

## REVIEW

### DRUG ADDICTION. *PART I*. PSYCHOACTIVE SUBSTANCES IN THE PAST AND PRESENCE

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Substances capable of changing the functions of the central nervous system are widely distributed in plant kingdom, and many of them were discovered by ancient food-gatherers at the dawn of humanity. In the Old World only a few substances producing euphoria or altered states of consciousness and having habit-forming properties are still widely used. They are the products of poppy (opium, morphine), hemp (hashish, marijuana), and of fermentation of various organic materials alcohol. This list has recently been joined by the psilocybin-containing mushrooms. The addiction-forming compounds originated in the New World and widely spread are tobacco (nicotine) and cocaine. In the 19th and 20th, century the development of medicinal chemistry resulted in several synthetic compounds, originally proposed as therapeutics, such as barbiturates, benzodiazepines and amphetamines. Due to legal problems, to avoid production of the substances already prohibited, many designer drugs were manufactured. In addition, several compounds were synthesized as recreational drugs. Also some compounds that were not regarded as drugs, such as aromatic hydrocarbons and other cleansing agents, as well as steroids were found to have properties of dangerous, habit-forming agents.

The attitude of society and the pattern of use of psychoactive substances have changed with time, particularly in the last decades. The active principles are now more addictive because of concentration, purification, chemical modifications and the way of ingestion, which now favors most rapid transport to the central nervous system. The substance abuse approaches the level of global epidemics, and the recent usage of drugs of addition is also reviewed.

**Key words:** addiction, substance abuse, morphine, cocaine, nicotine, Cannabis, hallucinogens, review

Rapid development of neuroscience in the last two decades revolutionized our views on abuse of addiction-forming substances. According to the actual position of the National Institute on Drug Abuse (NIDA), presented in The Sixth Triennial Report to Congress [46], drug abuse is a phenomenon that can and should be prevented, and drug addiction is a disease which can be treated.

Drug abuse gives rise to serious, negative consequences as well for abusers themselves, devastating their mental and physical health, as for the society. It is an indirect or direct cause of many crimes, and a spread vector of such epidemics as AIDS, hepatitis and tuberculosis. It is also very costly: in the USA each American taxpayer spends on the average almost 300 dollars per year to alleviate this problem. The total of 67 billion dollars comprises costs related to crimes, medical care, treatment and welfare programs for addicted individuals, and consumed and wasted working time. Treatment of drug addictions can reduce these costs, and it appears that each dollar spent for therapy yields 4–7-dollar saving. American society disburses 3600 dollars per month to support a non-treated abuser at liberty, while an upkeep of a prisoner costs 3300 dollars. On the other hand, monthly cost of methadone therapy amounts to 290 dollars [62]. In Poland, these costs are obviously lower, but they constitute also a considerable burden to the budget.

Level of our understanding of the nature of the problems related to drug addiction influences legislation and measures undertaken to deal with drug abusers. Ascertainment that a drug addict is a sick person made law-enforcement system aware that imprisonment is not a treatment of the disease. On the other hand, it was demonstrated that appropriate medical treatment in jails decreased reinstatement rate in drug abusers. Understanding that drug addiction is a disease should also cause a change in our attitude toward the addicts: even if drug addiction had been entirely a self-inflicted condition, such persons should be treated as sick and we have to learn how to live with them in the same way how we relate to the people suffering from schizophrenia or Alzheimer's disease. A drug addict is a person whose brain functions have been fundamentally disturbed by a drug, and it is necessary to implement treatment to straighten the impaired brain functions and related changes in person's behavior and functioning in the society. Thanks to recognizing the basis of addiction, we understand, why the

combat with drug abuse focused solely on criminal and social aspects of this problem proved inefficient.

We are entering 21st century aware that constantly changing pattern of drug abuse, uninterrupted spread of HIV infection among abusers, and necessity to lay efficient basis for addiction treatment and prevention is a challenge that we have to face, and we will be able to cope with it only after understanding of the nature of this disease. Therefore, the 21st century will be a period of intensive studies aimed at better understanding the mechanisms underlying addiction, and at using our knowledge to improve the methods capable of elimination of this plague. The first part of this review deals with the problems of the history of psychoactive compounds and presents how from the cult substances, which could be valuable in increasing the evolutionary fitness of a primitive tribe, they became a serious menace for the modern civilized society.

## PSYCHOACTIVE SUBSTANCE USED IN THE PAST

Substances influencing mood and thinking processes have been known to humanity at least from early, prepottery Neolithic times, i.e. 8000 BC [19, 57, 67], and there was no culture in which no substance of this type was known and used. Principally, they fulfilled a role of cult substances, having been used in religious ceremonies, and as medicines. Most likely, the use of these substances for entertainment to elicit pure pleasure was less important at that time. In this way they played an important role in survival of a tribe, increasing its coherence.

### Psychoactive substances of the Old World

The psychotropic substance used in the Old World at the earliest was a decoction of fly agaric *Amanita muscaria*, believed to have been used since as early as Neolithic times, i.e. 10 000 years ago. It is believed that characteristic ornament on some Neolithic vessels represents indeed fungal gills floating in the extract. The mysterious *soma*, brought to India by Aryan invaders was most probably fly agaric, and the cult of *soma* ruled Indian's religion and culture for centuries. Its sacramental use was described in Rig Veda [53, 67]. Most probably, *Amanita* decoction was also the basis of ri-

tual potions of Zoroastrian *baoma*, and it was proposed that the gods' food *ambrosia*, used in Dionysian rites, was the solution of fly agaric [20, 67]. The analysis of paintings of "tree of life" in Roman catacombs made some people think that the use of *Amanita* was important in the cults of early Christianity [1].

Memory of psychotropic properties of fly agaric, widely used at the dawn of our civilization, has disappeared from the civilized world. However, in 1730 the use of this mushroom as an orgiastic and shamanistic inebriant was discovered in Siberia. Subsequently, it was found to be used among several isolated groups of Finno-Ugrian peoples (Ostyak and Vogul) in western Siberia and three primitive tribes (Chuckchee, Koryak, and Kamchadal) in northeastern Siberia [57, 65]. The hallucinogenic principles of *Amanita* are metabolites of ibotenic acid, muscimol and muscazone, and not, as it had been believed earlier, muscarine [57]. Muscimol is the sole natural hallucinogenic chemical excreted unchanged from the body, and therefore Chukchees ritualistically drink the urine of men who have become intoxicated with the mushroom, thus recycling the hallucinogen. The reference in the Vedas to ceremonial urine drinking strengthens the hypothesis, that fly agaric really was the ancient soma [57].

The use of *Amanita* beyond religious ceremonies certainly was strongly prohibited by a powerful taboo, and conceivably, such taboo could have endured in society's subconsciousness until today, since fly agaric is commonly considered the most poisonous of all fungi, which obviously is not true.

Three psychoactive substances known from prehistoric times in the Old World survived and keep an important position in the present times.

The first of them, known for some 6000 years (mentioned in the inscriptions in cuneiform writing on Sumerian clay tablets) is opium, morphine being its main component determining psychotropic action. Opium withstood time passing and continues still to be used now. It is a condensed juice of the unripe seed pod of a poppy, *Papaver somniferum*. It was used mainly for medical but also for recreational purposes. While Eber papyrus 3500 years ago advised it "to prevent excessive crying of children", Helen of Troy entertained her uneasy guests with wine enriched with *nepenthes*, to dispel their sorrow. According to the description of *nepenthes* action provided by Homer, it could be only opium. Galen felt that opium is a kind of panacea, and also

mentioned its recreational use in form of cakes and candles, freely available on the streets of Roman empire [55]. The knowledge of opium languished in Europe during Dark Ages, but Arabs, whom Qur'an forbids any form of alcohol, used opium (and hashish) as primary social drugs, and continued to investigate its medicinal properties. Around year 1000 Biruni described for the first time opiate addiction [22]. The Iranian physician, the most famous and influential of the philosopher-scientists of Islam, Avicenna, used opium extensively in his practice, and it is believed that he died because of drinking excessive amounts of a mixture of opium and wine [53]. Yet, despite its healing and rewarding action, opium was not considered a cult substance by any major religion.

Only the preparations made from Indian hemp, *Cannabis sativa*, can compete with opium with regard to its antiquity and longevity. Geographical range of this plant is wider than that of fly agaric and poppy. In China and Central Asia, hashish, the most active product prepared from hemp plant, has been known for 5000 years: the earliest reference to it is contained in the pharmacy book of a Chinese emperor Shen Nung, written in 2737 BC [53]. The Chinese referred to *Cannabis* as "liberator of sin" and "delight giver" [57]. Lately thereafter hashish appeared in India. Pots for hashish smoking, discovered in grave-mounds of Scythian sovereigns in Pazyryk in the Altay Mountains, have been dated back to 5th–2nd century BC [57]. Around 1000 AD hemp was intensely used, particularly in the range of Islamic culture, in Middle East and Africa, where the use of another presently most widespread addictive substance with psychotropic profile, alcohol, was prohibited.

In Europe, at this time people started to believe in a legend about using *Cannabis* by the cult that committed murders for political reasons. The name of the cult was hashishiyya, and it was given the name for both hashish and assassins. Most of the legend was brought to Europe by a famous traveler, Marco Polo.

*Cannabis* started to spread in Europe after Napoleonic Wars, when some hashish was brought to France by the veterans of Egypt campaign [42]. In mid-19th century hashish became very popular among romantic French artists in Paris. The activity of this group, to whom belonged Baudelaire, Dumas and Gauthier, was described by the latter in the book *Le Club des Hachischins*, and Baudelaire

wrote about opium and hashish in *Les Paradis artificiels*.

The third great substance of abuse known from the ancient times in the Old World was alcohol. Of the three, it was the only which still retained its status as a legal substance in most of the world, with exclusion of religious Islamic countries. Alcohol use overspread practically all over the world, as it can be produced virtually of any organic material, which is susceptible to yeast action. It was extensively used for entertainment, sometimes in religious ceremonies, in all cultures of the world, except certain islands of Oceania and North American Indian tribes. The latter surprising fact (alcohol was known in the Latin America) was a cause of disintegration of North American native cultures, when they were exposed to this addiction-forming substance, since tradition did not teach them how to use it safely. Alcohol was used for cult purposes particularly by ancient Greeks during Dionysia. Wine has been used in Jewish and Christian ceremonies as well, and probably the earliest description of the consequences of alcohol abuse for entertainment we can find in the Bible [18], narrating the end of laborious Noah's day.

In addition to those three widely spread and abused substances, several plants containing other psychoactive agents were used in the Old World.

One of them, widespread both in the Old and New World, was jimsonweed, *Datura stramonium*, which contains scopolamine, atropine and hyoscyamine. It is a highly poisonous hallucinogen with repulsive action. The plant was used exclusively in cult rituals, not for entertainment. In ancient Greece, Pythia chewed jimsonweed leaves in Apollo's temple in Delphi before prophesying, and, perhaps, the leaves were also thrown into fire to produce trance-inducing smoke [53, 56]. Jimsonweed was also popular in China, especially among Buddhists, and in India, where it was used in Shiva cult. In many parts of Asia, even today, seeds of *Datura* are often mixed with food and tobacco for illicit use, especially by thieves for stupefying victims, who may remain seriously intoxicated for several days [57]. However, the ritual utilization of *Datura* preparations is more characteristic for the New World, where it was extensively used by Mexican Indians.

The ancient Greeks used also a hallucinogenic potion, *kykeon*, at the end of the initiation in Eleusi-

nian Mysteries. In addition to barley extract and mint it probably contained LSD-like preparation of ergot [66].

Among psychotropic substances of the Old World, ibogaine deserves mentioning as well. It was obtained from the root of African plant *Tabernanthe iboga*, and used in the ceremonies of syncretic religion Bwiti in the Central Africa by Fang tribe, especially in adolescence rites. Recently, ibogaine has incited considerable interest due to its ability to inhibit drug craving behaviors [50].

## Psychoactive drugs of the New World

Our knowledge of psychotropic substances used for cult, entertainment or medicinal purposes in the New World surpasses our recognition of those traditional in Asia and Europe. Undoubtedly, nicotine and cocaine are the most important of them, being commonly used all over the earth at present. It should be mentioned, however, that hallucinogenic substances played the crucial role in some of the New World cultures, particularly in Latin America. Some Indian societies were practically enslaved by the religious use of hallucinogens.

### Nicotine

Nicotine is an alkaloid occurring in plants of tobacco (*Nicotiana*) order. *Nicotiana* order is native to America, and comprises about 50 species, two of them, *N. tabacum* and *N. rustica*, serving as a source of nicotine for humans. *N. tabacum* derives from the South America, and now it is cultivated all over the world. North American Indians and West India inhabitants used *N. rustica*. Presently, after caffeine and alcohol it is the substance most widely used for its effect on mood [33].

The use of tobacco in the New World dates back to at least 600 AD [28]. Its European history began on October 12, 1492, when indigenous people of San Salvador offered tobacco leaves to Christopher Columbus. A monk accompanying Columbus during his second expedition in 1497 mentioned tobacco smoking as well, when describing customs of American Indians. American Indians believed in medicinal power of tobacco, and used it also during various ceremonies, e.g. calumet smoking [53].

Tobacco was brought to Europe as medicinal plant, practically a panacea. Medical properties of tobacco were described in 1529, and in the period 1537–1539 it was mentioned in 14 medical treat-



tises. In 1559, Jean Nicot, French diplomat assigned to Lisbon, came across tobacco and took it to Paris. The most prominent success of this diplomat consisted in healing the migraines of Catherine de Médicis with this product, making her the most passionate promoter of the new addiction. Although tobacco was brought to Paris earlier, Nicot was the one who was claimed to have introduced it into common use, and the plant was called *Nicotiana* in 1565. This name was given official approval by Linnaeus, introducing *Nicotiana* order in 1753. In 1828, an active component of tobacco was isolated and named nicotine. Its content ranges from 2 to 7% of dry mass of the leaves [53].

Tobacco use spread gradually across Europe. Trying to break Spanish monopoly, England started cultivation of *N. rustica* both in the Colonies and British Isles, without great success though. Tobacco cultivation accelerated in 1612, when John Rolfe from Virginia acquired *N. tabacum* seeds, while in 1619, the king Jacob proclaimed tobacco trade in England to be royal monopoly.

Tobacco use scattered in Europe during the Thirty Years' War in spite of some resistance to this phenomenon. For example, in Bavaria, tobacco use by peasants and lower classes was prohibited, while burghers and nobility could get it only in pharmacies upon medical prescription.

In consequence, tobacco smoking decreased greatly in the 18th century, but snuffing of powdered plant material, the snuff, became common. It was very popular also at royal courts: in England, a wife of George III, Charlotte, was called by a nickname "snuffy Charlotte" while in France, Napoleon reportedly used up to seven pounds of tobacco a month [53].

Chewing of tobacco leaves, so-called quids, was the second method of tobacco use. It was popular particularly in the United States, where in 1860 only 7 out of 348 tobacco companies manufactured tobacco for smoking. Cuspidors were standard furnishing of waiting rooms in federal buildings, disappearing therefrom as late as in 1945.

Cigars and pipes turned out to be a kind of transition between tobacco chewing and smoking, while modern cigarettes were slowly beginning to appear on the market. Cigarettes' design was based on the way of tobacco smoking by American Indians, as they packed it into thin reed stalks. At first, cigarettes were supplied for soldiers during the Crimean War. After returning home in 1856, the

veterans established the first factory manufacturing cigarettes in London, and, finally, at the end of the fifties of 19th century, an English merchant, Philip Morris, started to make cigarettes by hand. His enterprise developed into a powerful company holding at present, besides originally owned tobacco companies, *General Food Corporation* (manufacturing Maxwell coffee, besides other things), and *Kraft Inc.* (cheeses), one of the largest international companies in food industry. The United States of America relatively slowly switched to cigarettes, due to popularity of chewing tobacco, but even there cigarettes finally replaced other forms of tobacco use. However, return to smokeless tobacco, i.e. snuff and chewing tobacco, has been observed since the 1980's. This form of nicotine use is safe for surroundings, and slightly less harmful for users themselves [64].

### Cocaine

Cocaine is an alkaloid occurring in the leaves of coca shrub, *Erythroxylon coca*. It was used as early as in pre-Columbian times, particularly by the Andean mountaineers, in the area, where Peru, Bolivia and Ecuador are located at present. In this region, coca leaves mixed with lime or plant ash were chewed, not only for entertainment, but also to help people subsist hard work at large altitude, since cocaine removes symptoms of fatigue and hunger, and enhances endurance of an organism facing difficult environmental conditions, increases wakefulness level, and, when used infrequently, strengthens concentration. The contemporary miners in Andean mines still chew the coca leaves. Coca leaves were also used for religious purposes [34].

Chewing of coca leaves was also an important element of religious ceremonies of Incas in 16th century, in the times of Spanish *Conquista*.

For a long time, cocaine remained undiscovered by European civilization and only in the second half of 19th century, after its isolation from leaves, began to spread, particularly after 1885, when pharmaceutical companies began selling it in the United States and Europe. It was regarded as a drug useful in several circumstances, e.g. it was recommended by the Hay Fever Association as a remedy for that malady [32]. At those times the most important and lasting medical application of cocaine was discovered: an American doctor of Bohemian origin, Carl Koller, used it for the first time in 1884 as an anesthetic for eye surgery, opening the road

towards modern local anesthesia. Independently of its medicinal use, cocaine became a fashionable stimulant in Europe and America. In the same year 1884, Sigismundus Freud wrote to his fiancée that he was experimenting with a new wonderful drug. In the next year, he recommended cocaine as a stimulant, and later on as a drug that abolished the signs of morphine withdrawal [53].

Cocaine became a trendy drug among upper classes. The prototype mastermind detective invented by Sir Arthur Conan Doyle, Sherlock Holmes, in the book *The Sign of Four* is shown taking intravenously (!) cocaine and explaining to Dr. Watson why he takes it regularly and what it does for his mind (NB. Sir Arthur practiced medicine).

In the real life cocaine was the active principle of several "miraculous elixirs" that abolished tiredness and restored strength and vigor. Cocaine was quite likely the main component of many "miraculous elixirs" advertised in the press on the turn of 19th century, similarly as, e.g. *Buerlecithin* or *Red Bull* today. Wine extract of coca leaves, prepared by Corsican pharmacist Angelo Mariani, was the most popular of such tinctures. It was patented by its inventor as *Vin Mariani*. This wine acquired outstanding reputation, since it improved mood, being very savory at the same time. It was used to cure a wide range of diseases beginning from depression, across sore throat till gastrointestinal disturbances. Mariani was declared one of the most eminent personages in Europe and decorated by the pope Leo XIII with a special medal for his merits in enhancing humanity's welfare. In the protestant United States of America, where alcoholic beverages were treated suspiciously by a large portion of the society, particularly by Baptist Church and Jehovah's Witnesses, alcohol-free version of *Vin Marini* was developed by John Pemberton. It was *Coca Cola*. Original *Coca Cola* contained some wine, but it was quickly replaced by an extract from *Cola* nuts, and a beverage obtained in this way was advertised as "a drink of intellect and moderation". When in 1888 Pemberton replaced plain water with soda water, *Coca Cola* assumed practically its present form, save that at the beginning of 20th century dangers connected with cocaine use were recognized and it was replaced by higher amount of caffeine, which is also a psycho-stimulant, but a very mild one and not considered generally an addictive substance [63].

## Other South American psychoactive substances

Nicotine and cocaine do not conclude the list of psychotropic substances from beyond the Atlantic Ocean. They have aroused considerable interest and several books were devoted to this topic (e.g. [14, 16, 23, 57]).

The Spanish missionary Bernardino de Sahagun described "an herb, called coatl xoxouhqui (green snake), which produces seeds that are called *ololiuqui*. These seeds stupefy and deprive one of reason: they are taken as a potion. *Ololiuqui* was found to be a seed of *Rivea corymbosa* or *Ipomoea tricolor* of the morning glory family. Albert Hofmann, the discoverer of LSD, identified lysergic acid amide, lysergic acid hydroxyethylamide, and alkaloids closely related to them as the active principles in the seeds [27]. It is, therefore, not surprising that *ololiuqui* evoked visions and mystic experiences [24, 31]. The Hofmann's discovery was surprising, as at that time it was believed that ergot alkaloids are only the constituents of lower fungi. Their identification in higher plants contradicted the experience that certain substances are typical of and restricted to respective plant families.

Columbus mentioned inhalation of a powder through a double tube to the nose. It was most probably *yopo* (known also as *parica* or *cohoba*), still in use today. It is a strong hallucinogen obtained from seeds of a tree *Anadenanthera peregrina* or *Piptadenia peregrina*, and N,N-dimethyltryptamine, N-monomethyltryptamine, 5-methoxydimethyltryptamine, and several related bases are its hallucinogenic principles. Bufotenine, also present in *A. peregrina* seeds, apparently is not hallucinogenic. One of the common hallucinations induced by *yopo* is macropsia (an abnormal exaggeration of the size of objects) [11, 57].

Another South American cult potion, used mainly in the Amazon drainage basin, was a beverage called *ayahuasca*, *huasca*, *caapi* or *yajé*. This is a psychoactive plant mixture typically prepared of the -carboline-rich bark of vines *Banisteriopsis caapi* and *B. inebrians*, and the hallucinogenic plant *Psychotria viridis* [15]. South American Indians maintained that this liquid had medicinal properties and endowed a person with clairvoyance. It was used by Incaic priests to prophesy future. Western researchers have confirmed that it induced extraordinary experiences, including a sensation of

levitation. It is still used by some Indian tribes, e.g. by Ese'ejas in south-eastern Peru [12] and Brazil [21]. Controlled studies on healthy volunteers revealed that *ayahuasca* can be described as inducing changes in the perceptual, affective, cognitive, and somatic spheres, with a combination of stimulatory and visual psychoactive effects of longer duration and milder intensity than those previously reported for intravenously administered N,N-dimethyltryptamine [54]. In another study, harmine (up to 222.3 ng/mL), harmaline (9.4 ng/mL), tetrahydroharmine (134.5 ng/mL), and N,N-dimethyltryptamine were found in the blood plasma of healthy male volunteers after the ingestion of a standard drink of *ayahuasca* [9]. Studies on the long-term members of a syncretic church that utilizes *huasca* as a legal, psychoactive sacrament revealed no evidence of personality or cognitive deterioration [21].

Another hallucinogen was obtained from jurema *Mimosa hostilis*. A brew prepared from this mimosa, called *ajuca* or *vinho de jurema* is believed to evoke marvelous visions in warriors before a battle, and it was used in a ceremony called *ajuca* by followers of Jurema cult in eastern Brasilia. Several tribes in Pernambuco – the Kariri, Pankarurú, Tusha, and Fulnio – consume the beverage in ceremonies. It appears, however, that the hallucinogenic use of *M. hostilis* has nearly disappeared in recent times. The active alkaloid in *ajuca* is N,N-dimethyltryptamine, which under physiological conditions is destroyed by monoamine oxidase (MAO) in the intestinal wall. Thus, the jurema drink must contain also an ingredient having MAO inhibitor properties [57].

An important role in religious cults of pre-Columbian America was played by hallucinogenic mushrooms. Small prehistoric sculptures of mushrooms, found in Guatemala, indicate that they were cult objects in Mayan culture. They played also an important role in Aztec cults, being called by them a body of the god. The sacred mushroom Teonanácatl aroused some attention in mid-50's, when its hallucinogenic properties were described in popular press [27]. The first descriptions of use of mushroom in religious ceremonies came from Spanish chronicles of 16th century. The earlier quoted Franciscan friar Bernardino de Sahagun mentions the magic mushrooms and describes their effects and their use in several passages of his famous *Historia General de las Cosas de Nueva España*, written between the years 1529 and 1590.

The history of sacred mushrooms was described by Valentina Pavlovna Wasson and her husband, R. Gordon Wasson, who also described the modern cult [67]. The cult is now a mixture of old rites and Christian faith: the Indians believe that God can speak directly to them through the mushroom because they cannot read the Bible. The mushroom is eaten in a sacramental way and may be taken only by "clean" persons – those abstaining from sex for four days before and after the ceremony. Alfred Hofmann was the first who identified the hallucinogenic principle from the mushrooms *Psilocibe mexicana* and *Stropharia cubensis*, as psilocybin (O-phosphoryl-4-hydroxy-N,N-dimethyltryptamine) and its dephosphorylated precursor, psilocin [25].

Recently, it has been found that psilocybin is present in four genera of family *Agaricaceae*: *Psilocybe*, *Stropharia*, *Conocybe* and *Panaeolus*. All of them grow in Europe and North America, and the last two genera are, in fact, cosmopolitan [57]. Psilocybin was also found in genus *Copelandia* in Taiwan [2]. The presence of psilocybin is associated with intensive blueing of the mushrooms when handled [6]. Owing to that, with the spread of the knowledge of the hallucinogenic properties of psilocybin, the illegal use of *Psilocybe* has spread, particularly as these mushrooms cannot be eradicated.

The use of hallucinogenic drugs has spread from America among adolescents in Europe [7, 38, 39, 44, 58] and in Far East [2, 17, 43]. The way of ingestion of *Psilocybe* varies – it has been discovered that in coffee shops in Denmark a mixture of mushroom and honey may be bought [7].

The German police data indicate that the hallucinogenic mushrooms most frequently found are *Psilocybe cubensis*, followed by *P. semilanceata*, *Panaeolus cyanescens* and *Psilocybe tampanensis*. The highest concentrations of hallucinogens (up to 1.15% of psilocybin and 0.90% psilocin) were found in *P. cyanescens* [44].

Hallucinogenic activity is also exhibited by the preparation made of the dried top parts of a cactus peyote *Lophophora williamsi*, containing mescaline. In the second half of 19th century, Moureaux de Tours and then Kraepelin proposed to use mescaline to induce experimental psychoses (see [41]), and following their suggestion Kraepelin's disciple, Knauer, carried out observations on visual hallucinations, induced by mescaline [35]. Earlier introspectional studies on peyote were reported during the 1890s by Havelock Ellis and Weir Mitchell



[41], and detailed accounts on changes in perception of reality after taking mescaline, *peyote* and other psychoactive drugs were also provided by an eminent Polish painter and writer, Stanisław Ignacy Witkiewicz (1885–1939), who carefully noted on each of his paintings what kind of drugs he was using while working.

Problems with *peyote* arose in the USA when its use spread from Mexico to several Indian tribes in the United States. Despite harassment of the people who used *peyote*, American Indians defiantly tried to uphold tradition of its use. In 1918, they established the Native American Church, and mescaline has played an important role in their ceremonies. Followers of peyotism believe that God put some of His Holy Spirit into the *peyote*, which is eaten in the same way as sacramental bread and wine are used by certain Christian churches [33]. Contrary to allegations that *peyote* use is harmful and leads to degeneration, no adverse reactions were observed in the members of the Native American Church [53].

### Synthetic psychoactive drugs

Development of chemistry in the 19th century enabled to obtain psychoactive substances by chemical synthesis. First, they appeared on the market as medicines, and later their addictive properties have been discovered.

Barbiturates occupied a prominent place among such drugs, being synthetic substances with strong addiction liability, used at the same time as sedative-hypnotic and antiepileptic drugs. The barbiturate precursor, barbituric acid, whose name is believed to derive from “urine” and an unknown “Barbara”, was synthesized by the future Nobel Prize winner, Adolph von Baeyer in 1864, and the hypnotic properties of the first pharmacologically active compound of this group, barbital, were discovered in 1892 by Josef von Mering and Emil Fisher. The drug was introduced in 1903 as a sedative and hypnotic under the trade name Veronal. Several other derivatives, were subsequently synthesized, including the most known phenobarbital (Luminal) in 1912 [36]. In addition to their dependence-forming potentials, barbiturates, owing to their low therapeutic index, were the most common drugs taken for suicidal purposes. In a mixture with other agents they are used to carry out death sentence in several states in the USA.

Currently, barbiturates have largely been replaced by benzodiazepines which have a high therapeutic index and a relatively lower incidence of development of life-threatening dependence. They were first synthesized in 1933 [33] by Leo Sternbach at the Jagiellonian University, and the studies in Roche, in the USA, in mid-fifties, revealed that they produce a taming effect on laboratory animals [51, 52]. The first two investigated benzodiazepines, chlordiazepoxide and diazepam, rapidly entered the market under the names of *Librium* (in 1959) and *Valium* (in 1963), and benzodiazepines, that are used mainly as antianxiety, hypnotic and antiepileptic drugs, are the most frequently prescribed psychopharmaca today [5]. Unfortunately, they were proved to have a liability to abuse, but their abuse is not a major public health problem [13]. However, they are frequently abused for non-medicinal, even criminal purposes as club drugs (*vide infra*).

Amphetamine, a very dangerous addiction-forming drug, was synthesized as a remedy for asthma. This disease was successfully treated by ephedrine, a drug known for 5000 years in China and introduced to the West since 1924 [10]. Ephedrine originates from a shrub *Ephedra vulgaris*, which grows exclusively in China. Amphetamine was cheaper and more potent than ephedrine as a sympathomimetic agent and bronchodilator [3, 4, 49], and in the thirties it was widely used as a medicine in a variety of conditions, including obesity and fatigue, while nobody suspected its addictive action [30]. The use of amphetamine and its congeners, particularly methamphetamine, erupted during the World War II, when they were shown to annihilate sleepiness and weariness, and to sharpen concentration. Methamphetamine was added to chocolate for pilots, who were to perform long night flights. Chocolate supplemented with amphetamines was used by air force as well in Germany as in England and Japan. The United States of America did not supply amphetamine chocolate to their pilots, but Americans and Englishmen shared their air bases in Great Britain, and obviously nobody refused to share this tonic chocolate with a friend. True amphetamine epidemics erupted in postwar Japan, where so enormous amounts of methamphetamine were manufactured during the war that after unexpectedly early capitulation, they were decided to be introduced on the market as a tonic used



for fun. As a result, 20% of young Japanese were amphetamine addicts in 1946–1948 [8].

The synthetic hallucinogenic compound which gained large popularity and notoriety is LSD, whose hallucinogenic properties were discovered accidentally by Albert Hofmann. The drug, D-lysergic acid diethylamide, was synthesized in 1938 in Sandoz laboratories by Stoll and Hofmann, but nothing peculiar about it was noted [33]. Only 5 years later, working with LSD Hofmann experienced vivid hallucinations [26]. Assuming that he accidentally ingested minute amounts of LSD he ingested 0.25 mg of the compound. As the dose was five times higher than that needed to induce hallucinations the effects were quite spectacular. The results of a systematic investigation of LSD in human subjects, carried after the end of the World War II, confirmed the original findings of Hofmann [60].

Until mid 20th century, synthetic addictive substances were discovered by chance, and addictive properties were detected for the compounds synthesized as medicines and so used. The situation changed in the 60s, after implementation of *Narcotic Drug Control Act of 1956* in the USA, supplemented with a list of prohibited drugs. This immediately incited syntheses of derivatives of the prohibited substances (mainly unlisted amphetamines), which could be distributed without punishment since they were not pronounced illicit. Such production of designer drugs was limited by amendment to the Act, including whole groups of compounds in the list, but it led to the synthesis of many strongly addiction-forming derivatives of known drugs.

### CHANGING PATTERN OF USE OF PSYCHOACTIVE DRUGS

Psychoactive drugs, particularly hallucinogens, were used either as medicinal products or to evoke religious experiences, and sometimes for military purposes or entertainment. They have been used under strictly defined conditions, and in ritualized manner, being often taken in as a sacrament. The use of these substances was generally accepted, remaining, however, under rigorous control of spiritual leaders of the group. Their use beyond ceremonies was prohibited and put under a taboo, and as a consequence, the substance became regarded as deadly poisons when used illegitimately. Such practice caused that psychoactive substances, even

in spite of common use, brought about neither detrimental health effects nor addiction. It is interesting that the substances, which underwent acculturation, were without serious adverse effect, though they were considered very dangerous by the members of other cultural circles. Opium is an example of such phenomenon. It was commonly used in India in 19th century, while in England it was deemed extremely harmful. At the end of 19th century, at a request of *Anti Opium League*, British Parliament established the royal medical commission to study a problem of opium use in India. Having examined a large number of persons using opium, the commission evidenced that opium use in India was not more hazardous than alcohol use in England, being even beneficial in some situations [61]. As mentioned above, also alleged harmful action of *peyote* for the followers of the *Native American Church* and *ayahuasca* drinkers in Brazil proved groundless.

Low noxiousness and slight addiction liability of historic psychotropic substances resulted also from their moderate power. They were the substances of natural origin and usually used directly in a form of fresh or dry plant material or fairly diluted decoctions. At the beginning, alcohol was also used only as a product of natural fermentation, so its concentration did not exceed 12–14%.

Currently, the use of psychoactive drugs has undergone critical changes, which considerably increased a risk of addiction. Firstly, these substances started to be used mainly for entertainment, to experience unusual pleasure. Secondly, they have been used without any control of naturally respected persons or organizations. Thirdly, efficient methods of purification of natural products were developed, which enabled the use of concentrated active components. Distillation technology allows to obtain 96% ethanol without much effort, and alcoholic drinks contain up to 40–45% of ethanol. Morphine, which is a naturally occurring substance, was isolated in crystalline form, and subjected to chemical modification. As a consequence, instead of natural opium, a crystalline diacyl derivative of morphine, heroin, was made available, which instead of being taken by sniffing or smoking is now injected intravenously. Cocaine was once ingested by chewing coca leaves, then alcohol extracts (*Vin Mariani*) were in use, and subsequently it was used in the form of crystalline hydrochloride for sniffing, and finally, in a form of crack, a homemade free base

obtained from crystalline form of cocaine for smoking. Because of the increased concentration of a substance decreases time to its penetration into the brain and its brain level, a compound of abuse acts more quickly and strongly. The shortening of the interval between drug application and pleasurable effect increases its addiction liability. An additional factor that significantly elevates addiction liability of drugs of abuse is criminalization of their use. Irrespective of social consequences of such legal status, it induces stress in the users of illicit drugs, who may be subject to sometimes very severe penalty. However, numerous studies [40, 48, 59] have demonstrated that stress sensitizes an organism to the action of psychoactive substances, which increases their addictive liability. This issue will be discussed in the second part of this review.

Unlike other psychotropic substances, hallucinogens typically do not evoke addiction, defined as the prevalence of compulsive drug-seeking behavior over all other activities. It can be attributed to dysphoric symptoms preceding hallucinations. Nevertheless, hallucinogens are used and abused since resultant visions are frequently regarded as religious experiences, so they are used by certain small communities. In the USA, such communities emerge most frequently among white inhabitants of big cities, who move to lowly populated rural areas to avoid harassment, or even try to survive without basic means provided by our civilization. The use of hallucinogens in such environment can lead to fatal consequences, sometimes even to group suicides.

#### **ILLICIT ADDICTIVE DRUGS IN THE WESTERN CIVILIZATION ON THE TURN OF SECOND MILLENNIUM**

Social factors, detailed above, and advances in chemistry caused that drug addictions became a serious plague of the developed societies. The use of two powerful addiction-forming substances, nicotine and alcohol, is lawful in the western culture. The studies conducted in the USA showed that in this country a number of nicotine abusers, i.e. tobacco smokers and smokeless tobacco (quid, snuff) users amounted to 62 million and 6.8 million citizens, respectively in 1995 [47]. It was estimated that tobacco kills 500 000 persons each year. On the other hand, a number of alcohol addicts and abusers was estimated at 18.4 million [68], while

rate of death of alcohol-related causes (mainly car accidents and cirrhosis) exceeded 111 000 in 1995 [45].

Despite the fact that licit addictive substances are abused by significantly larger population and cause much higher mortality than illicit drugs (principally due to availability of the former), illicit substances evoke much stronger interest and emotions, although many of them can be lawfully used as medicines under the controlled conditions. The review presented below is based mainly on NIDA materials and relates to the situation in the USA. In recent years, a number of illicit drug abusers has not increased and remained stable at about 13 million persons in the USA. In Poland, a number of drug abusers is still lower than in the USA but it is constantly on the rise.

As mentioned above, the use of psilocybin in the USA, Europe and Far East is spreading. The mushroom users face a life-threatening risk because of possibility of wrong identification of a mushroom, and ingestion of highly toxic species, particularly *Amanita phalloides*.

#### **Cocaine**

Cocaine creates the most serious problem in the USA, despite the fact that its use is much lower now than in mid-80s. In 1996 an estimated 1.75 million Americans were cocaine users (in 1985 – 5.7 million). Cocaine supply is abundant in large cities, but number of the users, death rate and drug price have recently stabilized. Main cocaine users include older inhabitants of suburban areas, who smoke crack, but a new group is emerging: teenagers who smoke blunts, i.e. cigarettes with cocaine and marijuana.

#### **Heroin**

A number of new heroin users in the USA still increases. In 1996 there were 216 000 regular heroin smokers. Although traditionally heroin has been injected intravenously, many new users prefer to smoke or sniff it. It is a safer route since it eliminates a danger of HIV infection by blood. However, mucosa damage, occurring after some time of such heroin use, can compel the users to switch to injections. Aggressive promotion of heroin expands, and its prices drop. However, heroin-related death rate remains constant or increases, depending on a region.

## Marijuana

It was estimated that one third of the USA population 12 years of age and older, i.e. 72 million Americans had contact with marijuana, while in 1998 18.7 million were active marijuana smokers. Number of marijuana smokers increases, especially among teenagers. Marijuana-related hospital admissions also rise due to the increased strength of cigarettes and combination of marijuana with other addiction-forming drugs, especially with crack in blunts called *3750s*, *diablitos*, *primos*, *oolies* and *woolies*. Joints and blunts are often dipped in phenacyclidine (PCP) solutions, and called *happy sticks*, *wick sticks*, *illies*, *love boat*, *wet* or *tical*. Marijuana smoking is frequently accompanied with alcohol drinking.

## Stimulants

Methamphetamine is the most frequently used psychostimulant. It can be injected, sniffed, smoked (*chasing the dragon*) or taken orally. The studies conducted in 1996 estimated that 4.9 million Americans came into contact with methamphetamine. Amphetamine is much less popular. Besides, youngsters and heroin abusers are inclined to use methylphenidate (Ritalin), methcatinon (*cat and goobs*) and methylenedioxyamphetamine (MDMA) known as *Ecstasy*. The latter is used mainly during parties, night-long dancing in clubs and on rock concerts, and is considered a club drug. The number of chronic and occasional MDMA users was estimated at 3.4 million.

In addition to the illegal stimulants mentioned above, products containing ephedrine are also in use. As natural products, they are available on the market in all states of the USA, besides New York, being sold mainly in health food shops.

## Downers and club drugs

Downers, which include calming and sedative compounds, constitute another large group of addictive drugs.

Downers comprise mostly drugs belonging to benzodiazepine group, and  $\gamma$ -hydroxybutyric acid (GHB). They are classified as "club drugs" and used especially as date-rape drugs, since when taken with alcohol they disable women who then could be sexually abused without even knowing

what has happened. Due to expansion of this practice, the Congress of the USA passed *Drug-Induced Rape Prevention and Punishment Act of 1996*, inflicting severe punishment on the use of any illegal substance in connection with sexual abuse. In the countries of Central Europe, similar mixtures have been used to rob train passengers. Out of benzodiazepines, flunitrazepam and clonazepam are used as club drugs. GHB is also used for its euphoric and anabolic properties, in addition to the properties of a downer.

Ketamine, a quick-acting narcotic drug with hallucinogenic properties, represents another club drug. Though it can be used on rape dates, it is mainly used as hallucinogen. Known also as *Special K*, ketamine is sometimes mixed with alcohol and GHB, and then called *Special K-lude*, since this mix resembles action of another club drug, methaqualone (Quaalude). Club drugs are considered very dangerous with respect to their social consequences.

The most powerful hallucinogen, lysergic acid diethylamide, has also been included among club drugs. LSD evokes overwhelming hallucinations, which can sometimes unexpectedly return long time after drug use (flashback) that can be very dangerous, especially if it happens, e.g. during driving a car. More than 1.8 million Americans used LSD at least once, but this compound does not produce addiction, similarly as most of hallucinogens and it never triggers drug seeking behavior.

Phencyclidine (PCP) is another popular hallucinogen. It is similar to ketamine with respect to its action, and similarly as the latter it was synthesized as a new type of general anesthetic, which induces so called dissociative anesthesia. An estimated 700 000 Americans had an experience with PCP use. In contrast to other hallucinogens, it is a strongly addictive drug, quickly evoking drug craving.

## Inhalants

Inhalants are relatively underestimated, important and dangerous group of addiction-forming substances [29]. They are frequently the first psychoactive substances abused by youngsters. The largest group of these substances comprises solvents based on benzene, toluene and other aromatic hydrocarbons, used in households as cleansers and paint solvents, and also in highlighters, etc. In addition, gasoline and gases such as propane (lighters)

Table 1. Main groups of abused drugs in the USA

Classic	Stimulants	Downers	Hallucinogens	Others
Cocaine	Methamphetamine	$\gamma$ -Hydroxybutyric acid (GHB)	Phencyclidine (PCP)	Anabolic steroids
Heroin	Methylphenidate	Ketamine	Lysergic acid diethylamide (LSD)	Solvents
Marijuana	Metcatinon	Methaqualone	Psilocybin	
	MDMA	Flunitrazepam	Mescaline	
	Ephedrine	Clonazepam		

and butane (gas cookers) belong to this category. They are easily available so they become the first subject of children' and teenagers' experiments but due to immediate (suffocation, heart arrest) and remote (lasting neuropathies, liver damage) consequences, they are very dangerous. Chronic inhalant addictions are among the most difficult to treat. Seventeen percent of American school children have used inhalants.

Another group of inhaled substances of abuse include aliphatic nitrites. They have been introduced by gay environment as orgasm-intensifying substances. For this purpose, amyl nitrite, a prescription drug in the USA, butyl nitrite (prohibited) and still available cyclohexyl nitrite have been used. Nitrite use is on the decline.

The last group of inhalants comprise drugs used for inhalation general anesthesia, such as chloroform, ether, and halothane. Their use is now limited, although before the World War I ether drinking was a popular habit in mountain rural areas in eastern parts of Austrian Empire.

## Steroids

Anabolic steroids, testosterone derivatives, are also included among abused drugs. They are used principally by sportsmen and athletes to promote muscle growth. Currently, steroid use by sportsmen is treated as illegal doping. The most commonly abused steroids comprise oral preparations: oxymetholone, oxandrolone, methandrostenolone and stanozolol, and sustained action preparations injected intramuscularly: nandrolone (as decanoate or propionate), boldenone and testosterone cypionate. Many steroids are available in the USA in health food shops as dietary supplements. Approximately 3% of American teenagers used steroids at least once in their lifetimes, and an estimated several hundred thousand Americans abuse steroids at least once a year.

Steroids increase aggressiveness and excitability, enhance energy, evoke euphoria and sexual arousal, cause dramatic mood changes, distraction and cognitive problems connected with memory and orientation.

## General risks connected with administration of illegal drugs

Regardless of the risk of development of drug dependence and of health risk related to the central and peripheral action of substances of abuse, an additional risk is posed when the substances are obtained illicitly. The unreliability in the strength of preparations on the illicit drug market can lead to dangerous overdose. The street drugs have no certificate of the manufacturer and the content of the bought dose may be much different from declared. It is usually lower, but might be dangerously higher. Even worse, it may be contaminated with very toxic substances, as exemplified by "street heroin" contaminated with a potent neurotoxin, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) that was first noticed when it caused fatal destruction of dopaminergic neurons in two young addicts [37]. Hofmann [27] describes the death of a young man who was sold strychnine instead of LSD. This, in addition to serious social consequences of illegal drug taking, particularly imprisonment, should deter anybody from exploring the world of alternate consciousness.

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