The importance of such a scientific approach was demonstrated by the publication of data obtained from the positron emission tomography of the brain by British scientists T.J. Crou and E. Johnston in 1976 [15]. This publication illustrates the expansion of the lateral ventricles in progressive mental pathology among schizophrenia patients with predominantly negative symptoms. In 1980, T.J. Crou [16] revealed that such patients showed an absence of pronounced dopaminergic pathology. Based on this data, Crou formulated a hypothesis about two types of schizophrenia, differing in etiology and pathogenesis with a predominance of negative symptoms (1), and with a prevalence of productive symptoms (2). In the second type of disorder, there is an increase in the activity of D2 dopamine receptors (during posthumous autopsy, an increase in their density was found) [16].

Research by T.J. Crou was supported by the American psychiatrist N.C. Andreasen (1995) [26]. She correlated the data on positive and negative symptoms with defects in cognitive and emotional spheres during therapy with

antipsychotics, revealing that their long-term use leads to atrophy of the prefrontal cortex. Autopsy, including posthumous autopsy, over the last 20 years has lent a new impetus to the cytochemical direction in the search for the causes of schizophrenia. For the last 20 years, scientists have been turning to the analysis of brain substrate in schizophrenia, both posthumously and during intravital morphometric studies. The most common picture shown by CT and MRI scans are enlargements of the lateral and third ventricles of the brain, reduction of the frontal and temporal cortex, changes in the basal ganglia and hippocampus-amygdala complex, and a decrease in cerebellar volume [49–52]. These and other researchers emphasize a decrease in the volume of the brain (especially the hippocampus and amygdala) due to the expansion of the cerebral ventricles. This fact, from a biological point of view, proves that schizophrenia is an organic mental illness. The concept of the “functional” nature of schizophrenia as an aspect of its organic nature began to attract more attention after associated markers were found in patients. This indicated an impaired excretion of substances from the interhemispheric spaces into the blood, which is a sloughing off of cells with waste substances and toxins (endotoxicosis) in 80% of patients [51–52]. These authors also reported that the neurodegenerative process in schizophrenia is combined with autoimmune inflammatory changes in the brain in a significant number of cases [52]. However, MRI scans of the brains of patients did not produce significant results in support of this theory. In the available literature, this statement was commented in terms of the need to continue the indicated studies. A number of studies have noted the connection between changes in cognitive functions in schizophrenia and progressive loss of the gray matter of the brain [53, 54]. This confirms the long-standing statement by K. Kahlbaum (1874) [55] that anatomical justification may also be important in the understanding of mental illnesses. Neuroimaging studies in schizophrenia have shown frontal white matter abnormalities associated with clinical symptoms [52].

Viral theory

Furthermore, at the beginning of the 20th century, the onset of schizophrenia was associated with an unknown virus or infection [56]. The viral theory was “supported” by describing the existing seasonal patterns: in winter, mothers suffer from infectious and viral diseases more

frequently, which affects the fetus, especially boys born in February (their risk of developing schizophrenia was higher). Supposedly, it is also connected to the peculiarities of the genome and sexual dimorphism [54, 57, 58]. However, the interpretation of these data and changes in the frequency of disorders of gene locus (16p11.2 and 22q11.2) [59, 60] in schizophrenia in boys born in winter requires complex development of a general concept, clarifying the connections between the role of genetic factors in the fetus and the presence of a viral disease in the mother [57, 58]. A number of studies of schizophrenia identified that viral RNAs were in certain ways similar, at least to an extent, to the HIV, herpes, and Epstein-Barr viruses [61, 62]. It is believed that elucidating the effect of HIV infection on the psychopathology of endogenous disorders is important in understanding the etiology and pathogenesis of schizophrenia [63, 64]. In another hypothesis, the development of schizophrenia is associated with a distorted immune response to the Epstein-Barr virus and Type W (HERV-W) retrovirus [65].

Another theory that was common in the 20th century had a religious context [66–68]. According to this theory, destructive satanic views destabilize the psyche and lead to schizophrenia. This process was called “diabolizing” [67, 68]. Perhaps this is due to the fact that, almost a century later, traditional religions were supplemented by destructive satanic beliefs that destabilize the psyche [69, 70].

Immunological theory

Since the 20th century, psychiatrists’ interest in immunological factors as the cause of schizophrenia was significant. Almost until the end of the 20th century, priority was given to research into cellular immunity [71, 72] and autoimmune factors — antibodies to one’s own brain, including those of the brain [73–80]. Since the first decade of the 21st century, priority has been given to those immunological factors that are not products of one’s own brain — interleukins, in particular Ig-2; Ig-10. The authors of Russian and foreign scientific studies consider their development to be caused by stress [81–86]. The place of these factors in the onset of the disease is also not entirely clear; it is possible that they are either its consequence or a correlating factor [82–84, 86]. In addition, the connection between immunological disorders and negative manifestations of schizophrenia has recently been identified. Thus, in patients, direct

correlations (a close relationship of pathophysiological signs) were established between severe negative symptoms and one of the informative indicators of innate immunity, namely the activity of leukocyte elastase [87]. A greater severity of negative symptoms and cognitive impairments was revealed with a decrease in the level of regulatory T cells (a decrease in their level contributes to the development of autoimmune reactions in schizophrenia) [88–90]. This contradicts some of the work of other years, according to which pronounced psychotic symptoms are “consistent” with a significant distortion of immune indicators [91–93]. Although no satisfactory interpretation has been given, the unfavorable course in carriers of the AB (IV); Rh (-) phenotypes is deemed to be important. In the last 20 years, considerable attention has been given to the permeability of the blood-brain barrier (BBB) in mental disorders, including schizophrenia. A promising direction is the study of the BBB permeability for a number of cytoplasmic proteins, such as a violation of the BBB is currently referred to as additional diagnostic and prognostic parameter of mental disorders, including schizophrenia. The role of the abovementioned violation of BBB in the etiology of schizophrenia also cannot be ruled out [93–96].

Cortical disintegration theory

During the same period, a hypothesis was put forward about the cortical disintegration as the basis of mental disorders, including schizophrenia. This hypothesis is supported by the analysis of interhemispheric coherent connections, showing a decrease in gamma activity during EEG in patients with schizophrenia (absence or weakening of gamma waves) [97–99]. In an attempt to understand psychopathology, quantitative electroencephalography began to develop. Thus, the evoked potentials showed differences in the parameters of the P 300 wave in patients with schizophrenia, with a connection established between this parameter and impaired interhemispheric interactions [100]. However, the International and American Societies of Electroencephalography and the American Academy of Neurology consider even quantitative EEG to be a functional diagnostic method only, without linking its results with the possible causes of the disorder. A.S. Tiganov (2016) [101] stated that objective (paraclinical) research methods in psychiatry do not have an independent meaning as

yet, and should be considered — within the context of the diagnostic process — as part of the system that includes other data. The same opinion is supported by A.A. Aleksandrovsky (2016) [102].

Thus, it can be concluded that the etiology of schizophrenia is largely unknown and there still remains no unified concept of its discovery. Scientists are trying to find the “starting point of the disease” based on their own scientific ideas and methodological interests. A systematic interdisciplinary approach seems to be required to be able to draw some solid conclusions regarding the etiology of schizophrenia [4, 10, 16, 17, 31, 39, 44, 47, 66, 91, 100].

2. Course of schizophrenia

In the majority of studies and in the reports of forensic psychiatric examination written prior to the introduction of antipsychotics into practice, schizophrenia was considered a disorder with an almost unavoidable progression and an unfavorable outcome [103–105]. Psychiatrists of the “pre-antipsychotics period” [106] considered a diagnosis of schizophrenia to be synonymous with incurability. They did not attach much importance to temporary improvements in patients’ condition, considering them incurable. N.P. Tatarenko (1960) [107] supported the view of psychiatrists of the 1920s [108] regarding the progression of the course of the disease and the worsening of the condition of patients after each attack, emphasizing that “the patient’s fate is determined by the limit of his compensatory mechanisms”. Despite such practical views, the concepts of remission and intermission have been known in science since the 19th century. For instance, J.-E. Esquirol (1838) [109] insisted that there was a need to distinguish the terms “recovery” and “incomplete recovery” or “recovery only to a certain degree”. The latter term indicated not only the tendency to relapse, but also a “damage to the brain and reason, expressed in the fact that patients, living in society, cannot play the role that they played before the disease”. Improvements in the condition of patients with schizophrenia that meet the criteria for remission were described in the 19th century by the Russian authors V.P. Serbsky (1895) [110], I.G. Orshanskii [111], V.I. Akkerman (1937) [112], A.N. Buneev (1950) [113], E. Kraepelin (1911) [114], and E. Bleuler (1941) [115], who admitted the possibility of long and complete remissions, describing a picture of practical recovery with symptoms

of mental weakness and some alienation from the outside world. They categorized the defect conditions according to their severity. Both scientists believed that remission did not exclude new attacks of the disease and doubted that recovery from schizophrenia is possible (especially E. Kraepelin) [114].

According to A.I. Molochek (1941) [115], the schizophrenic post-process stage, or remission, is a stage of functional restructuring. Patients may demonstrate vulnerability, autism, even impaired thinking, but are subject to reactive mechanisms. M.Ya. Sereisky (1939) [116] included in the definition of remission cases of nosocomial improvement — the most insignificant therapeutic improvement in mental state — remission “D”.

K. Kolle (1961) [117], around the same time, argued that the most frequent outcome of the disorder is recovery with some form of defect, and described three types of defect state:

1. Emotional coldness, autism, intrapsychic ataxia with impaired motility, facial expressions, speech, irritability.
2. The disease does not manifest itself in clinical symptoms, but in a break in the life curve, professional activity, and social growth.
3. The mildest form of violations manifests in spiritual life: a paradoxical interest in literature and art. This break in the life curve in these patients can only be detected by detailed research.

D.E. Melekhov (1981) [118] emphasized that the researchers of the defected states and remissions are in fact analyzing the same conditions. In the 1960s, according to his data and materials pertaining to N.M. Zharikov’s [119] patients with “A”-type remission (according to the classification proposed by M.Ya. Sereisky) [117] amounted to about 4.5% of all patients. Such figures could be explained by the narrow use of antipsychotics in patient therapy. G.V. Zenevich (1964) [120], and V.M. Morozov and Yu.K. Tarasov (1951) [121, 35] emphasized that in the case of remission, there is a desire to overcome the defect, whereas in the case of a defective state, it is some sort of adaptation to it. In general, the remission was viewed as a dynamic concept.

In 1981, D.E. Melekhov [118] emphasized that 90% of remissions involve a defect state that is milder than dementia. The concept of “practical recovery” remains ambiguous — this is just the disappearance of the

symptoms of the disorder without complete restoration of mental functions or “new health”, as described by F.V. Kondratyev (2010) [29]. It is important to note that despite more than a half century of research, remission in schizophrenia remains poorly described in practical psychiatry [122–125]. It is stated both in Russian and foreign studies that so-called psychosocial remissions are observed in no more than 15% of patients [35, 122–126]. A.V. Potapov et al. (2010) [127] note that symptomatic remission is possible for about 20% of patients if modern therapy is administered (in compliance with international criteria). In our view, this fact demonstrates a very incomplete understanding of the etiology and pathogenesis of schizophrenic spectrum disorders. It seems that the existing theoretical developments of positive dynamics in the course of schizophrenia represent only the basis for future research.

A.V. Snezhnevsky and R.A. Nadzharov (1968–1970) identified three types of schizophrenia: continuous, paroxysmal-progressive (shift-like), and periodic [128, 129]. In the 1930s, febrile schizophrenia was described [130, 131]. After the 1960s, that is, in the “antipsychotic era”, V.A. Romasenko (1967) [130], L.A. Ermosina (1971) [131], A.S. Tiganov (1982) [132], and A.V. Snezhnevsky (2008) [129] suggested that febrile seizures are possible in recurrent and paroxysmal-progressive schizophrenia, which are more common among young people. Such attacks are rare and should be differentiated from neuroleptic malignant syndrome. In the 1960s, in agreement with E. Bleuler’s [133] idea of the secondary importance of acute productive symptoms in the long-term course of schizophrenia, A.V. Snezhnevsky [134] introduced the concept of “sluggish schizophrenia”. The polymorphism of clinical manifestations led to the ongoing controversy regarding this disorder, and ultimately it was not included in the ICD-10 or ICD-11. DSM-5 describes the diagnostic criteria for schizotypal disorder, which is the closest in symptomatology to sluggish schizophrenia, but which is categorized amongst “personality disorders” [17, 135, 136].

3. Diagnosis of schizophrenia

Over the last 20 years, in Russian and foreign psychiatry many specialists hoped to capture the essence, course, and diagnosis of schizophrenia using psychometric methods [12, 137, 138]. At the same time, other Russian researchers completely reject measurement and instrumental approaches in psychiatry, attempting to find an adequate

replacement for them in the form of a functional characteristic of the patient’s condition [139–141, 24]. It seems that the rapid development of “technogenic” medicine, along with the attitude to the brain as a “great mystery” [142, 143], may not only allow for some form of consensus to be found but also an understanding of deeper mental processes.

The main changes in the diagnosis of schizophrenia in comparison with ICD-10 in ICD-11 are: a) decrease in the significance of first rank symptoms; b) the introduction of “six dimensions”; c) exclusion of clinical forms; and d) inclusion of such sign as “the course of the disease” [144, 145, 9]. In ICD-11, schizophrenia is characterized by multiple mental dysfunctions. Chronic delusional symptoms, hallucinations, thought disorders, and impaired self-awareness are considered the most significant symptoms, and at least two of these must be present for 1 month or more [18].

The six main diagnostic criteria for schizophrenia adopted in previous versions of the DSM with minor changes were retained in DSM-5: delusions, hallucinations, disorganized speech, severely disorganized or catatonic behavior, and negative symptoms. At the same time, the clinical “borders” of schizophrenia are limited only by its most severe forms. DSM-5 also excludes all relatively mild forms of the disorder [8, 9, 146].

Considering the development of medical science, an increase in dimensions can be assumed in the diagnosis of schizophrenia. Possibly, knowledge of neuroanatomical dimensions, reflecting the specific localization of structural and functional disorders, may help to clarify the clinical symptoms, course, and outcomes of schizophrenic spectrum disorders. Back in 1940, A.S. Kronfeld [141]. believed that “the syndrome can only be understood as a result of the activity of the whole brain”. Later, it became obvious that in addition to knowing the localization of the pathological process in the brain, it is necessary to take into account the reaction of the whole body, in particular, neurohumoral and neurochemical changes [147]. Therefore, ICD-11 and DSM-5 are not the “ultimate truths” [136, 147]. In daily work, clinicians may continue to use many of the undefined constructs of the first classification (ICD-11), and researchers — of the second (DSM-5), along with the further development of diagnostic criteria [8, 9, 24, 43, 145]. Appealing to the undesired stigmatization of patients, many

scientists admit that the term “schizophrenia” has already outlived its usefulness as a clinical concept denoting an independent disease [148, 149]. There are proposals to replace it with neurophysiological terms at the level of syndromes [8, 28]: “dopaminergic system dysregulation syndrome” [150] or “saliens dysregulation syndrome” [151]. In 2002, by the decision of the Japanese society of psychiatrists and neurologists and the community of relatives of patients, the diagnosis of schizophrenia was changed to “disorder of loss of coordination” [152]. In South Korea, schizophrenia has become a “violation of internal attunement” or “psychosis susceptibility syndrome” [153]. However, destigmatizing patients is not possible through the simple replacement of the terms established in psychiatry. Such substitution may arise from socio-psychological desires, but it does not correlate with medical realities. It is necessary to change the attitude of the society towards mentally ill patients as a part of its humanization as a whole [154, 155].

In the middle of the 20th century, a non-academic approach to psychopathology called the “antipsychiatry movement” emerged that opposes the orthodox view of schizophrenia as a disease. According to the members of the antipsychiatry movement [156–158], mentally ill patients, including patients with schizophrenia, are not really sick but are rather individuals with non-standard thoughts and behavior that is inconvenient for society. It was noted that society is unfair, classifying their behavior as a disease and “subjecting it to treatment”. T. Sass [158] even argued that schizophrenia does not exist, claiming that it is a societal construct based on the notion of norm and not norm. However, ambiguous criteria for necessity or needlessness of therapy may contribute to the usage of psychiatry and especially of the diagnosis of schizophrenia for manipulative purposes [159]. It seems that “antipsychiatry” is a topic for a separate analysis, and will not be included further in this article.

4. Errors in diagnostics of schizophrenia

The highest frequency of overdiagnosis of schizophrenia in accordance with the ICD-10 criteria was observed in examples of manic and manic-delusional attacks of bipolar disorder and schizoaffective disorders [26, 160–162], polymorphism, and atypical manifestations of bipolar disorder and personality disorders which, in combination with low levels of social adaptation, can lead to diagnostic

errors [24, 163, 164]. As is known, no unambiguous criteria have been found to distinguish between bipolar disorder and schizophrenia during the last one hundred years [24, 165, 166]. It is concluded that clinical interviews, such as MINI, CIDI and SCID (MINI (The International Neuropsychiatric Interview) is a structured interview to identify the most common disorders according to DSM-IV and ICD-10 criteria [165, 166]; CIDI (Composite International Diagnostic Interview) is a highly structured tool for the diagnosis and classification of mental disorders, this scale was created as a part of a project by the World Health Organization and the US Office of Alcoholism, Addiction and Mental Health, it consists of 288 symptom questions, and takes longer to complete than MINI [165, 166]; SCID is a Structured Clinical interview for DSM-IV diagnosis), conducted in dynamics are important to reduce the role of the subjective factor in the differential diagnosis of endogenous mental disorders. The sensitivity and specificity of diagnosing schizophrenia by SCID [167, 168] is 19% and 100%, respectively, so this interview should only be used by clinicians in comparison with empirical data. P.Y. Muchnik (2020) noted that extensive diagnostics of schizophrenia is associated with biased or dogmatic ideas about the essence of affective psychoses, their incomplete coverage in the clinical state in manuals, and giving decisive importance to non-specific psychotic symptoms [169].

Differential diagnosis in the underdiagnosis of schizophrenia can be complicated by various factors, such as the pathomorphosis described above, the possibility of dissimulation [37, 170, 41] by psychiatrists [37, 36, 46, 25, 170], and comorbid pathology. A.A. Dvirsky (2001) [171], T.V. Klimenko [172], and other authors noted the difficulties in diagnosing schizophrenia when combined with chronic and acute intoxication more than 30 years ago [173, 174]. In recent decades, it has been stated that the factor of comorbid psychoactive substances addiction has taken a large place in the differential diagnostic process of schizophrenia [175, 176].

As has long been known, in schizophrenia the influence of a psychogenic factor on the clinical picture cannot be ruled out. According to S.P. Yelkin (1999) [171], stressful situations take place in many cases around the onset of paranoid schizophrenia. This has been confirmed in different years in the works cited above. With regard to diagnostic errors, the role of stress was described by N.S. Lebedeva (2003) [172], and A.A. Shmilovich (2013) [173].

According to N.S. Lebedeva [172], 4–6% of patients with schizophrenia get an incorrect diagnoses annually. Atypical psychopathological conditions caused by exogenous factors may have significant phenomenological similarity to responses to stress in disharmonious personality [173, 174]. Each exogenous factor contributes its psychopathological elements to the structure of the clinical picture of schizophrenia. Reactive states can develop against the background of remission, which is especially difficult in the case of differential diagnostics. At the same time, differences with true exogenous disorders may be minor and unstable.

In addition, simulation for different purposes can be the reason for the erroneous diagnosis of schizophrenia; it is facilitated if the patient possesses a certain supply of psychiatric knowledge [175, 38, 176]. No less relevant in this regard are mental changes that mimic the manifestations of schizophrenia and are caused by somatic diseases, social factors, including macroeconomic ones (difficulties with work, etc.). At the same time, a decrease in the energy potential, apathic-abulic disorders can be noted not only in the framework of the schizophrenic process, but also in chronic infections (tuberculosis, infectious hepatitis, etc.), oncological processes, which has also been observed since ancient times. In recent years, HIV infection has become relevant and more recently — the consequences of COVID-19 [177].

According to the observations of N.G. Shumsky [178], fear of damaging the patient by a schizophrenia diagnosis is a certain subjective reason causing the underdiagnosis of schizophrenia. This can be psychologically explained by the predominance of people with the onset of this disease during childhood and adolescence, when the presence of a psychiatric diagnosis due to stigmatization can strongly affect social adaptation. Some doctors hope for age compensation of psychopathology with the formation of a picture of a non-endogenous disorder. Several authors [20, 178] noted that until the moment of correct psychiatric diagnosis, the duration of the disease may often span from 10 to 20 years. It is highlighted in the literature that the number of people in different countries of the world who suffer from schizophrenic psychoses is almost the same. However, the symptoms on the basis of which the diagnosis is made depend significantly on time and culture. This is why the clinical picture and the severity of all manifestations of the disease are

susceptible to cultural pathoplasty (which coincides with the data of M.V. Yakovleva) [179].

Subjective errors in the diagnosis of schizophrenia can be caused by insufficient study of the anamnesis when the past psychotic state remains undetected and this fact subsequently remains hidden. In such cases, patients at some stage of life may appear before a psychiatrist as primary cases, which becomes a cause of the confrontation between the patient with schizophrenia and doctor, when a patient believes that the diagnosis will estrange them from society and dissimulates their anamnesis for this reason. Objective information about the mental state can be quite contradictory, which may be related to the very essence of schizophrenia.

Subjective reasons for under- and overdiagnosis of schizophrenia may also be connected with the psychiatrist being insufficiently qualified, preventing a proper assessment of the mental state, with a psychiatrist's bad mood or lack of time [180]. It is known that in the ICD-10, several diagnoses can be placed on the same axis, which does not facilitate compliance with methodological standards and does not reduce the frequency of diagnostic discrepancies. This trend also persists in the ICD-11, leading to a blurring of the boundaries between psychopathology and behavioral characteristics, which is already a concern for psychiatrists around the world. This contributes to objective and subjective causes of diagnostic errors. In many cases, they are connected with the incorrect explanation of mechanisms at the adaptation level — high or low. However, the criteria for the level of adaptation may change in parallel with social change. Objective and subjective causes of diagnostic discrepancies may be related to the inaccurate understanding or application of dimensional and categorical diagnostic models. This, in turn, can erase the boundaries of normality and pathology and underscores the importance of following a systematic approach at all stages of diagnostic analysis [151, 181]. Disagreements in the diagnostic approaches of general psychiatry often have a negative effect on the diagnostic argument in forensic psychiatry, and can, of course, have legal consequences. Another cause of misdiagnosis may be linked to the indifference of specialists to their work and, accordingly, the fate of the patient. [150, 151, 153]. This, in turn, corresponds with the data that at the end of the 19th century doctors were much more likely to pay attention to their own mistakes

than in the 20th to early 21st century, when mistakes were ignored [182]. In general, diagnosis in psychiatry is still largely subjective, so the “doctor factor” is one of the main issues in assessing psychopathology [150].

In recent years, the differential diagnosis of schizophrenia is often difficult due to significant migration of the population, including ethnically diverse groups. Ethnocultural factors in the diagnosis of schizophrenia are important in many countries and objectively complicate the diagnostic process. According to an extensive study, British citizens of African-American descent are twice as likely to be diagnosed with psychosis in comparison to citizens who are not a part of racial minority, but are 3–9 times more likely to be diagnosed with schizophrenia [151]. However, schizophrenia may be diagnosed on the basis of a smaller number of symptoms in comparison with white patients [151]. Such a situation can be regarded as a result of pathoplastic influence of culturally and socially conditioned forms of behavior on the design of the picture of psychopathology — that is, as an error in differential diagnosis. In other cases, according to the findings of the abovementioned study, there is more reason to assume that psychiatrists are biased when diagnosing non-white people. However, according to other data, in different ethnic groups with different content of psychopathological experiences, there is a basic similarity of psychoses, which allows a correct nosological hypothesis to be constructed [183–185]. Studies have shown that migration is an objective factor in the potential triggering of the manifestation or exacerbation of endogenous diseases [186]. Certain groups of migrants in the Netherlands and Sweden showed an increased risk of non-affective psychotic disorders compared to indigenous peoples and other migrants. At the same time, it is acknowledged that this problem has not, to date, been sufficiently studied [186]. Non-optimal language skills and psychogenic pathoplasty, along with subjective factors (mutual distrust of the migrant and non-migrant doctor and patient, ethnosocial barriers, etc.) can objectively complicate the diagnostic process [187–189].

Similar diagnostic problems in recent decades, as noted above, have been noted in many countries. In the case of follow-up change of the diagnosis of endogenous disorder (schizophrenia), diagnostic error may have a complex genesis — objective and subjective, as well as deliberate aggravation of the diagnosis.

Diagnostic discrepancies and errors in psychiatry in all countries are analyzed not only according to medical, but also to social and legal aspects. A special place is occupied by naturally unacceptable abuses of psychiatry for various purposes (political, with the aim of appropriating the property of patients, unjustified deprivation of certain rights, approbation of little-studied methods of treatment, etc.). As a rule, it is a question of the legality or illegality of diagnosis of schizophrenia and mental underdevelopment. It should be noted that abuses in this field of medicine have long been identified, which is reflected in works on the history of psychiatry [190, 191]. The problem appears to require separate consideration beyond the scope of this article.

DISCUSSION OF THE RESULTS OF THE REVIEW

Thus, as shown by the analysis of the literature conducted, the causes of schizophrenia remain mostly unclear. However, over the past few decades, research has gained depth and evidence (genetic, immunological, morpho-cytochemical, and others). The roles of biogenic amines, in particular dopamine, are being studied increasingly comprehensively in schizophrenia. Although some of the results of schizophrenia research are controversial, this research is ongoing. This is explained by the vast medical and social significance of the disease and the hopes of scientists for the development of science. This will change the lives of patients, since it will be possible to discuss optimal therapy and possible prevention.

The present review of the literature suggests that psychiatrists have always had the basis for various views on the course of schizophrenia and criteria regarding its dynamic stages, including remission. Remission in schizophrenia combines many complex issues (differential diagnosis, therapy, pathomorphosis, comorbid pathology) and can be considered an independent aspect of the disorder under consideration. In various years, scientists have found arguments for looking at schizophrenia both as a single disorder or as a group of disorders. The polymorphic symptoms and typical dynamics of diverse forms of schizophrenia have been systematized but neither in Russia nor in other countries has the concept of pathogenesis been formed. Given the constant multifactorial pathomorphosis of schizophrenia and the rapid changes in ecology, society, and pharmacotherapy, its clinical criteria may change. Nevertheless, there is no reason to agree with the

assumptions that the term “schizophrenia” has become obsolete. From our point of view, the abovementioned causes of under- and overdiagnosis of schizophrenia cannot cover all the possible difficulties that arise in the diagnostic process.

In general, as follows from rather controversial Russian and foreign literature, it will still take a very long time before the problem of schizophrenia is solved. It seems that this timeframe is largely depends on the position of society, the development of the biological sciences and technology, and the pathomorphosis of the disorder itself. Many aspects of schizophrenia may become clearer and less controversial with systematic studies based on previous and subsequent data.

A review of the literature on the above mentioned aspects of schizophrenia should focus scientific attention on certain research results at a new stage of methodological possibilities, with a different analysis and synthesis of information.

CONCLUSION

The present literature review contributes to a better understanding of schizophrenia research and might be used to improve the quality of life of patients with schizophrenia and reduce the burden on society associated with such patients. The data presented on the etiology, psychopathological and diagnostic criteria of schizophrenia can guide scientists in choosing the most promising areas of schizophrenia research and practice. The review may be useful for the further research of schizophrenia and diseases on the schizophrenic spectrum.

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