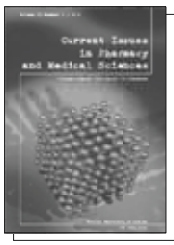

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"Legal highs" – drugs of the twenty-first century

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ABSTRACT

"Legal highs" is a term that embraces many compounds, including plant substances and synthetic derivatives. Trends in the use of traditional drugs of abuse by young people, are downward. On the other hand, we can observe an increasing prevalence of "smart drugs" use. These are often sold by online shops offering a wide range of products as alternatives to illegal drugs. However, the degree of risk posed by the use of "legal highs" for individual users, and for public health is unknown and difficult to assess [2,9,18]. The health risk may also increase when people use high doses of these products or mix these with alcohol or other drugs of abuse [18]. These drugs increase the risk of serious interactions and may lead to the poisoning of the body. Moreover, there is no information on their packaging about the active ingredients of the products, their dosages and their potential negative side effects. In addition, considerable variation was noted regarding the amount of information provided by online retailers about the mode of use and the health risks of the products they were selling [9]. What is more, these products fall outside pharmaceutical licensing regulations and control, and consequently their quality is not subject to scrutiny. This paper describes some of the selected substances known as "legal highs". It should be noted that the list of species of psychoactive, hallucinogenic and narcotic species, mainly plants and fungi, used to produce highs in the world, is much greater. Moreover, new psychoactive substances that appear require numerous and thorough research, and it is impossible to immediately determine the short- and long-term effects of the use of these substances. Let us hope that most of these substances will be soon under control and will be on the list of controlled substances.

Keywords: legal highs, BZP, TFMPP, Salviae divinorum, Diviner's Sage, Kratom tree, *Mitragyna speciosa*

INTRODUCTION

The term "legal highs" or "smart drugs" includes a wide range of products (synthetic or designer drugs, herbal mixtures) including mephedrone, Lion's Tail (*Leonotis Leonurus*), 1-(3-trifluoromethylphenyl) piperazine (TFMPP), Fly agaric (*Amanita muscaria*), 1-Benzylpiperazine (BZP), Kratom (Mitragyna speciosa), Salvia divinorum, Dream Herb or Leaf of God, (Calea zacatechichi) and Spice. This is a group of different psychoactive substances that are not controlled under the provisions of the act on counteracting drug addiction.

Before the changes in law that prohibit the sale of "legal highs", online stores that dealt with these items posted information about studies proving the harmlessness of these substances. Dealers claimed that "at least some of "smart drugs" were safe alternative to the harmful effects of illegal and addictive drugs". However, the information from these studies related only to the fact that they did not contain substances that were illegal at that time, and it did not mean that they were safe for users. It is true that the number of reliable research and analysis concerning "legal highs" is limited. However, laboratory analysis has revealed that the products sold as "legal highs" contained many impurities, thus showing the low quality and high randomness of the production process. Moreover, laboratory analysis revealed that amphetamines were one constituent in several of the sampled products, while others were complete fakes. Thus, the abuse of "smart drugs" can cause serious health consequences, including the death for users.

In general, products that are marketed as "natural" or "herbal" by retailers are perceived as being synonymous with the word "harmless." In regard to "Legal highs", they are claimed to be sold for use only as animal feed, plant fertilizer, room deodorizers, herbal incenses or even bath salts. They are also marketed as collectibles, absolutely not intended for human consumption.

The most popular source of information about such illegal drugs and their use is the Internet [9,19]. In recent years, a dramatic increase in the sale of "smart drugs" via the Internet has been observed, especially among young people [16]. The range of "smart drugs" includes herbs and "party pills" which have a stimulant, relaxing, psychedelic and hallucinogenic effect, and consumers of such items are considered youthful and 'with it'.

This paper presents the characteristics of a few examples of the substances belonging to the products deemed "Legal highs", as well as the impact they exert on human health.

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MEPHEDRONE

Mephedrone (4-methylmethcathinone) is a pharmacologically active alkaloid that is structurally similar to methcathinone, and can be found in *Catha edulis.*

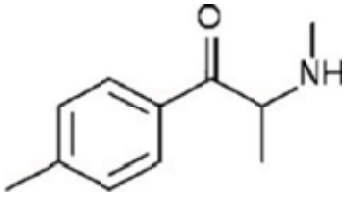

Fig. 1. Structure of mephedrone [13]

This drug is the most widely experienced "legal high" [7,16]. Due to the chemical similarity of this substance to amphetamines and methcathinone, it is often used as an alternative to the above-mentioned drugs [16]. Mephedrone acts as a central nervous system (CNS) stimulant by promoting the release of monoamine neurotransmitters norepinephrine, serotonin, dopamine and probably by inhibiting their re-uptake [16].

Accumulating evidence suggests that mephedrone is usually consumed orally (as a powder or tablets) or nasally (sucked through a straw or a banknote). It can also be taken by intramuscular/intravenous injection and rectal insertion. This drug is chemically unstable, so it is not suitable for smoking [13,16]. Clinical evidences suggest that mephedrone increases the libido and may lead to risky sexual behavior. Concerning its mechanisms of action, e.g. increased release of dopamine and serotonin and inhibition of their re-uptake (which is similar to amphetamines), mephedrone causes euphoria, empathy and reduction of appetite. Moreover, talkativeness, mood enhancement, mental clarity and hallucination are observed after mephedrone use. These mentioned effects are typically seen within 15–45 min after an oral administration. The onset of action following nasal insufflation is reported by users to come about within a few minutes and with peak effects observed within 30 min.

The main adverse effects reported by users of mephedrone include nose-bleeds, dilated pupils, blurred vision, dry mouth/thirst, hot flushes, tachycardia, hypertension, severe anxiety/agitation, vasoconstriction, nasal irritation secondary to insufflation of the powder, restlessness, bruxism and shrunken genitals (but only in men). The after-effects related to mephedrone use include numbness, headache, skin rashes, fatigue, dizziness, depression, short-term memory impairment and minor amnesia [13,16].

Additionally, mephedrone is sometimes used together alcohol or other drugs including heroin, cocaine, cannabis, ketamine and 3,4-methylenedioxymetamfetamine (MDMA). It is also reported that mephedrone is taken in combination with a variety of other compounds, e.g. methylone, butylone, methylenedioxypyrovalerone (MDPV), gamma-butyrolactone (GBL), Kratom, CNS depressants such as benzodiazepines, and many other items. As some users have reported cravings for mephedrone after use, it is probable for the use of mephedrone to carry the risk of dependency [16].

BZP

BZP is a synthetic phenyl analog of piperazine.

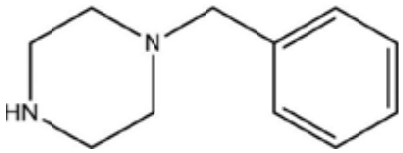

Fig. 2. 1-Benzylpiperazine [15]

BZP affects mostly the dopaminergic neuronal transmission in a manner similar to amphetamine. Research has shown that BZP inhibits dopamine re-uptake and post-synaptic activity of dopamine receptor agonists [4]. This drug is rapidly absorbed, extensively metabolized and has a relatively short half-life. BZP-party pills make users feel confident and relaxed in social situations, and thus the products facilitate social interactions. Young women also identified weight loss as a positive outcome of BZP use [4,15].

The negative immediate effects of BZP observed in clinical studies include psychological, neurological, cardiovascular and other systemic effects like tachycardia, hypertension, headaches, vomiting, nausea, dehydration/inability to quench thirst, racing heart, sore or shaking body, loss of appetite, trembling mouth or jaw, and an inability to urinate. Furthermore, consumers of BZP experience stomach pains, dizziness, sore eyes, teeth grinding, increased rates of smoking and bleeding nose, as well as agitation, anxiety and paranoia after the use of this drug [4]. The after-effects of BZP use occurred in the hours or days after taking the drug, and may include insomnia, lack of appetite, tiredness/lethargy, dehydration, headache, sore or dry mouth, aching/shaking body, depressed mood, tension and anxiety [4,15]. This drug is often ingested with other drugs of abuse such as ethanol, MDMA, cannabis, and other stimulants.

TFMPP

The popularity of TFMPP has increased in the last 10 years. This drug has little resemblance to dopaminergic stimulants and lacks adrenergic effects [6,8]. Moreover, evidence suggests that it has direct serotonergic activity. Indeed, it has been shown that TFMPP binds to serotonin (5-HT) receptors in the brain and prevents the re-uptake of 5-HT. TFMPP selectively binds to 5HT1 and 5HT2 receptors with minimal affinity for the 5HT3 receptor. Interestingly, the putative 5-HT receptor agonist properties of this drug resemble those of lysergic acid diethylamide (LSD), 1-[3-chlorophenyl]-piperazine (mCPP) and fenfluramine. Moreover, it acts as a stimulant by causing enhanced

release of catecholamines from sympathetic nerve terminals [10,15]. The pharmacokinetic properties of TFMPP have not been widely investigated. Accumulating evidence suggests that it is rapidly absorbed and metabolized extensively. Moreover, it has a relatively short half-life.

When used alone, TFMPP does not cause the euphoric effects produced by common stimulants such as dexamphetamine, cocaine and MDMA, contrary to combination with BZP, when it produces a euphoria similar to MDMA consumption. Moreover, it induces mild psychedelic effects similar to LSD and psilocybin [10,15]. TFMPP can cause harmful effects which include palpitations, agitation, anxiety, confusion, dizziness, headache, tremor, mydriasis, insomnia, urine retention and vomiting. TFMPP is often ingested with other stimulants [15].

SALVIA DIVINORUM

Salvia divinorum ("Diviner's Sage", "Mystic Sage", "Magic Mint") is a plant used in traditional spiritual and ethnopharmacological practices by the Mazatec Indians of Oaxaca. Other native uses for the plant include the treatment of diarrhea, headache, and rheumatism.

Salvia divinorum is one of the most widely marketed recreational botanicals available via the Internet [3,14]. The active component of *Salvia divinorum* is salvinorin A, which is a neoclerodane diterpene with potent and selective agonist activity at the κ-opioid receptor [1,11]. Stimulation of these receptors produces psychotomimesis, spinal analgesia and diuresis, but does not result in respiratory depression [3].

Fig. 3. Salvia divinorum [3]

Inhalation of either vaporized salvinorin A extract or smoked dried leaves produces psychoactive effects within seconds. Hallucinations occur rapidly after administration and are typically very vivid. *Salvia divinorum* produces synesthesia of the senses, like hearing colors or smelling sounds. The literature data mention that these hallucinogenic effects are typically brief, lasting only an hour or two hours. *Salvia divinorum*'s effects are similar in part to that of LSD, psilocybin, marijuana and MDMA [1,3]. The selectivity of salvinorin A for the λ-opiod receptors suggests that this natural product could be used as a probe to ascertain the molecular basis of a number of psychiatric conditions. In addition, there is an interest in the therapeutic potential of salvinorin A as an antipsychotic agent or novel antidepressant [3].

KRATOM (*MITRAGYNA SPECIOSA*)

Kratom tree (*Mitragyna speciosa Korth)* is an indigenous tree of Southeast Asia and Africa. Kratom has long been considered unusual in its dual stimulant and sedative properties. Interestingly, the leaves of Kratom have been utilized as a drug to enhance the ability to work, as a narcotic or as an alternative to opium due to its opioid-like effects. As early as the nineteenth century, Kratom use was prescribed to treat pain and opium withdrawal [3,12].

Kratom contains many alkaloids. Accumulating evidence suggests that mitragynine is the main alkaloid of the more than twenty alkaloids that have been isolated from Kratom. However, alkaloids of Kratom such as corynantheidine or 7-hydroxamitragynine are pharmacologically active.

Fig. 4. *Mitragyna speciosa* [3]

Interestingly, mitragynine is an indole alkaloid, structurally similar to yohimbine. In addition, it acts as a μ- and δ-opioid receptor agonist, and it may be involved in the activation of descending noradrenergic and serotonergic pathways in the spinal cord receptors [3].

Kratom leaves, which are very bitter, can be chewed, while their other ways of administration include eating dried leaves ground to powder, smoking, drinking teas, or using Kratom resin [3, 12]. The clinical effects of *Mitragyna speciosa* are dose-dependent. Indeed, in humans, Kratom has stimulant effects at lower doses and opiate effects at higher doses. Moreover, the antitussive, antinociceptive and antidiarrheal properties of mitragynine have been described as clinically similar to codeine. The withdrawal symptoms observed in Kratom users include vomiting, nausea, diarrhea, irritability, yawning, rhinorrhea, myalgias and arthralgias. Additionally, in chronic users, weight loss, hyperpigmentation and psychosis have been described [3].

"SPICE"

"Spice" is a mixture containing varied plant/herbal ingredients (e.g. betonicine, aporphine, leonurine or nuciferine). Unfortunately, there is a lack of information about the complete chemical composition on the packaging of the "Spice" products. Chemical analysis revealed that their psychoactive effects were due to the presence of synthetic cannabinoids such as JWH-018, JWH-073 and cannabicyclohexanol [17]. They are functionally similar to the active principle of cannabis Δ9-tetrahydrocannabinol (THC). The above-mentioned drugs act by binding to the same cannabinoid receptors in the CNS and other organs, as the endogenous ligand anandamide [5, 17, 19].

"Spice" products can be smoked, alone or with cannabis, or consumed orally. Drug users reported cannabis-like effects after smoking a "Spice" mixture. In this case, tolerance to the "Spice" products may develop comparatively rapid and might be associated with the phenomenon of dependence. Furthermore, there are reports that demonstrate signs of dependence linked to the chronic abuse of "Spice". Abstinence symptoms after withdrawal of these drugs are similar to syndromes observed in cannabis abuse. Negative effects after inhaling the smoke of "Spice" often include paranoia and memory loss. Moreover, during a phase of abstinence, internal unrest, tremor, palpitation, insomnia, headache, diarrhea, nausea, and vomiting are reported. Additionally, users have suddenly felt depressed and desperate [17]. Symptoms usually disappear after taking the drug again.

JWH-018, the synthetic cannabinoid added to "Spice" mixtures, causes fuzziness and mood improvement. This drug's users report that they felt tired, stoned and fuzzy, especially by the end of the day. Furthermore, JWH-018 has a potential carcinogenic effect [17, 19].

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