

The reasons for use of cannabinoids and stimulants in patients with schizophrenia

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Summary

Aim. Both cannabinoids and psychoactive substances from the group of stimulants can have a significant effect on the induction, course and treatment of severe mental illness. They also can be treated as self-medication. Many patients feel subjective benefits of using psychoactive substances in the areas of social competence, to cope with side effects of neuroleptics, stress accompanying mental illness or to control its symptoms. Our research tries to explain the causes of taking psychoactive substances by patients with schizophrenia.

Method. A total of 50 schizophrenia patients using cannabinoids, including 25 of them using also stimulants, took part in our research. They filled out questionnaires about the causes of drug use and subjectively perceived mental complaints. We analyzed medical documentation.

Results. It was found that subjects using both cannabinoids and stimulants pointed to spirituality as a cause significantly more often than subjects taking only cannabinoids. Marijuana and hashish were significantly more often taken to improve social relations. In both groups, the most common reasons were: curiosity, the need to relax, problem solving, improving relationships, and remedy for 'shyness'. In the group using only cannabinoids, it was observed that people who felt misunderstood often smoked marijuana to solve problems. Individuals using stimulants often complained of poor concentration.

Conclusions. Ignorance of the consequences of using psychoactive substances in people at risk of schizophrenia or in those already ill is an additional risk factor. The results may indicate an increased demand for psychoeducation and social support regarding many areas of life of patients suffering from schizophrenia.

Key words: schizophrenia, cannabinoids, stimulants

Introduction

The pathogenesis of schizophrenia is not fully explained. Despite the popular concept of dopamine, other important factors as genes and the influence of psychoactive substance use are also considered. The most commonly used drugs in patients with schizophrenia are cannabinoids and stimulants [1–3]. Besides the well-known neurotransmitter systems, the endocannabinoid system plays here an important role. It is responsible for different sensations and processes, such as appetite, pain, mood, memory, and psychoactivity. Cannabinoid receptors type 1 and 2 (CB1 and CB2) belong to the group of membrane receptors coupled to protein G [4]. Their most well-known agonists are exogenous substances – alkaloids of cannabis (*Cannabis sativa*): delta-9-tetrahydrocannabinol (Δ -9-THC), cannabidiol (CBD), cannabinol, also their synthetic derivatives, and endogenous substances: anandamide (AEA) and 2-arachidonoylglycerol (2-AG).

CB1 receptors are found in the olfactory bulb, cortex, hippocampus, amygdala, basal ganglia, thalamus, hypothalamus nuclei, cerebellar cortex, the nuclei of the bridge, and other parts of the brain [5]. They act as a neuromodulator – their activation weakens the release of GABA, causing suppression of inhibition in the central nervous system. CB1 agonists reduce the influx of calcium through calcium channels. They also affect the activity of potassium channels in the hippocampus: increase the strength of potassium currents type A by weakening the phosphorylation of potassium channels. As a result, they inhibit neurotransmitter release [6].

Action of endo – and egzocannabinoids slightly differ from each other. Endocannabinoids play an important role in modulating the strength of synaptic transmission, acting on presynaptic neurons in the mechanism of retrograde conduction. In inhibitory synapses they are excreted in postsynaptic parts, then go to presynaptic axon terminal, affecting the CB1 receptors here and reducing the secretion of glutamic acid or GABA, reducing GABA neurotransmission depending on the GABA-A receptor. This short-term plasticity caused by the activation of CB1 receptor is called depolarization-induced suppression of inhibition (DSI).

The release of endocannabinoids may be triggered in two ways: either by activating potential-dependent calcium channels due to postsynaptic cell depolarization – the high level of calcium within the neuron causes production and release of endocannabinoids [7–12]. The second mechanism is based on the activation of protein G receptors located on postsynaptic neurons [13–15]. These mechanisms may also overlap, which takes place during the activation of glutamatergic synapses [16–18]. The exogenous cannabinoids inhibit the secretion of acetylcholine [19], GABA [20] noradrenaline [21], and dopamine [22] from axon terminals. Administration of CB receptor agonists results in reduction of GABA level, especially in the prefrontal cortex. In the hippocampus the inhibition of neurons releasing glutamate plays a key role in selectivity of memory processes.

In turn stimulants, such as amphetamine or cathinones (e.g., mephedrone) affect catecholamine transporters – noradrenaline, dopamine and serotonin [23, 24]

strengthening neurotransmission in mechanisms of uptake inhibition and enhanced release. Amphetamine acts primarily on the area of dorsolateral prefrontal cortex, triggers psychomotor hyperactivity by an increase in dopaminergic activity at the level of basal ganglia. The sense of reward and increase of energy after ingesting it results from an increase in extracellular levels of dopamine and prolonged duration of its receptors in the striatum. Amphetamine increases the level of dopamine in three main ways: (1) as a substrate for the dopamine transporter (DAT), which delays the uptake of dopamine; (2) causes the dopamine movement outside the bubble; and (3) increases the secretion of dopamine into the synaptic cleft by DAT-related reverse transport [25, 26].

The best-known effects of cannabis use are changes of perception, euphoria and a sense of deep relaxation. It also causes the phenomenon of synesthesia – sound has its color, the color – its smell etc. [27].

In people with diagnosed mental illness, cannabinoids can exacerbate symptoms, trigger relapse and worsen the clinical course, although they are not enough to be the cause of the illness. Cannabis products can cause depersonalization and derealisation and even acute psychotic symptoms (delusions, hallucinations), as well as impair attention and memory. These symptoms are sometimes accompanied by anxiety, panic attacks and psychomotor agitation [28]. Typically, marijuana smoking is associated with increases mood, carefree, sedation, less common are anxiety attacks and hallucinations, particularly described in subjects using synthetic cannabinoids [29]. However, most of patients do not take cannabis to treat productive symptoms. They smoke because of social isolation, lack of emotions and feelings to other, low level of vital energy, difficulty sleeping, depression, anxiety, agitation, tremor, or boredom. These symptoms can result from mental illness, additional anxiety disorder or depression, or be side effects of medications [30].

Stimulants cause increased mood and drive, which is associated with a higher (often uncritical) self-confidence, activity or periodically more efficient cognitive functioning. In case of these drugs use, we may observe panic attacks, hallucinations or delusional interpretation of reality, even in previously mentally healthy people. Stimulants are among the most widely used psychoactive drugs in people with psychosis. They are used to reduce the severity of apathy and lack of energy associated with schizophrenia. However, they can cause psychotic states similar to schizophrenia among mentally healthy persons or exacerbate symptoms in already existing mental illness (e.g., schizophrenia). Dose which is large enough can induce a transient psychotic disorders, and regularly taken – even a chronic psychotic disorder that may not subside for several months after cessation of drug use. The main symptoms include paranoid states accompanied by hallucinations, delusions and disorders of the will that resemble schizophrenia. These symptoms may come back in the form of so-called flashbacks even after long periods of abstinence, e.g., due to stress [30].

Thinking of the risk of productive symptoms, increase in tension, anxiety and worsening of psychosis, we can wonder why patients with schizophrenia use drugs

of the above groups. According to the literature (2002), young patients suffering from schizophrenia often experience a subjective benefits of taking psychoactive substances, and therefore usually reluctantly cooperate with the doctor to give up the habit. They take drugs in order to: reduce depression (72%) and anxiety (64%), intensify the feeling of pleasure (62%), improve the ability to learn and work (17%), bear the side effects of medicines (15%), eliminate hallucinations (11%) and a feeling of suspicion (4%). They especially enjoy cannabis because, in their opinion, they stimulate activity, while having anxiolytic and antidepressant effect. However, they cause exacerbation of productive symptoms [31, 32]. Similar causes are mentioned by Canadian authors: an increase of pleasure, feeling “high” and reduction of depression [33].

Material

The study of 25 people with schizophrenia, 4 women and 21 men, with a history of cannabinoids use (the group hereinafter referred to as G THC): all of them smoked marijuana, including 1 subject who used synthetic cannabinoids, and 6 who used hashish. The age range was 18–38 years, median age – 29 years. In the next group of 25 schizophrenic patients (4 women, 21 men) all patients smoked marijuana (including 3 persons who used synthetic cannabinoids and 4 – hashish) and used stimulants (the group hereinafter referred to as G THC+S): 24 amphetamine, 1 methamphetamine, 5 persons MDMA, 13 derivatives of cathinone (mephedrone, buphedrone). The age range was 19–41 years, median age – 27. The study excluded people with a history of use of other drugs and major somatic diseases that might influence the course of schizophrenia (chronic somatic diseases, organic brain damage, mental retardation, alcohol dependence).

Method

All subjects completed the 15-item questionnaire, developed by the authors, on the causes of drug use. Medical documentation review was conducted. We also checked out what occurred first – contact with psychoactive substances or the first signs of schizophrenia. Patients also completed a 17-item form, developed by the authors, for symptoms that hindered their well-being the most. A limitation of the study was the current lack of validation of the proposed questionnaires. The following statistical methods were used: mean, median and standard deviation were used to describe quantitative traits. In the case of qualitative characteristics quantitative and percentage distribution was used. Due to the size of the analyzed groups, we did not evaluate the normal distribution of numerical variables. The analysis was performed using nonparametric methods. To compare the two groups we used the Mann-Whitney test. To evaluate the existence of the relationship between the quality characteristics we used the Pearson Chi-square test and the Fisher’s exact test. Results were considered statistically significant at $p < 0.05$. The analysis was performed with Statistica 12.5

software. The study was approved by the Bioethics Committee of the Medical University of Białystok (Resolution No. R-I-002/561/2012 of 25.10.2012, as amended R-I-002/561A/2012 on 20.12.2012).

Results

No statistically significant differences between the age of schizophrenia onset in both groups were observed. The mean age was 21–22 years. Subjects who were additionally using stimulants significantly earlier reached for psychoactive substances (SPA) for the first time – on average at the age of over 16 years, while the cannabis group – at the age of almost 18 years.

Table 1. Age, age of onset and age of reach for the psychoactive substances by subjects

Years	G THC+S (n = 25)			G THC (n = 25)			p
	Mean	Median	Stand. Dev.	Mean	Median	Stand. Dev.	
Age	28.28	27.00	5.52	28.60	29.00	5.42	0.712
Age of first schizophrenia symptoms	21.48	21.00	5.58	22.00	22.00	4.87	0.546
Age of first drug intake	16.44	16.00	2.35	17.96	18.00	1.99	0.016

It has been shown that in both groups ingestion of psychoactive agent came out ahead of the first symptoms of schizophrenia in 76% of patients. In each group there were 14 subjects declaring the use of drugs in the past year.

The average time from the moment of contact with psychoactive substances to the first signs of the illness in marijuana smokers was approx. 5 years and 5 months, while in the group using stimulants about 4 years and 5 months. There were no statistically significant differences between the two groups.

The reasons for reaching for psychoactive substances in the questionnaire listed:

- curiosity – as a desire to check how the subject will feel after taking the drug;
- the desire to explore altered states of consciousness (understood as different from the basic standby and from conscious experiencing of intrapsychic processes, subject's body and the environment with preserved ability to react properly to stimuli);
- the desire for spiritual experiences (hereinafter referred to as 'spirituality') – understood as a sense of contact with the Higher Power/Absolute, concerning religious experience in the context of the subject's life philosophy;
- the desire for internal development – subjectively perceived improvement of functioning on the intellectual and spiritual level;
- relax – also understood as reduction of the severity or disappearance of anxiety which can be felt during the course of the illness;
- improved memory and concentration – subjectively felt by a subject;

- solution of mental problems;
- improving social relations;
- regulation of psychological well-being – declared by the subject self-medication with the drug to achieve specific, desired psychological well-being;
- unreliability of drugs prescribed by a doctor – understood as insufficient effectiveness of the proposed medical treatment in the context of the fight against the symptoms of the illness;
- a desire to help themselves instead of going to the doctor;
- getting rid of shyness;
- disappearance of hallucinations;
- replacing feeling of emptiness – subjectively perceived symptom often occurring in the course of schizophrenia;
- improving sleep – falling asleep, sleep continuity and length of sleep.

It was found that the THC+S group, when asked about the reason for drug use, pointed to spirituality (40%) significantly more often ($p = 0.008$) compared to the THC group (only 16%). Marijuana and hashish smokers statistically ($p = 0.021$) significantly more often declared that they used drugs to improve social relationships (76%). This reason was reported in the other group by only 44% of subjects. There were no statistically significant differences between the two groups regarding other reasons.

Summing up the results, the most common reason was curiosity (up to 92%), the need to relax (up to 96%), other important reasons were: solving problems, improving interpersonal relationships (76% in the group using stimulants), getting rid of shyness (52% in the group using stimulants), achieving altered states of consciousness, mood regulation, and to replace feelings of emptiness (52–60% in the THC+S group, and 36–52% in the THC group).

Table 2. Reasons for using psychoactive substances in the THC+S and THC groups

Reason	G THC+S		G THC		p
	N	%	N	%	
Curiosity	21	84%	23	92%	0.384
Altered states of consciousness	14	56%	9	36%	0.156
Spirituality	10	40%	2	8%	0.008
Self-improvement	9	36%	4	16%	0.107
Relax	20	80%	24	96%	0.082
Memory/Concentration	7	28%	5	20%	0.508
Problem solving	15	60%	13	52%	0.569
Improving relationships	11	44%	19	76%	0.021
Well-being regulation	15	60%	13	52%	0.569

table continued on the next page

Medications failure	7	28%	5	20%	0.508
Instead of visiting a doctor	5	20%	4	16%	0.713
Shyness	10	40%	13	52%	0.395
Ceasing hallucinations	4	16%	3	12%	0.684
Replacing emptiness	13	52%	7	28%	0.083
Sleep improvement	9	36%	12	48%	0.390

Patients were asked what bothers them most every day in their well-being. The listed symptoms were subjective in nature; they were formulated deliberately in non-medical language to make them more accessible to the subjects. In case of doubt, the investigator specified the nature of the symptom. The questionnaire included:

- anxiety;
- feeling of emptiness – as subjective experience of emotional deficits found in schizophrenia;
- sadness – subjectively experienced depressed mood;
- sense of manipulation of patient's thoughts – experiencing delusions of influence;
- auditory hallucinations;
- visual hallucinations;
- other hallucination;
- feeling that people say/think bad things about the patient – experiencing persecutory delusions;
- difficulty in concentrating – subjectively felt in the context of difficulties in focusing on the content of TV news, program or reading magazine or book;
- memory problems – recalling the events of the past day, week (short-term memory) and youth/childhood (long-term memory);
- trouble sleeping – falling asleep, sleep continuity and length of sleep;
- feeling of being misunderstood;
- loneliness – subjectively experienced sense of social isolation;
- difficulty to speak up/formulating thoughts;
- difficulty in establishing contacts with other people;
- physical symptoms (tremor, muscle stiffness, difficulty in moving);
- no experience of pleasure – subjectively experienced anhedonia.

To complemented this study we conducted a series of neuropsychological tests confirming the objective cognitive impairment experienced by respondents. Discussion of the results, however, exceeds the scope of this article.

After analyzing the most common causes of using drugs (curiosity, the need to relax, solving problems, improving relationships, regulation of mood, getting rid of shyness), we found out that the following relationships are significant: people using stimulants often complained of poor attention, which was associated with using drugs because of curiosity. Likewise, subjects feeling the emptiness in their life, frequently used psychoactive substances to get rid of shyness.

Table 3. The relationship between the use of psychoactive substances because of curiosity and subjectively experienced attention problems in patients from THC+S group

G THC+S		Poor concentration		Total
		yes	no	
Curiosity	yes	16	5	21
	no	0	4	4
p = 0.010 total		16	9	25

We found that in the group using only cannabinoids the following relationships are significant: people who feel misunderstood often smoked marijuana to help themselves in problems solving. Those who negated sleep disorders often used drugs in order to improve relationships with other people.

Table 4. The relationship between the use of psychoactive substances in order to solve the problems and a sense of being misunderstood among patients from THC group

G THC		Misunderstood		Total
		yes	no	
Problem solving	yes	12	1	13
	no	5	7	12
p = 0.011 total		17	8	25

Summing up the data of all respondents, we paid attention to the following relationships: among those who did not indicate visual hallucinations as a factor significantly deteriorating well-being, the vast majority was taking drugs for relaxation (36 out of 38 people), and also for solving problems – 24 people (interestingly, in patients experiencing visual hallucinations, relaxation was also fairly common motivation: 7 out of 11 persons, in contrast to the desire to solve the problems with psychoactive substances – only three persons). Among the respondents who denied sadness as one of the most troublesome symptoms, most of them took psychoactive substances in order to improve social relations. Among patients who did not have trouble sleeping, drugs were also often used to improve relationships.

Table 5. The relationship between the use of psychoactive substances in order to improve social relationships and poor sleep among all respondents

Respondents		Poor sleep		Total
		yes	no	
Problem solving	Yes	5	24	29
	no	12	8	20
p = 0.002 total		17	32	49*

Discussion

Asking respondents about the reasons for using psychoactive substances, we made reference to the assumptions of the popular theory of self-medication – specific substances are used to relieve productive and negative symptoms as well as stress. More recent studies indicate that the most common motivation is to reduce the intensity of dysphoria. Some respondents also indicate that cannabis eased the productive symptoms and helped to endure the side effects of treatment [34]. The study of Pettersen et al. from 2013 rated motivation of people with mental illness (mainly schizophrenia and bipolar disorder) to use psychoactive substance at following issues: controlling the symptoms of mental illness, counteracting side effects of medication and achieving balance [34]. Our results also allow to respond to these categories – questions regarding improvement of memory and attention, regulation of psychological well-being, getting rid of shyness, ceasing hallucinations, replacing emptiness, improving sleep can be related to the desire to control the symptoms of mental illness, the questions regarding unreliability of drugs prescribed by a doctor and a desire to help themselves instead of going to a doctor – to cope with discomfort resulting from pharmacotherapy, and questions regarding the solution of mental problems, desire for spiritual experiences, desire for internal development – the internal desire to achieve balance.

In our study, in the THC+S group subjects frequently used drugs in order to achieve spiritual balance, and in the THC group – to improve social relations. In both groups the most common reason for using drugs was curiosity, but also the need to relax, which indirectly supports the desire to “break from the symptoms and difficulties” experienced in the course of the illness. Other social issues as the fight against shyness and desire to solve personal problems in this way, were also mentioned.

The study of Pettersen et al. [34] the most frequently cited reasons were to take a break from experienced difficulties (described as an “escape”, “sedation”, “break”), which can be related to the need to relax, which was one of the most common causes of drug use among our patients. One of the participants of the study of Pettersen et al. claimed that cannabis makes voices more silent than psychiatric drugs, and derivatives of amphetamines work here even stronger than cannabis. In our study, 4 people in the THC+S group and 3 in the THC group came to such conclusions, however, these

answers were least popular comparing to other chosen options. The least important reason in the group of cannabis smokers was the use of psychoactive substances instead of visiting a doctor.

The theory of iatrogenic action of neuroleptics is based on the assumption that antipsychotic drugs block some types of dopamine receptors to control psychotic symptoms. This can lead to an underactive dopamine reward system and increased susceptibility to psychoactive substance abuse [35].

Patients treated with neuroleptics of second generation take less amount of substance with respect to those treated with classic neuroleptics [34]. In our study, the use of psychoactive substances because of the unreliability of the medicines prescribed by the doctor was declared by 24% of all respondents. In the study of Pettersen et al. [34], the bulk of patients used drugs because in this way they coped with the side effects of medication and amphetamine derivatives were preferred substances in this matter. Patients wanted to have a few more “aroused” days because the medicines made them too sedated and sleepy. These substances also facilitate them to participate in social activities, which was also observed in our study. During periods of intensified pharmacotherapy patients used more amphetamines to actively manage with their own lives. Stimulants were treated as the opposite pole of neuroleptics and used to achieve balance. Stimulants helped them when they experienced auditory hallucinations, compensated for shallow emotions, as well as helped to lose weight. Patients were taking the substances in precise doses to minimize side effects. Here, the most popular were stimulants. Respondents reported that the excessive amount of psychoactive substances caused deterioration of psychosis. They had to take them very precisely to achieve a balance, so they knew their limits and were taking just as much substance as needed. Therefore they perceived more advantages than disadvantages associated with this procedure.

It is important, however, that in the study of Pettersen et al. [34] psychoactive substances use was secondary to the mental illness – one can consider drug use as a self-medication in each case. In our study the situation was opposite – the majority of patients with schizophrenia first had been taking drugs, then they started to be mentally ill. However, despite the illness, they continued to use psychoactive substances: in each group there were 14 people declaring using drugs in the past year.

Conclusions

Taking psychoactive substances usually precedes the onset of schizophrenia, which may indicate the role of inducing agent or paving the way for psychotic processes.

We found that the most common causes of drug use in the population of people suffering from schizophrenia were curiosity, the need to relax, solving problems, improving social relationships, well-being regulation and adjustment panacea “for shyness”.

Ignorance of the consequences that may result from the use of psychoactive substances, both in people burdened with a family history of mental illness, as well

as patients, is associated with the independent searching for help and “coping” with symptoms (e.g., impaired attention) with the help of these measures. Using drugs as “self-medication” may actually worsen the clinical picture of the illness, but patients are often not aware of it. Fear accompanying psychotic processes also leads to searching ways to “relax and unwind”. This brings temporary relief and short-term expected result, however, loaded with long-term side effects. Another problem are negative symptoms and social situations. Patients often experience discomfort accompanying the interactions between people, feel ashamed of their illness, fear of rejection, which intensifies the withdrawal and shyness. Here, patients often reach for cannabinoids products. Coping with everyday life problems, continuing education, which require efficient memory and attention, entering into relationships and sexual contacts – encourage to use stimulants.

The results may indicate an increased demand for psychoeducation and social support regarding many areas of life of patients suffering from schizophrenia. Further studies are needed in order to deepen this issue and plan further strategies for dealing with the problem of drug use by people with schizophrenia.

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