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Relationship between schizophrenia and tobacco smoking - literature analysis

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ABSTRACT

Introduction: There is common statement, that schizophrenia patients are more likely to smoke comparing to the total world population.
The aim of the study: The aim of this article is to find out why do schizophrenic patients smoke, how does it affect them and what can be the cause of susceptibility to smoking.

Material and method: The research of the scientific articles was made on a database of PubMed and Google Scholar.
Description of the state of knowledge: Many different associations were found during the research such as these describing that patients with schizophrenia have up to two to five times higher risk of developing type II diabetes. Also patients with diagnosed schizophrenia are characterized by low neuronal activity of the frontal and temporal lobes of the brain. In post mortem studies in schizophrenic patients a decrease in the number of M1 and M2 receptors in the brain was found, mainly in the dorsal lateral part of the prefrontal cortex, hippocampus, striatum and cingulate cortex, and decreased number of nicotinic receptors in the hippocampus, thalamus, cingulate cortex and prefrontal cortex
The key process of undergoing of nicotine is the induction of the cytochrome P450 1A2 enzyme (CYP 1A2), thus increasing the metabolism of antipsychotic therapeutics, e.g. olanzapine, clozapine what explain why usage of nicotine is told to be self-treatment in schizophrenic people.
Summary: This article gathers scientific research on the relationship between schizophrenia and susceptibility among patients to smoking addiction and its impact on both mental and physical health. However, not all mechanisms are known yet.

Key words: schizophrenia disease; nicotine; tobacco; smoking;

1. INTRODUCTION

Schizophrenia is a chronic disease that belongs to the group of psychoses. Although it affects only 1% of the world's population, it has serious consequences. The most important symptoms of the disease are: an inadequate perception of the world, experiencing, receiving and bad assessment of reality. These disorders make it very difficult for patients to function normally in the society. Schizophrenia is most often diagnosed in young adults around 18-35 years old. The diagnosis is made on the basis of an interview with a doctor, but there are no specific laboratory tests that could confirm or exclude schizophrenia.

People with schizophrenia often have comorbidities. These include depression, anxiety disorders and other psychoses. In addition, nearly 40% of patients abuse psychoactive substances.

Factors that can affect schizophrenia are genetic and environmental conditions, including stress, sociological and neurological processes. Very high heredity of schizophrenia is reported. If one of the parents suffers from schizophrenia, the probability of getting it by the child raises up to 18%. When both parents are sick, this probability increases even above 20% [1].

This disease consists not only of its symptoms, but also the consequences arising from them. With such disorders as in schizophrenia, social problems are also common - in dealing with other people, finding a job which increases the percentage of unemployment, poverty and homelessness. Overall, it is said, that the reduction of quality of life for people with schizophrenia relative to a healthy population is present [2]. The patients themselves state that

their level of education and social status is lower [3]. What is more, the life expectancy of schizophrenia patients is also shortened, as there is a correlation between schizophrenia and diabetes (patients with schizophrenia have up to two to five times higher risk of developing type II diabetes) [4]. In addition, suicides are much more common in the group of patients compared to the healthy population [5].

On a neurological basis, schizophrenia is distinguished by increased dopaminergic activity in the mesolimbic pathway in the brain. Due to the fact that the D2 dopaminargic receptor appears to be the most important, the treatment of schizophrenia is based on blocking the D2 receptor by classic neuroleptics or on blocking other receptors (especially 5-HT2 and α1, H1 and M1 receptors) by alternative neuroleptics. Blocking the D2 receptor is especially important for patients complaining about excess environmental stimuli and over-estimating them. However, it is worth noting, that pharmacological treatment of schizophrenia with neuroleptics may result in the onset or worsening of the symptoms of pharmacologically released Parkinson's syndrome [6].

Researchers who have studied neurology and schizophrenia have found that the volume of the entire brain of a person with schizophrenia is smaller than that of healthy people while the volume of their left hippocampus is increased. What's more, there is evidence that the left hippocampus is the responsible mediator between the negative symptoms of the disease and the memory of sounds and speech which is associated with the pathomechanism of schizophrenia [7]. There is increased activity of many places in the brain such as: bilateral dorsolateral prefrontal cortex, posterior parietal cortex, anterior cingulate cortex, and supplementary motor area. This is because of the higher density of D2 receptors. Then, because of these receptors and the use of amphetamines with a similar chemical structure to dopamine, the symptoms of schizophrenia may get worse after consuming amphetamines.

However, in addition to increased brain activity, sites with increased inactivation have also been found. These are, for example: ventral medial prefrontal cortex and posterior cingulate cortex which are part of the default mode network [8]. The default mode network is especially active when someone does not get excess stimuli from the outside, when he relaxes, thinks about himself, remembers the past or plans the future [9]. So if there is even an excess of stimuli, the default mode network will then be distinguished by increased deactivation. What's more, studies prove gray matter disorders and global functional connectivity density (gFCD), both of which are disturbed in many places in the brains of schizophrenia patients [10].

2. MATERIALS, METHODS AND AIM

The aim of this article was to find out the relationships between smoking tobacco and the schizophrenia. The articles were found in PubMed and Google Scholar database according to following keywords: schizophrenia disease, nicotine, tobacco, smoking.

3. USAGE OF PSYCHOACTIVE SUBSTANCES BY SCHIZOPHRENIA PATIENTS

Psychoactive substances (PAS) include substances that affect the central nervous system (CNS) by directly affecting the brain. Some of them, such as opioids and cannabioids, can be

used in medicine as painkillers. Cannabidiol - cannabis oil, obtained from cannabis leaves has healing properties attributed to neuroleptic drugs. It is a substance that does not belong to PAS, in contrast to the cannabis in which it is found. It also has fewer documented side effects belonging to extrapyramidal symptoms, which are the least desirable side effects of neuroleptics [11].

Others, however, as stimulants are used by society to exert some effect on the body. Some of them can be used to stimulate the body - stimulants (e.g. amphetamine, ecstasy, methamphetamine), and others as hallucinogens (e.g. LSD, hallucinogenic mushrooms, marijuana), where hallucinations may occur after consumption larger amounts of them. The effect depends on the receptor on which the substance is working. Thus, e.g. morphine or heroin as opioids, by stimulating the opioid receptors of nerve cells, cause analgesia, reduction of gastric peristalsis and bradypnoe.

Hensala et al. found that the use of LSD accelerates mental episodes and hospitalization of patients, which is associated with about 25% of cases of this disease. The rest are responsible for poor premorbid adjustment of the patient, high risk associated with the patient's family history, and abuse of other PAS [12].

PAS abuse is very popular. Statistically, schizophrenia patients use cocaine, cannabis, hallucinogens, inhalants, caffeine and tobacco, either significantly more or to the same extent as healthy or ill people with other mental illnesses [13]. Statistics show that up to 60% of patients with schizophrenia abuse the PAS [14]. Most often, because almost every fourth person (24%) abuses alcohol, and less by 10 percentage points (14%) other PAS. In 27.5%, PAS abuse occurred before the first symptom of schizophrenia. In 37.8%, it was only after the first symptom that the patient began to abuse the PAS. Every third patient (34.6%) started drug abuse in the same month in which the first symptom of schizophrenia occurred [14].

What's more, research shows that from people who suffer from schizophrenia, those who abuse one of the PAS have a higher level of intelligence, which may be associated with a higher socioeconomic status before falling ill, as well as with higher cognitive functions of the body. In addition, they often come from families with a higher social status and have better language skills [15]. However it is worth noting, that patients who currently abuse PAS have a lower level of quality of life but also fewer negative symptoms of disease than patients who do not abuse any PAS. A very important observation in the Addington study is the fact that people who have used PAS in the past had an earlier age of schizophrenia recognized, but also had no personality problems [16]. Patients in PAS look for the effect of being "high" to alleviate the symptoms of depression and for relaxation or pleasure, while ignoring the side effects of these drugs [17].

However, if you consider how long the patient has been taking the PAS before, you can see the relationship that the longer (more than 6 months) patients were using them, the more such symptoms occur, have more pre-illness personal disorders, have a greater risk of developing schizophrenia and other disorders [18].

The impact of PAS (alone) and schizophrenia on the brain has been examined in magnetic resonance imaging on patients suffering from schizophrenia and on people taking PAS. Studies have shown the effect of drugs on increased neuronal activity on the limbic lobe and prefrontal part of the brain compared to the control group. People with long periods of drug abuse are characterized by the loss of gray matter of the brain in these regions. In turn, patients with diagnosed schizophrenia are characterized by low neuronal activity of the frontal and temporal

lobes of the brain. However, the largest brain volume losses occurred in patients with schizophrenia abusing PAS [19].

4. SMOKING TOBACCO BY SCHIZOPHRENIA PATIENTS

Tobacco smoking has been seen for many years. Today, cigarettes are the most well-known and widely available tobacco products.

According to WHO, every fourth person in the world smokes cigarette. In connection with the addiction, about 7 million people die every year, of which about 890 thousand are passive smokers who are only exposed to inhalation of cigarette smoke from smokers [20].

Cigarettes are the most common form of tobacco use. Right next to them there are cigars, electric cigarettes and others. Cigarettes contain tobacco leaves and a psychoactive agent - nicotine [20]. As it is well known, smoking these products harms health on many levels, contributing to lung, larynx, as well as to tounge cancers, and other respiratory diseases. Tobacco leaves contain, among others, tobacco glycoprotein (TGP). It is a substance that has factor XII activating properties. This activates blood coagulation. In turn, increased coagulation may have its effects in hematopoietic diseases and affect vascular embolism [20].

Metals that are dangerous to human health can accumulate in tobacco plants, from which they enter the human body during smoking, even as carcinogens. Such metals can be, for example, arsenic, cadmium, chromium, nickel, lead, which over the years 2009-2012 have been isolated in cigarettes available on the Chinese market [21]. Six brands of cigarettes available in the United States have been tested for lead-210 and polonium-210. It was confirmed that the filters found in cigarettes significantly reduce the amount of metals and tar entering the body. After all, the amount of lead-210 in 4 out of 6 brands of cigarettes is about twenty times higher than the amount of this naturally occurring element even in the air [22].

Another study dealed with the difference in metals found in leaves, smoke and tobacco ash, such as arsenic and cadmium. The same research shows that there is much more arsenic and cadmium in tobacco ash than leaves before burning. Studies state that their quantity is not high enough to have a harmful effect on human health, but as it is known, addictive smokers can smoke a lot of tobacco a day, every day which could have some impact on their health as some substances tend to accumulate in a human body [23].

An important question arises here: why do people reach for tobacco products, despite the fact that they have negative effect on the human body? Tobacco has always been associated with relaxation. This is why people who live in constant stress often choose them as a form of escape from reality. A large amount of stress in human life negatively affects the well-being of people, causing them to change their behavior and perception of the world. They often have anxiety and excessive aggression, and contact with them is becoming increasingly difficult. Smoking only

allows an apparent escape from the problem, which only increases stress levels and the number of cigarettes smoked. Is it therefore possible to boldly associate smoking and stress with the development of schizophrenia?

It turns out that yes, because the latest research shows that during the action of a stressor, human genetic variation (changes in function or expression) of the CACNA1C gene that encodes the alpha-1c subunit of Cav.2.2 type L calcium channels (LTCC) can affect the development of neuropsychiatric disorders including major depression, bipolar disorder and schizophrenia through serotonergic mechanisms [24]. The results of other studies confirm that stress exposure during critical periods of life can be an important factor in the development of brain dysfunction, which represents susceptibility to psychosis, including schizophrenia [25]. Interestingly, subsequent studies indicate that even maternal stress and obstetric complications increase the likelihood of children developing schizophrenia later in their lives [26]. Thus, the above research confirms the relationship between stress in human life and the development of schizophrenia.

Referring to the topic of smoking, researches indicate that smoking is very common in schizophrenia. A meta-analysis of 42 studies from 20 countries showed that 62% of patients with schizophrenia were smokers, so the number is much higher than in the general population (OR = 5.3). One explanation for the high percentage of smoking in schizophrenia is the very controversial, so-called "self-healing hypothesis", which postulates that nicotine alleviates negative symptoms, extrapyramidal side effects (EPSE) and cognitive dysfunction by stimulating dopaminergic and glutaminergic prefrontal neurotransmission. Despite the controversy of this hypothesis, studies have shown that smokers had significantly less severe EPSE compared to non-smokers [27]. A very interesting discovery was also the fact that people with schizophrenia have much more problems with quitting smoking than healthy people and what's more - compared to the general population, people suffering from schizophrenia are four times more likely to smoke and then suffer from relatively greater negative health consequences. This increased smoking frequency is a potential cause of the observed increased risk among people with schizophrenia due to cardiovascular disease and diabetes [28]. In addition, patients with schizophrenia inhale the smoke deeper and extract a significant amount of nicotine from the cigarette. They are highly addicted to tobacco, and their attempts to stop smoking are more likely to fail [29].

The above studies confirm the relationship between stress and smoking, and the development of schizophrenia. People suffering from schizophrenia very often reach for cigarettes and it is much more difficult for them to cope with addiction. Stress in human life has a significant impact on both the appearance of the first symptoms of the disease and its progression. People with schizophrenia often stress more than healthy people, and also fall into the habit of smoking cigarettes more often, which in combination has a very negative impact on their health, making them more vulnerable to cardiovascular diseases and diabetes, among others.

5. THERAPEUTIC PROPERTIES OF NICOTINE IN SCHIZOPHRENIA

Research has reported that specific brain structures - subcortical and cortical - are responsible for the symptoms of schizophrenia. Positive symptoms are associated with the front part of the hippocampus, frontal peripheral region, medial prefrontal cortex, thalamus, ventral area of Globus pallidum, striatum, black substance and abdominal epithelial region. In contrast, negative symptoms associated with decreased frontal lobe activity - anterior, medial and dorsal prefrontal cortex [30].

There has also been a decrease in the activity of the thalamus, in particular in the medial dorsal nuclei. It is worth noting that the amygdala is especially important in the processing of emotions [31]

These structures form neural circuits. The way they are organized - connected and which receptor proteins in them, determines their function and correctness of information processing.

Classically, schizophrenia therapy is based on interaction with dopaminergic transmission. These drugs block D2 receptors in the neuronal pathways, in this way, eliminating positive symptoms [30].

The dopamine content is about 80% of the total catecholamines in the mammalian brain [30]. This catecholamine in the brain is responsible for the regulation of motor functions, is important in the learning and memory processes and controls emotional and motivational activities. It is located in the substantia nigra pathways; mesocorticolimbic system, often divided into two separate parts: mesocortical and mesolimbic [30].

Cholinergic deficits observed in the course of schizophrenia and their interaction with the dopaminergic system, gave the basis for the study of substances modulating the cholinergic transmission - muscarinic, nicotinic receptor agonists, allosteric receptors of these receptors and acetylcholinesterase inhibitors [31].

In post mortem studies in schizophrenic patients a decrease in the number of M1 and M2 receptors in the brain was found, mainly in the dorsal lateral part of the prefrontal cortex, hippocampus, striatum and cingulate cortex, and decreased number of nicotinic receptors in the hippocampus, thalamus, cingulate cortex and prefrontal cortex [30]. Acetylcholine in the brain is responsible for the regulation of, inter alia, excitation and cognitive functions, such as memory (including operational memory, spatial memory functions), learning, planning and others [31].

Moreover, in schizophrenia a strong decline in cognitive functions is observed, which is mainly due to glutamate and NMDAR receptors. This occurs with the equivalent inhibitory transmission - GABA. In the disease, this balance is disturbed in favor of inhibitory transmission in the cognitive pathways [32].

Nicotine's mechanism of action is multifaceted. This compound modulates the activity of dopaminergic, glutamatergic and GABAergic neurons [32]. They are destabilized in patients with schizophrenia.

To be precise, nicotine binds to the alpha 7 receptor placed on GLU neurons, and they activate themselves [33]. This improves cognitive functions. For this, it directly connects to the nAChRs receptor, which is located on dopaminergic neurons, and in this disease there is a reduction in its expression. But these receptors quickly desensitize, which makes it necessary to

stop using nicotine [33]. This explains the reason why the patients reach for a cigarette in the morning, after waking up.

In clinical trials, nAChR agonists and antagonists such as varenicline and mecamylamine have improved cognitive function in people with schizophrenia [34]. It has been shown that dopaminergic neurotransmission in the prefrontal cortex largely depends on the function of muscarinic receptors also refreshes the patterns of dopamine-dependent behaviours. This is probably due to the effect of cholinergic neurons on pyramid cells. Acetylcholine, through the muscarinic receptors M1 and M4, modulates the excitability of the CA1 and CA3 pyramidal cells of the hippocampus [31].

The disease is characterized by heterogeneity, according to some it is not one unit, but a set of symptoms. An interesting observation is that patients with schizophrenia are 3-4 times more likely to use nicotine than in the general population [35].

The liver is the main transformation site for nicotine in the human body, because nearly 90% of the absorbed nicotine is metabolized in liver cells [36]. The metabolic pathways of nicotine show a high degree of complexity. Despite the relatively simple chemical structure, nicotine in the human body undergoes very complicated transformations [38]. The key process is the induction of the cytochrome P450 1A2 enzyme (CYP 1A2), thus increasing the metabolism of antipsychotic therapeutics, e.g. olanzapine, clozapine [33].

6. SUMMARY

Schizoferenia is a serious disease classified as psychosis. Its development is influenced by a very large group of factors of various kinds, of which probably only a small part has been documented and already described. The relationship between the development of schizophrenia and tobacco so well described in the literature can be astonishing. When reading about the probability, one should not forget that each patient is different and reacts differently to different substances, including drugs and other environmental factors. A disturbing fact seems to be a large percentage of people addicted to psychoactive substances in a group of people suffering from schizophrenic disorders. Perhaps the development of pharmacology and understanding the mechanisms of development of schizophrenia will help reduce this percentage.

The fact that the positive and negative fields in brain disorders are disturbed is hopeful. This can be useful not only in the context of the therapeutic effects of tobacco, but also in the future understanding of the etiology of the disease, its prevention and effective pharmaco- and psychotherapy.

In tobacco, in addition to the already famous nicotine, we can find a lot of compounds, most of which are not inert to health, often showing negative and carcinogenic effects. This multitude of substances, with some of which we may not even be realized, explains the ironic relationship of tobacco as a predisposing factor for the development of schizophrenia, and on the other hand as a substance that makes the sick more strongly addictive and as a therapeutic compound in relation to schizophrenia. Thanks to such a large variety of substances, there will certainly be those that

have different effects. People are often afraid of the unknown, but in this case fear should be directed to thinking about the substances that we already know. However, such a spectrum of tobacco effects on the development and course of schizophrenia seems unbelievable, prompting further research in this area.

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