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Analysis of psychoactive and intoxicating substances in legal highs

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Abstract

"Legal highs" known also as "smarts", "legal drugs" or "boosters" contain in their composition psychoactive substances the production, sale and possession of which are not prohibited in legislation. They are offered for sale under the cover of collectors' items, a salt bath, aroma sticks, or plant fertilizer. Marketing was the reason for such high sales of these "highs" in Poland. The phenomenon became of concern when information became available about the first cases of tragic health consequences. Raising the awareness of youth about the level of imminent danger and serious consequences associated with the use of legal highs may be a very effective way to develop appropriate attitudes of young people, and in the light of their own health can help them take proper life decisions.

"Legal highs" are substances of natural or synthetic origin having psychostimulating properties. These compounds may differ in chemical structure, potency, half-life, metabolism and severity of side effects. Their pharmacological activity is associated with changes in the neurotransmitter system. After higher doses of "legal highs" psychotic symptoms may occur: visual and auditory hallucinations resembling schizophrenic endogenous psychoses. An alarming fact is the underestimation of the adverse effect of these substances on human health. Any actions aimed at improving this situation are extremely important; therefore, in one of the key projects undertaken at the Institute of Rural Health in Lublin, in cooperation with other scientific institutes, concerned the analysis of a selected series of "legal highs". This research was meant top serve as a source of information for science and medicine, and for popularizing knowledge about legal highs.

Keywords

legal highs, psychoactive substances, designer drugs, boosters

INTRODUCTION

"Legal highs" are substances of natural or synthetic origin having psychostimulating properties. These compounds may differ in chemical structure, potency, half-life, metabolism and severity of side effects. Their pharmacological activity is associated with changes in the neurotransmitter system [1, 2]. These compounds intensify the activity of dopaminergic and cathecholaminergic systems in the brain and inhibit the reuptake of serotonin, causing psychological and physical agitation, increased concentration, euphoria, or sometimes dysphoria, and impaired appetite. After higher doses of "legal highs" psychotic symptoms may occur: visual and auditory hallucinations resembling schizophrenic endogenous psychoses. Peripheral activity is related mainly to the effects on the cardiovascular system and the process of thermoregulation. This may manifest as an increase in blood pressure, tachycardia, cardiac arrhythmias, and hyperthermia. The skin and mucous membranes are dry, pupils dilated, there are tremors and convulsions. Acute poisoning with psychoactive substances can proceed with increasing signs of disorders of the central nervous system and cardiovascular system, a feeling of anxiety, increased mental tension, irritability, insomnia, fever, aggressiveness, hallucinations leading to delirium, panic attacks and suicidal tendencies [1, 2, 3].

The list of known substances with psychoactive activity is very long, and new derivatives are still being synthesized with as yet not fully known pharmacological and toxic properties. A study on the composition of the "legal highs" most common on the UK market has shown that the substances contained in them belong to three groups of compounds: derivatives of piperazine, cathinone (alkaloid constituent of *Catha edulis* leaves) and ephedrine / caffeine [4].

"LEGAL HIGHS" CHARACTERISTICS

Piperazine derivatives. The most common derivatives of this group of compounds are 1-methyl-4-benzylpiperazine (MBZP), 1-3-trifluoromethyl-fenylpiperazine (TFMPP);

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chlorophenylpiperazine (CPP), 1-benzylpiperazine (BZP) and 1,4-dibenzylpiperazine (DZP). These compounds are advertised as legal alternatives to MDMA – the product on the market known as "ecstasy". They block the reuptake of serotonin and dopamine, thereby increasing the concentration of these neurotransmitters in the brain. They do not, however, affect the release of monoamines which results in an effect weaker than psychostimulant MDMA [5, 6]. Oral administration of piperazine derivatives can cause euphoric reactions, psychomotor agitation, decreased need for sleep. The best known is the toxic effect of 1-benzylpiperazine, reported in the literature as serious hyperthermia, rhabdomyolysis, renal failure, seizures and even death after taking BZP [7, 8]. Synergistic effect of this group of compounds also have been reported [9].

Cathinone derivatives. Cathinone is a natural alkaloid occurring in the leaves of the khat tree (*Catha edulis*). It is released into the body while chewing the leaves of this plant, then metabolized to cathinesand norepinephrine, causing a biological effect similar to amphetamine. Cathinone produces euphoria, increased psychomotor drive, causes logorrhea. Regular intake of this plant raises blood pressure, causes inflammation of the gums and tooth loss. There have also been reported cases of cancer of the esophagus and stomach in patients treated with this preparation [10]. Cathinone was also used to treat post-traumatic stress [11]. The cathinone derivatives identified in "legal highs" are mainly ethcathinone, 4-metylmethcathinone (mephedrone), 3 - fluoromethcathinone, buphedrone (mephedrone analog) [12, 13]. These compounds are usually administered nasally, rather than orally or intravenously. Their function is to inhibit the reuptake of dopamine. The biological effect is euphoria, concentration and motivation improvement, logorrhea, increased empathy and a sense of closeness.

Cannabinoid receptor agonists. Cannabinoids are a group of chemical compounds originally extracted from the plant *Cannabis sativa*. These substances act on CB1 and CB2 cannabinoid receptors. They cause sensations such as euphoria and relaxation. Strengthening the collection of visual and auditory stimuli caused by marijuana is almost entirely due to the impact it has on those receptors in the brain. As with opioids, which bind directly to receptors for endorphins, cannabinoid receptors bind their specific molecule – anandamide. Anandamide is involved in regulating mood, memory, appetite, pain, cognition and emotion. Delta-9 – tetrahydrocannabinol (THC), the main psychoactive component of marijuana, also increases the amount of dopamine released by compensating for the inhibitory effect of GABA neurons. Long term use of cannabinoids may lead to the destruction of some neuronal receptors, modulating the release of acetylcholine. These substances exert an analgesic effect. Synergistic interactions of opioid and cannabinoid systems have been proved at trial antitussive effect of highly specific CB1 receptor agonist – WIN 55212-2. In the European and the US markets there are several synthetic compounds that stimulate CB1 receptors. For example, HU-210 – a cannabinoid synthesized in the late 1980s, a compound several hundred times more potent, bonded to the cannabinoid receptors and CP47-497, 2 - [(1R, 3S)-3-hydroxycyclohexylo] -5 - (2-metyloctan-2- yl) phenol, a compound synthesized by Phizer as an analgesic [14, 15].

TOXIC EFFECTS

A study on the composition of "legal highs" shows that the main active ingredients of these products are synthetic compounds originally produced in specialized laboratories as research chemicals with activity similar to illegal drugs. However, due to the fact that "legal highs" have become known more recently, there is still no reliable data concerning their toxic hazards. In the case of synthetic cannabinoids, some are known to have stronger affinity (up to 100-fold) to the cannabinoid receptors than natural THC, which may pose a threat to the health and lives of consumers [16]. They have not been thoroughly investigated in preclinical and clinical trials, and their duration of action and long-term effects are unpredictable. Another danger associated with the use of legal highs is the lack of guidance for consumers about the dose for users. The manufacturers' doses are inadequately specified, and the content of the active agent in these products is unstable and subject to considerable volatility. Therefore, the "legal highs" are not a milder version of the "black market" drug, where the dosage is well known to persons fairly well acquainted with the risks involved [17]. The presentation of "legal highs" by their manufacturers and retailers as natural alternatives to drugs (understood as narcotic drugs and psychotropic substances listed in the Act on Counteracting Drug Addiction) is a marketing technique under the guise that 'legal is safe' [17].

In the toxicology departments of hospitals in Poland there are more and more patients who overdosed on narcotic substances. In one of the toxicological wards in Lodz more than 20 people are admitted every week, an average of 3-4 patients daily. On reaching the hospital, the patients are usually unconscious or have hallucinations. Depending on the severity of poisoning, they are hospitalized (sometimes for a long period of time) or are outpatients. Often, those who are hospitalized are strongly stimulated mentally and physically. If psychotic symptoms persist, the patients are transferred to psychiatric hospitals for treatment [18].

Diagnostic laboratories do not have common patterns of substances found in the "legal highs". Patterns of physical, or in the form of an indexed list of substances (depending on the detection techniques), are necessary to detect their traces in the body (blood, urine). According to the description given by a physician toxicologists, a person under the influence of "legal highs" is aroused and behaves aggressively. Therefore, treatment involves the administration of sedatives and does not always require hospitalization of the patient. Unfortunately, the effects of repeated use of this type of narcotic substances unknown. Such problems might be encountered by health care representatives in touch especially with young people [18, 19].

USERS

Research conducted in many countries, including Poland, show that the users are basically three groups of individuals: 1) experimenters – interested in the action of various psychoactive substances, out of curiosity they use different types of drugs, 2) users of illegal drugs – which are legal highs, and thus for various reasons, less cumbersome alternatives to their preferred but illegal drugs, and 3) recreational users – who use drugs occasionally as an extra

attraction during weekend fun [20]. In 2009, using research conducted in Poland on substance abuse, respondents used measures and proved the most popular legal highs were associated with availability and legality [21]. Interviews with users of "legal highs" showed that the highs were treated by them as substitutes for illegal drugs. Therefore, the users chose the substances less friendly for health, the effects of which they were not always aware, but whose possession and use were not associated with criminal liability. The phenomenon was also observed of consumers returning to the "black market" version if certain substances were subsequently banned. Harmful "legal highs" are substitutes for the known and tested preparations and are new agents with unknown potential. Thus, they are substitute agents, even more dangerous and with severe consequences [3].

LEGAL HIGHS IN THE POLISH LAW

Over the past 40 years the global drug market has grown rapidly. At present, dozens of substances are known that may be substitutes for just delegalized synthetic compounds that are components of "legal highs". It seems that the removal of legal highs through the list of banned substances can take a very long time [22]. Proposed solutions are government efforts to prevent further development of the "legal drugs" market, which aim at: placing them on the list of banned substances regarded as the successors of existing substances, the possibility of e temporary suspension of trade in potentially dangerous compounds, obstruction of trade through frequent checks of stores, and prohibiting the use of associative advertising. Recently, due to adverse incidents caused by "legal highs", changes in legislation have occured more frequently. In 2009, the Polish Parliament amended the Act on Counteracting Drug Addiction, added 17 harmful substances to the list (mainly plant extracts, BZP and JWH-018) [23]. At the end of August 2010, the Act prohibited the trade of more "legal highs" containing mephedrone and some synthetic cannabinoides [24]. And at the beginning of October 2010, the Minister of Health ordered the Chief Sanitary Inspector to carry out checks on stores selling "legal highs", and close all premises which sold a substance named "Tajfun". The legal basis for this operation was Article 27 of the Act on State Sanitary Inspection, under which, in the case of "breach of hygiene and health requirements, which resulted in an immediate danger to life or health of humans, the State health inspector orders the immobilization of the workplace." Proof of the danger "to health and life" shoppers with legal highs were reports from all over the country of poisoning caused by the use of such substances [25].

After the entry into force of another amendment to the Act on Counteracting Drug Addiction and the Act on the State Sanitary Inspection in October 2010, shops offering "alternative measures" have disappeared from Polish streets [3, 26]. Some networks have resigned from the business, but the majority are still trying to rebuild their positions through online stores located on computer servers in countries with a liberal approach to the issue of "new drugs". Rebuilding the market position is associated on the one hand with a relatively aggressive sales policy, and the increase in "friendliness" of the sales process and availability of "legal highs" on the other. Maintaining the market dynamics for "legal highs" in Poland at the 2008-2010 level, however, seems to be impossible [3]. In the Act of 15 April 2011 amending the Act on counteracting drug addiction, new narcotic drugs and psychotropic substances were included. The list of controlled substances was extended by the addition of some synthetic cannabinoid agonists, derivatives of cathinone, piperazine and amphetamine [27].

MATERIAL AND METHODS

2,094 samples were collected during Sanitary Inspection checks of stores selling "legal highs", in the form of pills, tablets, gels, lollipops, powders and smoking mixes – sold as a natural herbal substances, or as products not for consumption – "collector's items", bath salts or plant fertilizers.

Chromatographic studies were performed with the participation of the Department of Chemistry at the Catholic University in Lublin. The test samples was subjected to ultrasound-assisted extraction with methanol. Analysis of the extracts was performed by high performance liquid chromatography, coupled with a tandem quadrupole/time-of-flight mass spectrometer. Chromatographic separation was achieved on the reversed-phase system using a C18 column and a linear gradient of mobile phase: 0.1% formic acid (A) and 0.1% formic acid in acetonitrile (B). Ionization of the compounds was carried out in an electric field (ESI). Positive ions were collected in the MS scan of m / z 100-1,000. Identification of compounds was based the database, developed for the purpose of determining suspected compounds.

RESULTS

In 1,796 samples from the 2,094 samples examined, 77 substances divided into 3 groups – the psychoactive substances on the list of narcotic drugs and psychotropic substances contained in Appendices 1 and 2 to the Act of 29 July 2005 on Counteracting Drug Addiction [28], the list of psychoactive substances not included on the list, and other substances that could be psychoactive were detected. In 1,002 samples (47.9%), one substance was detected, in 529 samples (25.3%) two components were found, in 179 samples (8.5%) three components, in 86 samples (4.1%) four components or more, and in 298 samples (14.2%), no substances were detected.

Depending on the chemical structure and specific activity, the most frequent compounds were cathinones – 985 times (15 compounds, MDPV most frequently), cannabinoids were found 951 times (16 different chemical compounds, and sometimes two or more in one sample, AM-694 and JWH-250 were the most frequent compounds). Less frequent were piperazine derivatives (detected 157 times – 4 compounds, most often TFMPP), psychoactive plants (91 times – 4 species, mainly *Piper methysticum*), and phenylethylamines (80 times – 7 chemical compounds, mainly ephedrine). Other compounds which did not fit into the above-mentioned groups were found 656 times (31 compounds, most frequently caffeine, but also dangerous substances like opiates derivatives, analgesics or toxic amines). In total, 77 compounds (or their isomers) were found in the total number of 2,920 findings.

The samples with substances from one group were the most frequent (it was not important how many and what

Table 1. Number of samples with different number of substances found depending on group, divided into provinces (LB – lubuskie, DS – dolnośląskie, PM – pomorskie, LL – lubelskie, OP – opolskie). Chi-square test was performed to check the homogeneity of counted frequencies, this showed that the distribution differed (X2 = 36.3, df=12, p=0.0003)

Number of groups	LB		DS		PM		LL		OP		Total	
	n	%	n	%	n	%	n	%	n	%	n	%
0	80	10	128	16	32	13	37	18	8	12	285	14
1	522	66	503	64	170	67	142	69	44	66	1381	66
2	145	19	128	16	34	13	22	11	9	13	338	16
3	41	5	23	3	16	6	4	2	6	9	90	4
Total	788	100	782	99*	252	99*	205	100	67	100	2,094	100

* percentage does not add up to 100 because of rounding.

Table 2. Number of samples found to be positive with substances from particular group, divided into provinces (LB – lubuskie, DS – dolnośląskie, PM – pomorskie, LL – lubelskie, OP – opolskie). Chi-square test was performed to check the homogeneity of frequency in every row (*p<0.05; **p<0.01; ns – not significant)

Positive result in a particular group	LB		DS		PM		LL		OP		Total		p
	n=788	%	n=782	%	n=252	%	n=205	%	n=67	%	n=2094	%	
1	225	29	182	23	48	19	40	20	21	31	516	25	**
2	552	70	527	67	196	78	131	64	47	70	1453	69	*
3	158	20	119	15	42	17	27	13	12	18	358	17	ns

substances were found, and from which group the substance came) – 66% in total, and 64-69%, depending on the province. Less frequent were samples with substances from two groups (16%, and 11-19%), with no substances found (14%, 12-18%), and with substances from three groups (4%, 2-9%). Although the percentage was similar in the provinces, chi-square test showed that the frequency was not homogenous between the provinces (Tab. 1).

On analysing a particular group of substances, the most frequent were samples with substances from the second group, found in 1,453 samples (69% of the total number, 64-78% depending on province), followed by samples with substances from the first group (516 samples, 25% of the total, 23-40% depending on province), and the last was the third group (358 samples – 17%, 13-20%). Test chi-square showed that the most similar distribution in the provinces was in third group of substances (Tab. 2).

Table 3. Number of substances found from particular group divided due to the type of the substance and provinces (LB – lubuskie, DS – dolnośląskie, PM – pomorskie, LL – lubelskie, OP – opolskie). Chi-square test was performed to check the homogeneity of frequency in every row (*p<0.05; **p<0.01; ***p<0.001; ns – not significant)

Type of substance	LB	DS	PM	LL	OP	Total	p
Cathinones	361	314	143	117	46	981	***
Canabinnoides	411	341	94	69	39	954	***
Amines	132	69	33	26	9	269	***
Other substances	55	85	33	9	3	185	***
Piperazines	48	72	30	7	0	157	***
Other pharmaceuticals	37	49	5	5	3	99	*
Other phenyloethyloamines	36	32	16	6	2	92	ns
Plants	46	33	10	1	0	90	*
Tryptamines	19	12	11	5	3	50	ns
Opiates	17	10	9	6	1	43	ns
Total	1,162	1,017	384	251	106	2,920	

In Table 3, the frequency of types of substances are shown where the substances found in samples were subscribed to one type from 10 types chosen to characterize the substance. The most frequent were cathinone derivatives, and in some provinces, cannabinoid receptor agonists; frequently found were also toxic amines, piperazines, and other substances (e.g. caffeine – which could not be subscribed to any of the remaining 9 types). The differences in frequency between provinces were measured with chi-square test.

Substances of a particular type were often found in one sample in multiple numbers. Cathinones and cannabinoids were frequently found as two, three or even four different compunds in one sample. Other types of substances were found sometimes twice in one sample (piperazines, plants, other pharmaceuticals, other substances or opiate derivatives (Tab. 4).

In general, most samples contained one (1,023) or two (531) substances. The next group were samples with no identified substances, followed in decreasing order with three, four or five substances. The proportions were similar in provinces,

Table 4. Number of samples with multiple appearance of one type of the substance

Types	Samples with multiple substances from one type			
	1	2	3	4
Cathinones	554	136	41	8
Canabinnoides	383	189	63	1
Amines	269			
Other substances	177	4		
Piperazines	121	18		
pharmaceuticals	81	9		
other phenyloethyloamines	92			
Plants	56	17		
Tryptamines	50			
Opiates	39	2		
Total	1,822	375	104	9

Table 5. Number of samples with multiple appearance of substances in different provinces (LB – lubuskie, DS – dolnośląskie, PM – pomorskie, LL – lubelskie, OP – opolskie)

Number of substances	LB	DS	PM	LL	OP	Total
0	80	128	32	37	8	285
1	388	388	104	109	34	1023
2	209	194	76	41	11	531
3	89	48	33	12	7	189
4	21	23	6	6	6	62
5	1	1	1	0	1	4
Total	788	782	252	205	67	2,094

with minor exceptions (LB and PM had more samples with three substances than with no substances) (Tab. 5).

When a particular type and number of substances were analysed in samples, the most frequent were samples with one cathinone derivative (276), and one synthetic cannabinoid (171), followed by samples where two cathinones (121) or two cannabinoids (112) were found, and the next was group with piperazine.

If the number of substances of one type was not taken into account, then the most frequent were samples with one or more cathinone derivatives (603), and one or more cannabinoid receptor agonists (412). The next group consisted of synthetic cannabinoids, together with toxic amines (166), piperazines (90), other phenylethylamines (65), and toxic amines (63).

DISCUSSION

Little data is available on substances found in "legal highs". Davies et al. [4] have found cathinone and piperazine derivatives, ephedrine and caffeine in samples obtained from Internet stores in the UK. Spiller found blood and urine in samples collected from patients who reported to toxicological centres after intentional abuse with :"bath salts". MDPV was found in the majority of cases, but no other cathinone such as mephedrone or methylone [29]. In the short description of substances at the National Institute of Medicines [30] on the same material, five groups of substances are mentioned: cannabinoids, cathinone and piperazine derivatives, phenyloethyloamines and tryptamines, and other substances (e.g. analgesic drugs). In the examined material, about 50 compounds acting on central nervous system were found that were not listed in the Act on Counteracting Drugs Addiction. No exotic plants were found in this study.

In September 2009, the prosecutor in Lodz ordered the examination of several samples of "legal highs" at the Institute of Forensic Research in Cracow which, however, did not reveal any prohibited drugs, and found that generally their consumption was not dangerous. In a few samples, small amounts of BZP were detected, but the substance was not yet on the Prohibited List in Poland [*31*].

Based on the literature data, several conclusions can be drawn on the implementation of preventive measures aimed at significantly reducing the number of people using such substances. According to the research, there is a need to provide reliable knowledge about drugs and their equivalents (i.e. based on scientific principles such as epidemiological data and reports), which will certainly be an effective tool for limiting the demand and harm associated with them among potential users. It is important to disseminate information, especially among young people, about the potential dangers of new drugs. Reliable transmission of information to the public on psychoactive substances will arouse public awareness, because to date this method of communicating – especially with young people – has been ignored, and the educational function of the penalties is imposed. Raising the awareness of youth about the level of imminent danger and serious consequences associated with the use of legal highs may be a very effective way to develop appropriate attitudes of young people, and can help them in taking the proper life decisions with regard to their health [32].

New amendment to the Act on counteracting drug addiction came into force on 9 December 2011**.** The amendments include the possibility of redemption proceedings in cases of possession of small amounts of drugs for personal use, and the utilization of alternative measures to criminal penalties for drug addicts. The duty to monitor patients in the drug treatment system was also introduced [33].

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