DRUG ABUSE TREATMENT AND PREVENTION

STUDY MANUAL
FOR
MEDICAL STUDENTS AND YOUNG DOCTORS

Volume 2

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Training of Medical Students and
Young People as Promoters of Prevention of Drug Abuse

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Chapter 3

Substances use and health problems

Modules developed by students

Module 3.1
Opioids - history, characteristics and effects

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Key messages

- Opioids are, substances producing effects similar to morphine. They are classified by their chemical structure, the way of production and effects;
- The opioids produce their effects by interacting with a specific receptor;
- Opioid dependence (addiction) is defined as a cluster of cognitive, behavioral, and physiological symptoms in which the individual continues use of opiates despite significant opiate-induced problems;
- The opiate addiction can lead to financial, health problems and high level of the criminal activity and mortality.

Contents

1. Description and classification

1.1 Various opiates

Opioids are substances with effects similar to morphine:

- Natural opioids, opiates;
- Semi-synthetic opioids;
- Synthetic opioids;
- Active metabolic products from heroin and morphine;
- Endogenic opioids, opioid peptides.

1.2 Morphine

Morphine is in a class of drugs called narcotic analgesics. It is used to treat moderate-to-severe pain. Brand names: Avinza, Kadian, MS Contin, MSIR, OMS, Oramorph SR, Rescudose, RMS, Roxanol, Roxanol 100, Roxanol-T.

1.3 Codein

In 1832 another opiate was isolated from opium: codeine, which is used mostly as a cough remedy.

Codeine is medically prescribed for the relief of moderate pain and cough suppression. Compared to morphine, codeine produces less analgesia, sedation, and respiratory depression, and is usually taken orally.

It is made into tablets either alone or in combination with aspirin or acetaminophen (i.e., tylenol with codeine). As a cough suppressant, codeine is found in a number of liquid preparations. Codeine is also used to a lesser extent as an injectable solution for the treatment of pain. Codeine products are diverted from legitimate sources and are encountered on the illicit market.

1.4 Heroin

When morphine is heated with acetic acid anhydrides, diacetylmorphine is produced. This substance was synthesized for the first time in 1874 by A. Wright and was put on the market commercially by the Bayer Company under the name by which the substance is still known – heroin.

What does heroin look like?

- Pure heroin is a white powder with a bitter taste;
- Most illicit heroin varies in color from white to dark brown;
- "Black tar" heroin is sticky like roofing tar or hard like coal, and its color may vary from dark brown to black.

1.5 Oxycodone

OxyContin® is the brand name of a time-release formula of the analgesic chemical oxycodone. OxyContin, which is produced by the pharmaceutical company Purdue Pharma, is prescribed as a pain medication. Instances of abuse of this drug have increased in recent years.

Street terms for Oxycodone: Hillbilly heroin, Oxy, Oxycotton.

2. Common and brand names and formulas

Different names of opiates

Opiates are derived from a sap taken from a seedpod of the plant "papaver somniferum". Collectively, opiates and synthetic opiates are called opioids.

Brand/generic names

Raw Opium, Opium, Codeine, Morphine, Heroin, Hydromorphone (Dilaudid), Oxycodone (Percodan), Oxymorphone (Numorphan), Hydrocodone (Vicodin), Meperidine (Demerol), Fentanyl, Methadone (Dolophine), Darvon, Talwin.

Street Names

Smack, Horse, Junk, "H", Hard Stuff, Shit, Mexican Brown, China White, Chiva, Goma, Gumball, Schoolboy, Downtown, Dolls, Dollies, Drug Store Heroin, Miss Emma, Morf, "M", Morpho, Big H, Black Tar, Boy, Brown Sugar, Crown Crap, Doogie, Hairy, Harry, Hazel, Henry, George Smack, Him, Horse Radish, Joy Powder, Mud, Muzzle, Scag, Schmeck, Smeck, Tecata, White Lady.

Table 1 Opiates

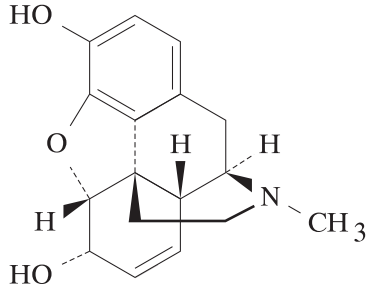
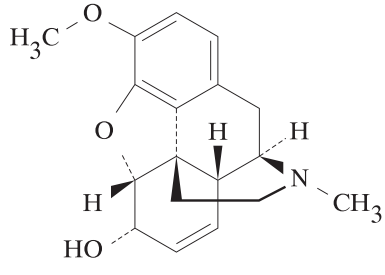
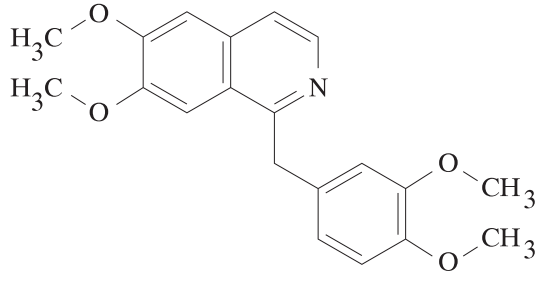
Morphine Morphium		Analgesic, natural opioid Duration of effect: 4-5 hours, in retard form 6-12 hours Elimination half-life: 3 hours (also in retard form) LD: 25 mg i.v. LD: 50 mg p.o.
Codeine 3-ortho-methyl-morphine		Antitussivum, (analgesic), natural opioid Duration of effect: 4-6 hours Elimination half-life: 3-4 hours
Papaverine		Spasmolytic, in itself no opioid effect Phosphodiesterase inhibitor

Table 2 Semi-Synthetic Opioids

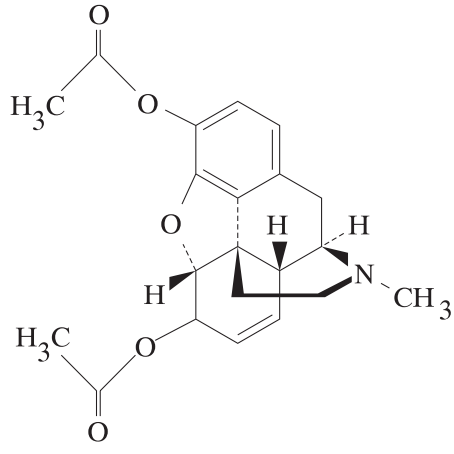
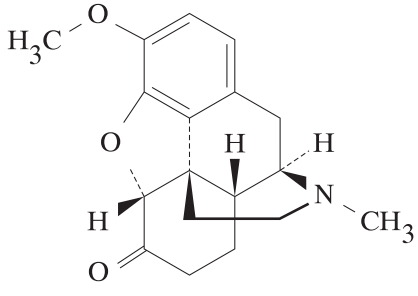
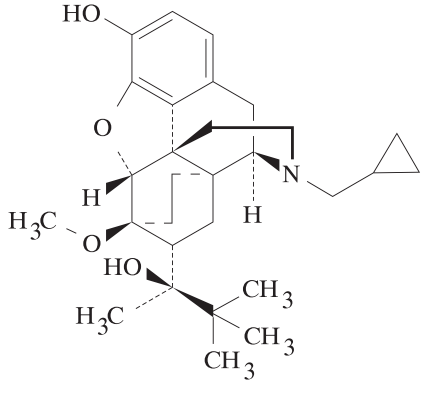
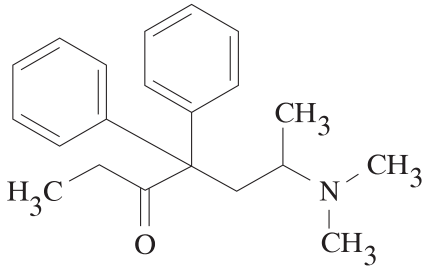
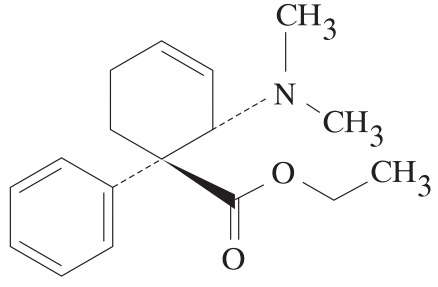
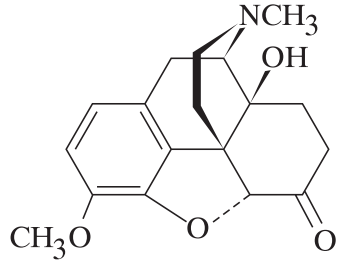
Heroin Diamorphine DAM 3,6-O-Diacetylmorphine		Analgesic Duration of effect: 4-5 hours Elimination half-life: 0.5 hours LD: 25 mg i.v. produced from morphine through acetylation by acetic acid anhydride
Hydrocodone Dihydrocodeinone		Antitussivum Duration of effect: 8-10 hours Elimination half-life: 4 hours
Buprenorphine		Analgesic Duration of analgetic effect: 6-8 hours Duration of withdrawal prevention effect in high doses up to 48 hours Elimination half-life: 5 hours Agonist/ Antagonist; synthetised out of Thebain

Table 3 Synthetic Opioids

Methadone		Analgesic Duration of analgetic effect: 8-48 hours Duration of withdrawal prevention effect in high doses: rarely less than 24 hours Elimination half-life: 15-22 hours LD: 25 mg i.v., 50 mg p.o., 25 mg L-Methadone p.o
Tilidine		Analgesic Duration of effect: 4-6 hours Elimination half-life: 3-5 hours
Oxicodone		Analgesic Metabolism: Hepatic Half life: 3 - 4.5 hours Excretion: Urine

3. History

Opium has been used for hundreds years to relieve pain. Word opium is derived from "opos" - juice in Greek. Opium is the dried milky juice of the unripe seed capsule of the poppy, the Papaver somniferum. It is a complex chemical cocktail of morphine (10%-15%), codeine (1%-3%), noscapine (4%-8%), papaverine (1%-3%), and thebaine (1%-2%).

The opioid analgesics are of inestimable value because they reduce or abolish pain without causing a loss of consciousness.

They also relieve coughs, spasms, fevers and diarrhea.

Archaeological evidence and fossilized poppy seeds suggest that Neanderthal man may have used the opium poppy 30,000 BC.

The first known written reference to the poppy "hul gil" - plant of joy appears in a Sumerian text dated around 4,000 BC.

The art of poppy-culling continued from Sumerians to Assyrians, Babylonians who passed their knowledge to the Egyptians.

460 B.C. Hippocrates, "the father of medicine", dismissed the magical attributes of opium but acknowledged its usefulness as a narcotic and styptic in treating internal diseases, diseases of women and epidemics.

330 B.C. Alexander the Great introduced opium to the people of Persia and India.

Stoic philosopher and illustrious opium-eater Emperor Marcus Aurelius (reigned AD 161 - 180) wrote Meditations where he explained how moral life leads to tranquility. He recommended opium-eating for headache, dizziness, epilepsy, asthma, fever, leprosy and other ills of the flesh.

Arabic physicians used opium quite often and Arabic traders brought opium from the eight century on, first to the East, to India and China, and later to Europe.

Medicinal use of opium was stimulated by the famous physician Paracelsus at the end of the Middle Ages by the introduction of tincture of opium.

An attempt to forbid the import of opium into China by the authorities, led to the so-called "Opium War" between England and China, launched by the biggest, and richest perhaps drug cartel the world has ever known, the British Empire.

In 1805 morphine was first isolated from opium by a German pharmacist, Wilhelm Sertürner (1783-1841). Sertürner named it morphium - after Morpheus, the Greek god of dreams.

In 1874, English pharmacist Alder Wright had boiled morphine and acetic acid to produce diacetylmorphine, a white, odourless, bitter, crystalline powder.

Heinrich Dreser - a head of Bayer's pharmacological laboratory from 1897 to 1914 was the first to see its commercial potential. Under his instructions it was synthesized by Hoffmann in Bayer laboratory and was named heroin (hero).

In 1898, heroin was introduced as the ideal nonaddictive substitute for morphine.

By 1899, Bayer was producing about a ton of heroin a year, and exporting the drug to 23 countries. There were heroin pastilles, heroin cough lozenges, heroin tablets, water-soluble heroin salts and a heroin elixir in a glycerine solution.

As early as 1899, researchers began to report patients developing "tolerance" to the drug, while a German researcher denounced it as "an extremely dangerous poison".

In 1906, the American Medical Association approved heroin for medical use, though with strong reservations about a "habit" that was "readily formed".

In 1913, Bayer decided to stop making heroin.

1924 - Heroin Act - made manufacture and possession of heroin illegal.

1930 - Federal Bureau of Narcotics (FBN) was created.

1970 - FBN divided drugs into categories, set regulations and penalties for narcotics.

4. Effects

4.1 Acute

- Euphoria
- Increased alertness and motivation
- Positive mood shift
- Sense of emotional detachment
- Absence of pain and stress
- Altered mood and mental processes
- Sluggish "rubber-like" movements
- Sleepiness
- Vomiting
- Loss of appetite
- Reduced sex drive
- Itchy skin
- Increased urination
- Sweating
- Inability to concentrate
- Impaired vision
- Death.

4.2 Chronic

- Mental and physical health problems
- Severe constipation
- Contracted pupils
- Moodiness
- Menstrual irregularities
- Lung, liver, kidney and brain damage
- Collapsed veins from injecting the drug
- Loss of weight
- Reduction of sex hormone levels
- Hepatitis, AIDS, and other infections from unsanitary injection
- Stroke or heart attack caused by blood clots resulting from insoluble additives
- Pregnancy complications including still birth
- Death.

Opiate dependence occurs very rapidly, sometimes within weeks. Once someone becomes addicted to opiates, they will continue to use the drug not only for the purpose of intoxication, but to avoid the painful withdrawal symptoms that naturally come with opiate addiction. Regular opiate users, who abruptly stop using the drug, experience withdrawal symptoms four to six hours following the last dose. Symptoms include uneasiness, diarrhea, abdominal cramps, chills, sweating, nausea, runny nose and

eyes, irritability, weakness, tremors and insomnia. The intensity of these symptoms depends on how much of the drug was taken, how often and for how long. These symptoms are usually strongest 24 to 72 hours after onset and can persist for seven to 10 days.

5. Criminal activity

There is a long-standing relationship in the literature between opiate dependence and increased rates of criminal activity. Opiate dependence is unequivocally associated with high rates of criminal behavior. These crimes range in severity from homicides to other crimes against people and property. It is clear that significant amounts of crime perpetrated by opiate-dependent persons are a direct consequence of untreated opiate dependence.

6. Health care costs

The consequences of untreated opiate dependence include much higher incidence of:

- bacterial infections
- endocarditis
- thrombophlebitis
- skin and soft tissue infections
- tuberculosis
- hepatitis B and C
- AIDS and sexually transmitted diseases
- alcohol abuse.

Because those who are opiate-dependent present for medical care late in their diseases, medical care is generally more expensive.

7. Joblessness

Opiate dependence prevents many users from maintaining steady employment. Much of their time each day is spent in drug-seeking and drug-taking behavior. Therefore, many seek public assistance because they are unable to generate the income needed to support themselves and their families.

8. Mortality

Annual death rates reported in four American studies of opiate dependence varied from 13 per 1,000 to 44 per 1,000, with a median of 21 per 1,000. Every study showed that death rates were lower in opiate-dependent persons maintained on methadone compared with those who are not. The median death rate for opiate-dependent persons in MMT was 30 percent of the death rate of those not in treatments.

9. What the opiate addiction is?

Opiate addiction is a chronically relapsing disorder that is characterized by compulsive drug taking, an inability to limit intake, and bouts of intense drug craving that can be precipitated by the mere presence of people, places, or objects previously associated with drug use. Long-term use of opioids causes tolerance to develop so that in order to achieve the same degree of euphoria, larger and larger doses must be taken.

It is primary, chronic neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviours that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving. The exact brain mechanisms that cause tolerance and addiction are not completely understood.

Opiates stimulate a "pleasure system" in the brain. This system involves neurons in the midbrain that use the neurotransmitter called dopamine. These midbrain dopamine neurons project to another structure called the nucleus accumbens which then projects to the cerebral cortex. This system is responsible for the pleasurable effects of heroin and for the addictive power of the drug.

10. Opioid receptors

The opioids produce their effects by interacting with a specific receptor.

The structural similarities between all substances with an opiate-like action and the discovery of opiate agonists and antagonists generated the concept of opiate receptors.

Based on their behavioral and neurophysiological findings three types receptors were distinguished - μ, δ, κ. An alternative classification system is based on their order of discovery the receptors being termed OP1 (δ), OP2 (κ), and OP3 (μ).

- μ-type for morphine, which induces analgesia, hypothermia, meiosis, addiction. μ-receptors are found mainly in the brainstem and the medial thalamus. There are two primary sub-types: μ-1 and μ-2. Stimulation of the μ-1 receptors is primarily responsible for the beautiful sense of euphoria, serenity and analgesia (Fig. 1).
- δ-type (antinociception). As compared with μ-type - greater relief of neuropathic pain, reduced respiratory depression, and constipation as well as a minimal potential for the development of physical dependence was identified (Fig. 2).
- κ-type (induces depression of flexor reflexes, sedation, mediates dysphoria) (Fig. 3).

More recently, cDNA encoding an "orphan" receptor was identified with high degree of homology to the "classical" opioid receptors. It has been named ORL1 (opioid receptor-like). This

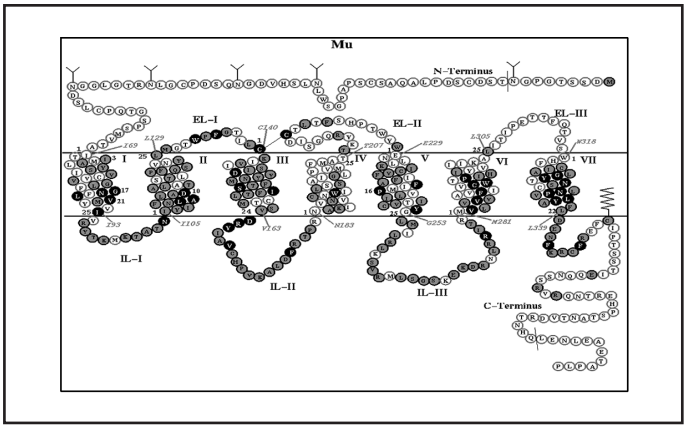


Figure 1 Mu receptor

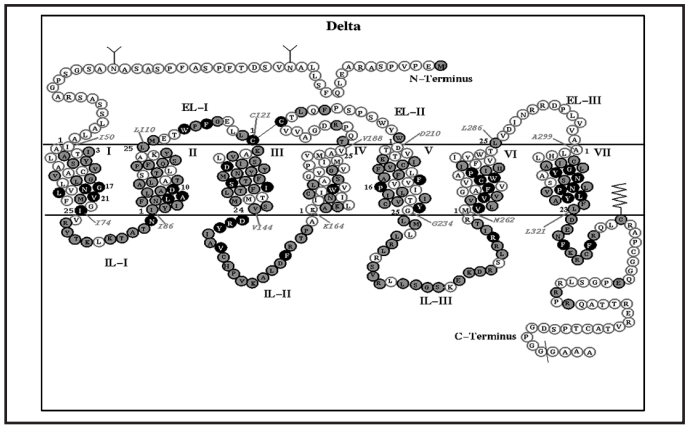


Figure 2 Delta receptor

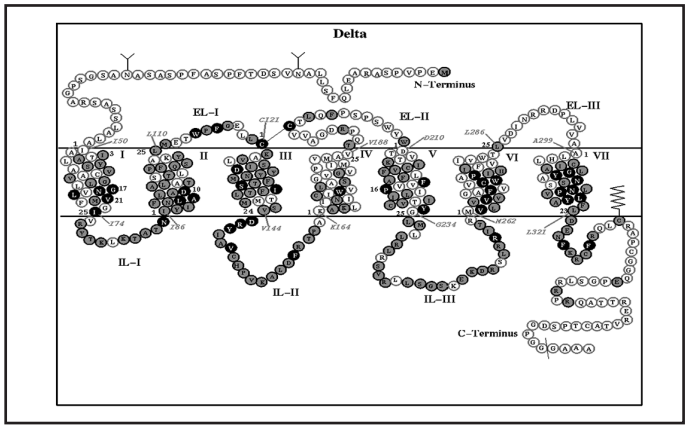


Figure 3 Kappa receptor

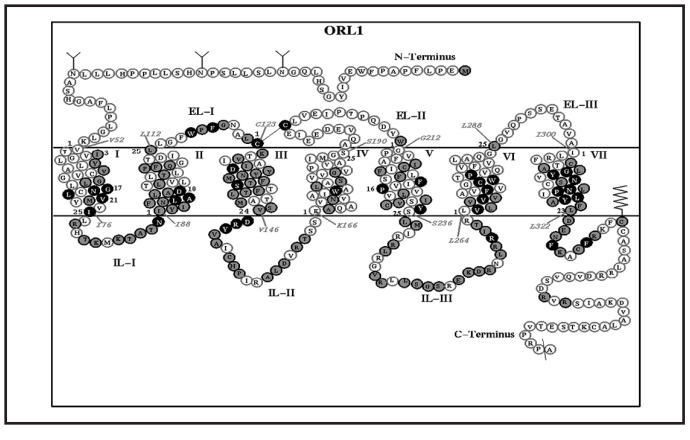


Figure 4 ORL1 receptor

receptor is widely distributed in the brain and is responsive to the novel peptide orphanin FQ also known as nociceptin. In contrast to the effects of classic opioid receptors, the ORL1 receptor appears to mediate hyperalgesia. ORL1 receptor can also mediate analgesia (Fig. 4).

Studies conducted on the cloned opioid receptors demonstrate that the amino acid sequence of the δ-, κ-, μ-opioid and ORL1 receptors are 65% homologous.

Some kind of preference for the different endogenous opioid ligands for the certain receptors was found:

- β-endorphin and endomorphins 1 and 2 for μ
- enkephalins for δ
- dynorphins for κ
- nociceptin-orphanin FQ for ORL1.

All classes of opioid receptor share key similarities. Their activation produces a wide array of cellular responses as analgesia, suppression of protein synthesis, schizophrenia, and immune response regulation.

Based on results of pharmacological investigations, δ-, κ-, and μ-opioid receptors have been further subdivided into receptor subtypes (μ1, μ2; δ 1, δ 2; κ 1, 2, 3).

There is pharmacological evidence for subtypes of each receptor and other types of novel, less well-characterised opioid receptors, e, l, i, z, have also been postulated.

References

1. www.wikipedia.com/opiodhistory
2. www.wikipedia.com/effectsopiod
3. experts.about.com/q/…adderall. effxor.weed.cocain.htm
4. Goodmans and Gilmans – Book of Pharmacology.
5. www.opioid.umn.edu/ptmut.html

Module 3.2
Marijuana use among medical students

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Key messages

- Marijuana is a common name for the leaves of the cannabis plant;
- The marijuana sold today has much higher THC chemical content than the marijuana sold in the '60s and '70s due to hybridization techniques;
- Marijuana is most commonly smoked;
- Marijuana affects many parts of the human body;
- Students from University of Medicine – Pleven, Bulgaria carried out the survey "Marijuana Use among Medical Students".

Contents

1. General information

Marijuana is a common name for the leaves of the cannabis plant (Cannabis sativa), also known as pot, grass or weed. It does not contain just one chemical. In fact, it contains about 60 known relatives of the primary active ingredient, Δ9-tetrahydrocannabinol (THC), and about 400 known chemical toxins. When burned, even more toxic compounds are produced. The marijuana sold today has much higher THC chemical content than the marijuana sold in the '60s and '70s due to hybridization techniques. Marijuana is made from the chopped leaves, stems, and seeds of the cannabis or hemp plant. Historically, hemp has been a valued crop because the woody fibres of the stem yield a fibre that can be made into cloth, rope, and paper for relatively cheap. When the dangers of marijuana were realized, hemp was made illegal to grow and possess.

2. Common methods of use

Marijuana is most commonly smoked. It can be rolled into a cigarette, known as joint, or smoked in a pipe. Smoking produces the quickest effects in a couple of minutes.

Marijuana can also be ingested to experience a high. It is commonly cooked into foods such as cakes or mixed with milk. When marijuana is ingested, the effects take longer to appear, sometimes a couple of hours, but they last longer and are more pronounced. Mental effects start within minutes of smoking and 30-90 minutes after eating marijuana in baked goods. Most effects from smoking are gone within 3-4 hours, while the effects after eating can last for 4-8 hours.

3. Age and reasons for using cannabis

The average age for starting to use cannabis in Western and lately in East European countries seems to be around 14-15 years of age. The idea that cannabis is a gateway drug that leads to other drug use has been proposed for years. It remains a mystery whether it is so, that is why this statement is rather controversial and vague.

The young people start using cannabis in order to:

- show independence;
- develop their own values (apart from parental and societal authority);
- develop strong peer connections;
- seek new and exciting experiences;
- take risks and satisfy curiosity.

The reasons for a person developing problems as a result of cannabis use usually stem from a variety of personal, family and school-related factors (for example, having mental health issues, poor family life and/or doing poorly at school). An indicator of likely problems is daily use. A small but important percentage of students report using cannabis daily, and in one survey, over half of all cannabis users reported that they had experienced at least one of

three indicators of dependence. Heavy use of cannabis is more likely among street youth and is related to:

- low self-esteem;
- delinquent behaviour (stealing, vandalism, fare dodging);
- having delinquent friends;
- hanging out on streets in boredom;
- other behavioural/mental health issues (those in special education programmes/schools tend to use more);
- truancy.

4. Effects

Marijuana affects many parts of the human body. The effects vary and they depend on:

- Way it is prepared and used;
- The dose of marijuana;
- Circumstances surrounding use.

The leafy part of the cannabis plant, has less THC than the resin (hashish) or oil (hash oil). A dose of cannabis that is eaten will have one-half to one-third the effect of the same dose smoked. The active ingredient in cannabis is tetrahydrocannabinol or THC, which gives the following effects: sense of well-being; relaxation; enhanced sociability; difficulty in concentrating; distortions in sense of time, vision and hearing; and at higher doses, auditory and visual hallucinations.

It is very difficult to determine the amount of actual THC that is consumed by each person when a joint is passed around. Being a plant product, THC amounts vary greatly and other factors, including the number of puffs, time between puffs, holding time and lung capacity, also affect THC levels taken in during use.
The circumstances surrounding use are really important and refer to the setting, the motives and expectations, and whether the cannabis is combined with some other drug.

Marijuana exercises numerous effects on the human organism:

- Feelings of isolation and depersonalization;
- Shakes, lack of coordination and headaches;
- Mental or emotional problems;
- Amotivational syndrome, including loss of energy and the urge to work;
- Increased heart rate;
- Cardiac problems;
- Reddening of the eyes,
- Sleepiness;
- Increased appetite;
- Relaxed muscles;
- Decreased air flow; loss of lung capacity in more than a month of regular smoking;
- Chronic irritation of nasal and lung passages;
- Increased symptoms of bronchitis, coughing and wheezing;
- Increased rates of pulmonary infections;
- Precancerous changes in the lungs of smokers in their 20s;
- Higher rate of lung cancer than in non-smokers;
- Decreased brain response, negative

effects on thinking and brain function;
- Problems with short and long term memory, distorted perception of time;
- Blackouts;
- Impaired driving skills;
- Increased brake response time;
- Decreased concentration;
- Distorted peripheral vision, especially in the first two hours after use;
- Impotence in some cases ;
- Harms on the developing fetus;
- Increased still births, neonatal deaths;
- Decreased birth weight and abnormal reactions in children born to mothers on marijuana.

5. Curious facts about marijuana

- 3-4 cannabis cigarettes a day are estimated to result in the same levels of bronchitis as 20 tobacco cigarettes.
- It contains 50% more tar per gram than tobacco.
- Serbian women mixed cannabis with egg whites, saffron and sugar to make guc-kand, a tonic which created a sexy mood or was given to young boys to lessen the pain of circumcision! Cannabis tonics were also given to crying and potty children, and it was reported to perk them right up into the smile zone.
- Marijuana has been used as an aphrodisiac for thousands of years, yet ironically it has also been used to decrease sexual desire. Ancient sacred texts reveal how to use marijuana to increase sexual pleasure, but modern research teaches an equally important lesson: marijuana's effects are determined by the personality, physiology, intention, environment, and culture of the user.
- Human bodies contain pleasure systems, which reward them for sex; human brains contain neurocellular circuitry which can only be activated by substances with THC's molecular structure. This makes the marijuana high a unique constellation of feelings, and there are only two sources for the substances which activate THC's very own neuroreceptor. The human brain is one source: it generates a neurochemical very similar to THC, called anandamide which means "bliss". The only other source for this bliss-producing substance is the cannabis plant.
- Being stoned or sexually aroused both produce similar physiological responses, such as increased heart rate, heightened sensitivity, changes in blood flow and respiration, relaxation – an acutely altered state of consciousness. Neurochemistry, hormonal systems, and brain regions such as the temporal lobe are affected by both marijuana and sexual arousal.

6. Results from the survey "Marijuana Use among Medical Students"

Drug abuse occurs to be among the most expensive social diseases of the modern society.

4,1% of the global population at the age of 15 years and above use illegal drugs. The number of the drug addicts registered in Bulgaria is more than 80 000 which makes about 1,14% of the population of our country. The medical students as future doctors feel responsible to make efforts to change this situation. The quick expanding of the problem leads to the need of more information in this field which could be obtained due to surveys and their detailed analysis.

Cannabis is the most common drug in the European countries and its use increases rapidly. As a matter of fact, the social perception on the problem is controversial and vague. One opinion is that it is a soft harmless drug, providing relaxation and stimulating appetite. The other opinion is that marijuana is a "gateway" to hard drugs such as heroine, cocaine, etc.

In the spring of 2005 a group of medical students from the University of Medicine – Pleven, Bulgaria, decided to carry out a survey aiming to inquire about:

- the attitude of the medical students in Pleven university to the use of marijuana;
- the number of medical students using/used marijuana;
- the knowledge of medical students of the harmful effects of marijuana on human health;
- the legal aspects of marijuana use.

Several volunteers – medical students who did not take part in filling the questionnaires – carried out the survey.

The target group consisted of medical students between 17-27 years of age. The total number of the students participating in the investigation was 76 (43 women and 33 men). The students were divided into 2 groups – tobacco smokers and non-smokers (41 and 35). According to the survey 47% of the students have tried marijuana and 69% of them were tobacco smokers.

In spite of the good knowledge of students in the field of medicine, it was found that most of them were not aware of the health risks of marijuana use.

They did not know that:

- marijuana use can lead to physical dependence;
- it has negative influence on the reproductive system;

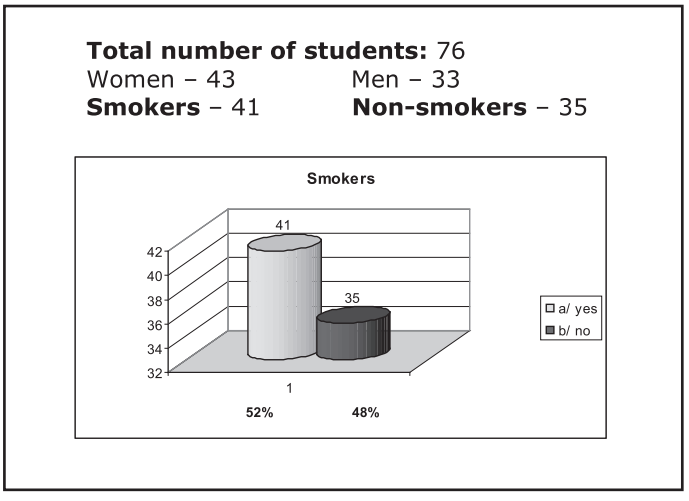

Figure 1 Students participating in survey

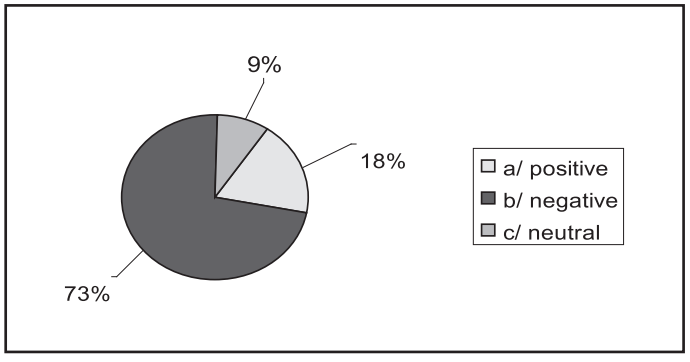

Figure 2 Students' attitude towards marijuana

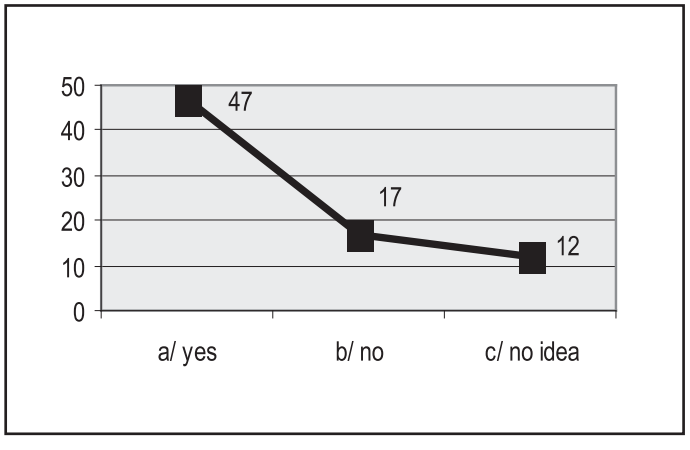

Figure 3 Is marijuana a gateway to drugs?

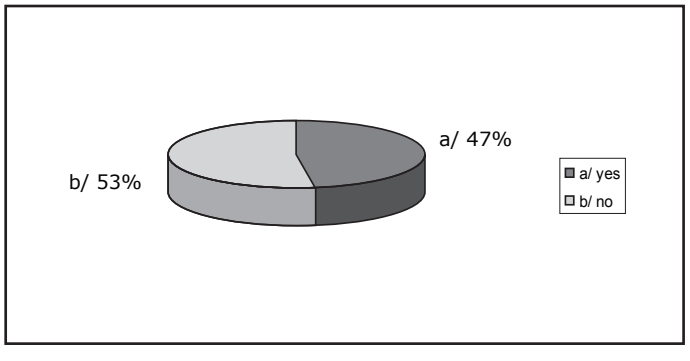

Figure 4 69% of the students who have tried marijuana are tobacco smokers

- negative effect on memory;
- negative effect on cardiovascular system;
- it may cause cancer;
- others.

The only acceptable level they demonstrated concerning psychological dependence of marijuana.

Apart from the harmful effects of marijuana, it should be paid attention to the most common reasons which make people use drugs: personal problems, influence of the social environment (including friends), and pursuit of delight or just for fun.

One of the questions of the survey was about the attitude of the students to the legalization of marijuana.

However, according to the results most of the participants in the survey did not have certain opinion about the legal aspects of marijuana use. Probably it is due to the fact that there are many unclear points of the problem and the opinions on this topic are extremely different and controversial. Along with the great number of answers "no idea" there were also negative answers. Another reason could be insufficient

level of knowledge about the harmful effects of marijuana.

The main conclusions based on this survey are:

- Although most of the target group have tried marijuana, they have a negative attitude toward it.
- Almost 2/3 of the students, who were smokers have tried marijuana, so there could be a correlation between smoking tobacco and marijuana use.
- According to this survey, the psychological dependence is the most common health risk (76%).

Despite of being medical students their level of knowledge about health risks of marijuana is very low. That's why there is a need of a special module on drug prevention to be included in the curriculum of medical students.

Drugs are part of the civilization and the subculture in the new century, they exist in our life no matter if we accept the importance of this problem or not. They are everywhere and nobody is protected from them regardless of their education, social and financial status. Medical students as future doctors are standing on

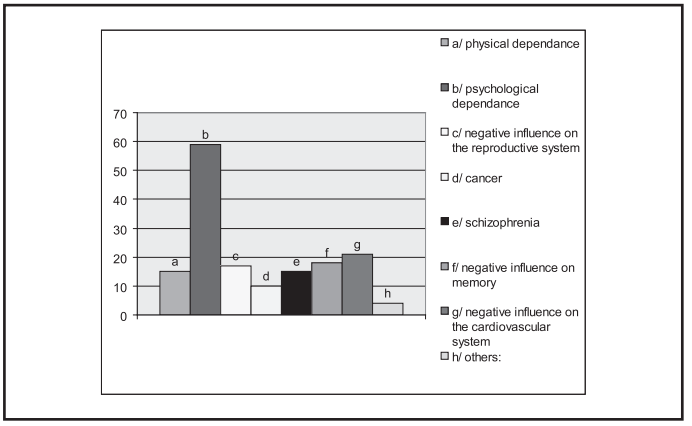

Figure 5 Student's knowledge about health risks of marijuana is very low

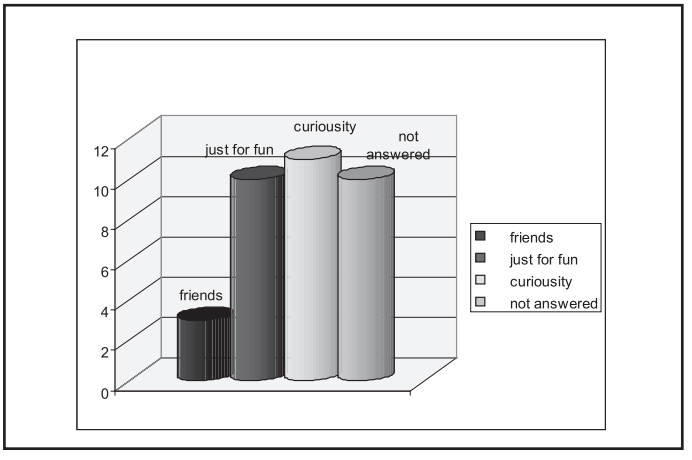

Figure 6 Why students use marijuana?

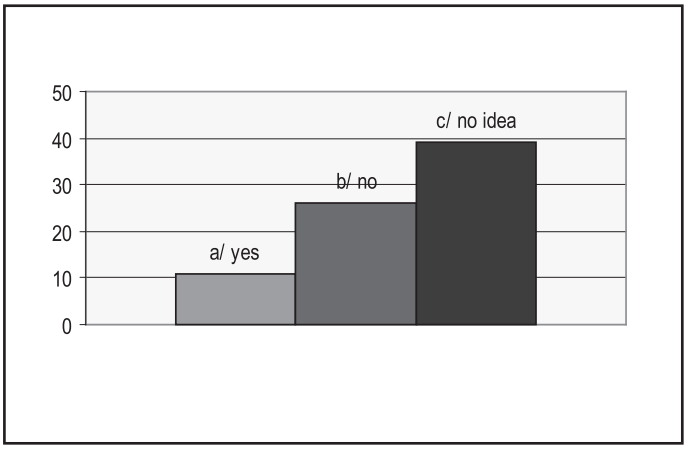

Figure 7 Attitude of students to the legalisation of marijuana

the first line for tackling with the negative effects of marijuana use and they need to be well educated on this problem.

References

1. http://cannabisculture.com/articles/1372.html
2. http://www.goofyfootpress.com/sexanddrugs/marijuana_sex.php
3. http://www.changetheclimate.org/news/sex.php
4. http://www.well.com/user/woa/fspot.htm
5. http://www.wellness.gatech.edu/information/2_drug_abuse/marijuana.php

Module 3.3
Neurobiology of cannabis

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Key messages

- The effect of cannabis depends on the effective components absorbed named cannabinoids and their metabolism in the human body. The most important cannabinoid is Δ9-tetrahydro-cannabinol (THC);
- The cannabinoids cannot be removed easily from the body; they are stored in fat tissue. From the fat tissue they slowly move to other tissues and organs including the blood and the brain;
- Cannabinoids are cell membrane-derived signalling molecules that are released from nerves, blood cells and endothelial cells, and have diverse biological effects;
- Cannabis effects on gastrointestinal tract, endocrine system, cardiovascular system, respiratory system and immune system could be classified generally as short-term and long-term effects;
- Marijuana has many possible medical uses.

Contents

1. Classification of cannabinoids

Family: Cannabaceae
Genus: Cannabis
Species: sativa; indica; ruderalis
Common Names: Marijuana Pot; Weed; Grass; Mary Jane.

Cannabis contains a mixture of many closely related therpeno-phenols. The major important psycho-components named cannabinoids include: Δ9-tetrahydrocannabinol, cannabidiol, Δ8-tetrahydrocannabinol, cannabigerol, cannabinol, cannabichromene, cannabicyclol, cannabielsoin. The most important cannabinoid is Δ9-tetrahydro-cannabinol (THC) (Fig. 1).

2. Administration of cannabis

Marijuana is most commonly smoked, though it can also be consumed as cooked into cakes. Marijuana users roll it into a cigarette, known as joint, or smoke it in a pipe.

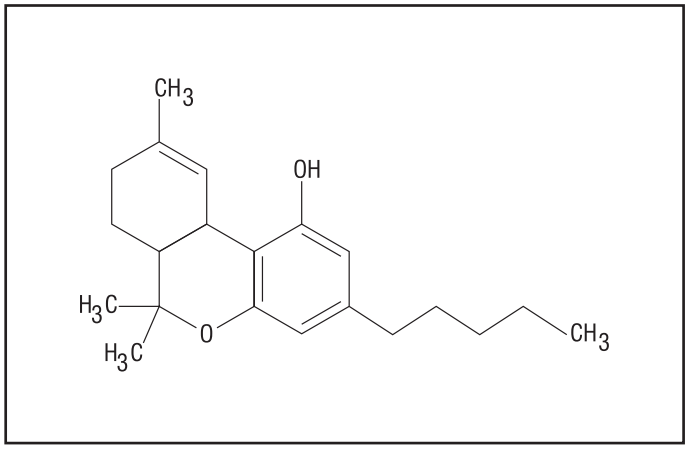

Figure 1 Chemical formula of Δ9-tetrahydrocannabinol

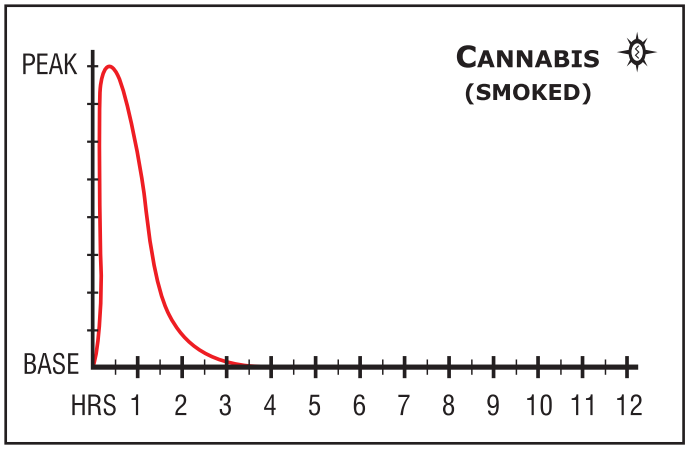

Figure 2 Graphics of effects of cannabis duration smoked

The effect of cannabis depends on the amount of the effective components absorbed and their metabolism in the human body.

When smoked, THC is rapidly absorbed through the respiratory tract flowed by quick penetration to the lymphatic system and into the brain; the effects appear in 3-5 minutes (Table 1), (Fig. 2). Smoking of THC produces an almost immediate intense experience and peak physical and psychological effects within 15 minutes. THC persists in the brain longer than in the blood because of its lipophilic nature. As a result the psychoactive effects last longer.

The effects of cannabinoids last for about 3 hours (Table 1 and Table 2). 2 mg of THC in a cannabis cigarette activates receptors and causes behavioural changes. Some components of cannabis cannot be absorbed. Inhaled smoke contains about 50% of THC, but only about 10–25% of it enters the blood.

Orally administered cannabis leads to slower appearance of effects. It takes approximately 30 minutes to enter the bloodstream. Maximum physiological and psychotropic effects are attained approximately 60 minutes after ingestion. General effects persist for 2-5 or up to 8 hours, depending on the dose. The quantity of THC absorbed after chewing cannabis is 2-3 times lower than after smoking the same dose. Usually, when chewing, the plasma concentration is still high for 12 hours. This is because after absorption in the intestine the active components of cannabis are metabolized in the liver before entering the circulatory system. After the absorption of the psycho-active components of cannabis they spread throughout the whole body.

First they reach the tissues supplied with the largest amount of blood such as brain, lungs, kidneys, ovaries and testis.

Table 1 Cannabis effects when smoked

Total Duration	1 - 4 h
Onset	0 - 10 min
Coming Up	5 - 10 min
Plateau	15 - 30 min
Coming Down	45 - 180 min
After Effects	2 - 24 h
Hangover / Day After	—

Table 2 Cannabis effects after oral consumption

Total Duration	4 - 10 h
Onset	30 - 120 min
Coming Up	30 - 60 min
Plateau	2 - 5 h
Coming Down	1 - 2 h
After Effects	6 - 12 h
Hangover / Day After	0 - 1 day

3. Metabolism of THC

THC is metabolized by the cytochrome P450 2C9 and 2C11 enzyme system in the liver into 11-hydroxy-tetrahydro-cannabinol. This metabolite is more active than THC and produces pharmacological effects of cannabis. The cannabinoids cannot be easily removed from the body because they are stored in the fat tissue. From fat tissue they slowly move to other tissues and organs including blood and brain. The elimination of cannabinoids from the body is a very slow process and takes about 15-30 days depending on the dose taken. Thus, regular use of Marijuana leads to accumulation of high concentrations of cannabinoids in fat tissues, which can be determined by urine, feaces, and hairs tests.

4. Mechanism of THC action

Numerous papers regarding the biochemistry and pharmacological effects of cannabis were published, but

the mechanism of its action remained enigma until 1980, when Howlett found out that cannabioids act through receptors. By using neuroblastoma cells, Howlett and his group demonstrated that cannabinoids interact with adenylate cyclase second messenger signalling pathway. This effect is transduced by the specific THC receptor connected to G-protein, and leads to inhibition of adenylate cyclase (enzyme producing cAMP from ATP). The level of inhibition of adenylate cyclase by variety of canabinoids in animal studies was in parallel with their biological effects.

5. Cannabinoid receptors

Cannabinoids act at two distinct types of G-protein-coupled receptors: cannabinoid CB1 and CB2 receptors. Cannabinoid CB1 receptors are highly localised in the central nervous system and are also found in some peripheral tissues, in the lungs, and in the heart. CB2 receptors are found outside the central nervous system, in particular in association with immune tissues. Novel actions of cannabinoids at non-CB1 non-CB2 cannabinoid-like receptors and vanilloid VR1 receptors have also recently been described. There is growing evidence that, apart from other roles, cannabinoids can act at prejunctional sites to modulate peripheral autonomic and sensory neurotransmission.

Inhibitory cannabinoid CB1 receptors are expressed in the peripheral terminals of autonomic and sensory nerves. The role of cannabinoid receptor ligands in modulation of sensory neurotransmission is complex. In the human brain, there are natural cannabinoid substances called monogenic substances or ligands. Several different compound are considered to have cross reactivity: anandamide – endogenous cannabinoid, 2-arachidonyl glycerol (2-AG) and endogenous vanilloid N-arachidonoyl-dopamine, which also activates vanilloid (VR)1 receptors. VR1 is coexpressed with cannabinoid CB1, which excites sensory nerves and causes a release of sensory neurotransmitter. The anandamide and N-arachidonoyl-dopamine span two distinct receptor families, both compounds are structurally related to the archetypal vanilloid capsaicin, all three are arguably members of the same family of signalling molecules.

Pathoanatomy data (human and animals) show that CB1 receptors are spread in different parts of the brain as well as in the peripheral tissues. In the brain the receptors are mainly distributed in the cerebral cortex, mostly in the frontal cortex, hippocampus, basal ganglia, cerebrum, and nucleus accumbiens. The location of cannabinoid receptors in the regions of nucleus accumbiens and striatum suggests the changes in motivation, as THC stimulates the release of dopamine. The brain stem regulates the main organism functions. One of them is breathing. Cannabinoid receptors in this area are very few; this explains why there is no risk of death when the breathing stops during the overdosage of cannabis.

CB2 receptors are found in the immune cells of the gut and the spleen – an organ with well established immune function. CB1 receptors can reemit some of the physical features of opiates and can also be included in the development of the physiological response to opiates.

6. Endocanabinoids – monogenic substances

Cannabinoids are cell membrane-derived signalling molecules that are released from nerves, blood cells and endothelial cells, and have diverse biological effects. The first monogenic substance found in the brain was arachidonyl-ethanolamide. It was named anandamide after Sanskrit word "ananda" meaning "bliss". Another important molecule binding canabinoid receptor is 2-arachidonyl glycerol (2-AG). The concentration of anadamide and 2-arachidonyl glycerol in the brain can be compared to the distribution of CB1 receptors.

It has been established that anandamide and presumably other polyunsaturated N-acylethanolamines, bind to and activate both the central (CB1) and the peripheral (CB2) cannabinoid receptors and elicit the effects of cannabis. The endocannabinoids produce neurobehavioral effects and may have important signalling roles in the central nervous system, especially in the perception of pain and in the control of appetite. Anandamide is believed to have important anti-inflammatory and anti-cancer characteristics. It was established that anadamide affects the cardiovascular system by inducing profound decreases in blood pressure and heart rate. Some of these effects appear to be independent of the two main receptors.

Elphic and Egertom described the functional model of cannabinoids in the brain in which anandamides take part in the release of neurotransmitters:

- Anadamide is produced and released by the post synaptic membrane, and then goes to the presynaptic membrane of other nerve cells and binds CB1 receptors.
- The activation of the receptors inhibits the release of neurotransmitters from presynaptic membranes.
- Neurotransmitters enter the postsynaptic membrane of other nerve cells realize the effect and are metabolized there.

During the past several years new biomedical developments have provided an opportunity to examine the physiological and biochemical events underlying the use and abuse of cannabis as well as elucidating the biological role of the endogenous cannabinoid ligands (endocannabinoids).

The biological targets for endocannabinoids include the cannabinoid receptors CB1 and CB2, the enzyme anandamide amidohydrolase (AAH), and the carrier protein anandamide transporter (ANT).

AAH is an enzyme responsible for the hydrolytic breakdown of anandamide and ANT is a carrier protein involved in the transport of anandamide across the cell membrane. The evidence obtained

so far, suggests that in combination these two proteins are responsible for the termination of the biological actions of anandamide.

The discovery of anandamide has revealed a novel class of more selective agents possessing somewhat different pharmacological characteristics than the cannabinoids. A number of such analogues have been reported. Many of them possess markedly improved cannabinoid receptor affinities and metabolic stabilities compared to those of the parent ligand. Generally, it was found that anandamide and other analogues exhibit significant selectivity with high affinity for the CB1 receptor and modest to very low affinity for the CB2 receptor. In a relatively short period of time, pharmacological and biochemical studies have confirmed initial speculations that

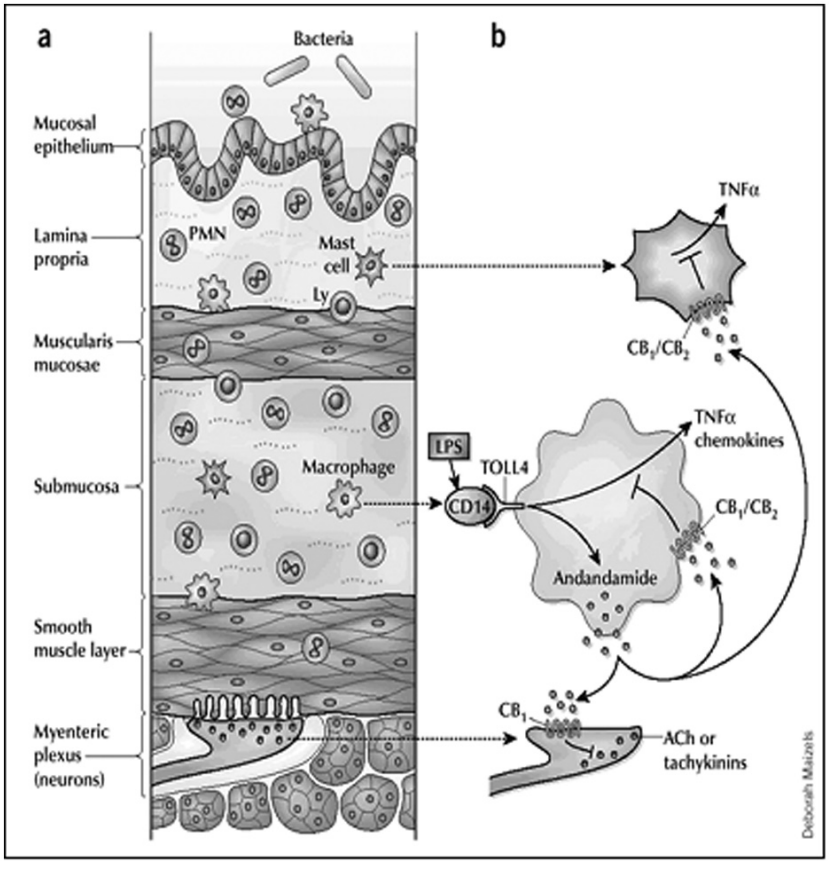

Figure 3 The structure-activity relationships (SAR) of anandamide for the CB1 and CB2 cannabinoid receptors (D. Maizels, Nature, Medicine, (2004) 10, 678 – 679)

anandamide is either a neuromodulator or neurotransmitter and has significantly advanced our understanding of cannabinoid biochemistry (Fig. 3).

7. Cannabinoid-ananamide system

Cannabinoid–anadamide system has an impact on many neurotransmitters in the neuro-modulatory system including cholinergic, noradrenergic, dopaminergic, serotonergic, GABA, NMDA, glucocorticoids', prostaglandin system. Their role in the pharmacological effects is not known.

Anandamide is released from nerves, but unlike classical neurotransmitters, it is not stored in and released from nerve vesicles, but is released on demand from the nerve cell membrane. In the central nervous system, cannabinoids function as retrograde signalling molecules, inhibiting via presynaptic cannabinoid CB1 receptors the release of classical transmitter following release from the postsynaptic cell. At the neuroeffector junction, it is more likely that cannabinoids are released from prejunctional sites, as the neuroeffector junction is wide in some peripheral tissues and cannabinoids are rapidly taken up and inactivated.
Anandamide is inactivated in central neurons by both reuptake and enzymatic hydrolysis. Inhibition of its reuptake causes potentiation of its action.

Understanding the actions of cannabinoids as modulators of peripheral neurotransmission is relevant to a variety of biological systems and possibly their disorders.

Anandamide and N-oleoylethanolamine are selectively decreased and increased in rat intestine during food deprivation and re-feeding through remodelling of the original acyl donor phospholipids. The products are thus in a state of dynamic equilibrium as part of the normal system of redistribution of molecular species in phospholipids.

8. Effects of the use of cannabis

Physical effects on the gastrointestinal tract, endocrine system, cardiovascular system, respiratory system and immune system could be classified generally as short-term and long-term effects.

8.1 Short-term physical and psychological effects

- Physical
  - Dysphoria
  - High pulse rate
  - Red eyes
  - Dilation of pupils
  - Increased blood pressure
  - Hyperglycemia
  - Hypertension
  - Increased appetite
  - Intolerance to bright light
  - Disordered coordination
  - Slow reactions.
- Psychological
  - Euphoria
  - High spirits.

The effects of smoking cannabis are usually lighter than those of many other recreational psychoactive substances. People are generally capable of carrying out normal actions and activities while high.

8.2 Long-term effects

Gastrointestinal system
Cannabinoides adversely affect the function of liver leading to chronic liver diseases. Cannabinoides have a direct effect on motility of intestinal tract through CB1 receptors. This effect leads to increased contraction of intestinal smooth muscles. Retention of food for a few minutes leads to increased appetite and vomiting.

Cardiovascular system
THC increases the blood pressure and pulse rate. The heart is overloaded especially the left chamber. This is the result of high level of catecholamines and of raised peripheral blood pressure. These effects appear rapidly – within 24 hours. These effects appear prominently after the regular smoking of marijuana for 8-10 days. This is a result of adaptation of parasympathetic system. In addition there can be orthostatic hypertension which is due to decrease in effectiveness of vascular reflux. It leads to heart failure.

Respiratory system
Cannabinoids lead to inflammation, fibrosis, hyperplasia of the bronchial tree and alveolus. Smoking of cannabis leads to bronchitic symptoms – cough, expectoration and breathlessness. THC directly damages the respiratory system.

The risk of developing cancer in lungs is 50% more in smoking marijuana than in smoking cigarettes. Apart from this THC has a bronchodilator effect which leads to retention of tar in the respiratory tract.

Immune system
Cannabinoids affect the immune system in different ways:
- macrophages produce less cytokines and TNF-α;
- loss of phagocytic functions of marophages (antivirus and antibacterial);
- proliferation of lymphocytes;
- production of antibodies from lymphocytes;
- decreased activity of T-killer cells;
- impaired activity of neutrophils and leukocytes.

The exact effect of cannabinoids on the immune system has not yet been determined.

Endocrine system
THC has impact on hypothalamic–epiphysis system. The impact of cannabinoids on it is not known but they take impare production of estrogen – the reason for fertility in women.

THC can pass through the placenta in the embryo/fetus or from mother's milk to the child and cause the same adverse

effects in the foetus as in the adult. These newborns need to be treated by hemodialysis after birth.

The effects of THC are classified as negative, neutral and positive effects.

8.3 Classification of the effects

- Negative
  - nausea, especially in combination with alcohol, some pharmaceuticals, or other psychoactives;
  - coughing, asthma, upper respiratory problems;
  - difficulty with short term memory during effects and during periods of frequent use;
  - racing heart, agitation, feeling tense;
  - mild to severe anxiety;
  - panic attacks in sensitive users or with very high doses (oral use increases risk of getting too much);
  - headaches;
  - dizziness, confusion;
  - lightheadedness or fainting (in cases of lowered blood pressure);
  - paranoid and anxious thoughts more frequent;
  - possible psychological dependence on cannabis;
  - clumsiness, loss of coordination at high doses;
  - can precipitate or exacerbate latent or existing mental disorders.
- Positive
  - mood lift, euphoria;
  - laughter;
  - relaxation, stress reduction;
  - creative, philosophical or deep thinking: ideas flow more easily;
  - increased appreciation of music, more aware of, deeper connection to music;
  - increased awareness of senses (eating, drinking, smell);
  - change in experience of muscle fatigue, pleasant body feel, increase in body/mind connection;
  - pain relief (headaches, cramps);
  - reduced nausea, increased appetite (used medically for this);
  - boring tasks or entertainment can become more interesting or funny.

- Neutral
  - general change in consciousness (as with many psychoactives);
  - increased appetite, snacky-ness;
  - slowness (slow driving, talking);
  - change in vision such as sharpened colors or lights;
  - closed-eye visuals (somewhat uncommon);
  - tiredness, sleepiness, lethargy;
  - stimulation, inability to sleep (less common);
  - blood shot eyes (more common with certain varieties of cannabis and inexperienced users);
  - mouth dryness, sticky-mouth (varies with strain);
  - interrupts linear memory, difficulty following a train of thought;
  - cheek, jaw, facial tension/ numbness (less commonly reported);
  - racing thoughts (especially at high doses);
  - increased emotional impact of music;

- time sense altered: cars seem like they are moving too fast, time dilation and compression are common at higher doses.

9. Withdrawal symptoms

- Mild to moderate, non life-threatening withdrawal symptoms occur after daily use in some users. These may last for 1-6 weeks after cessation of use and can include anxiety, anhedonia (reduced experience of pleasure), headaches, general unease/discomfort, difficulty sleeping, and a desire to smoke pot. Severity of symptoms is related to frequency of use and individual sensitivity;
- slight loss of appetite;
- finding non-stoned life a bit dull, increased boredom.

10. Medical use of marijuana

Marijuana has many possible medical uses. Positive effects are claimed for ailments such as cancer, AIDS, and glaucoma. AIDS can cause loss of appetite known as the "wasting syndrome", which may lead to drastic weight loss and weakness. Chemotherapy used in the treatment of cancer causes nausea resulting in an inability to keep down food. Marijuana's healing nature for these two illnesses is a result of its ability to increase a person's appetite as well as to relieve nausea allowing a patient to regain weight. Historically, marijuana has been used in the treatment of various conditions such as arthritis and glaucoma but it is no longer used for these ailments because of better and safer alternatives.

References

1. Cannabis: effects The effects of cannabis and THC by Grotenhermen F nova-Institut, Hurth, Germany. FGrotenhermen@compuserve.com Forsch Komplementarmed 1999 Oct; www.cannabis.net/overview/index.html
2. Erowid Cannabis (Marijuana) Vault An extensive collection of images and information on historical, spiritual, cultural, and medicinal use, safety, research, effects, experiences, laws, … www.erowid.org/plants/cannabis/
3. cannabis.net Cannabis: the devil's weed or nectar of the gods? www.cannabis.net/
4. http://www.nitricoxideresearch.com/showcitationlist.php
5. www.nhtsa.dot.gov/
6. D. Castle, R. Murray, Marijuana and madness, Cambridge University Press, 2004
7. Deborah Maizels, Nature, Medicine, (2004) 10, 678 - 679

Module 3.4
Synthetic drugs

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Key messages

- Synthetic drugs are artificially produced substances for the illicit market, which are almost entirely manufactured from chemical compounds in illicit laboratories;
- Usually synthetic drugs have mild to serious hallucinogenic effects and can be either stimulants or depressants of the central nervous system (CNS) leading to heavy health risks.

Contents

1. What are synthetic drugs?

Synthetic drugs are artificially produced substances for the illicit market, which are almost entirely manufactured from chemical compounds in illicit laboratories (amphetamine, benzodiazepines).

Due to their popularity among ravers and clubbers synthetic drugs are often referred to as **"club drugs"**, **"rave drugs"** or **"designer drugs"**, which are chemical analogues of controlled drugs. Illegal producers slightly modify the molecular structure of a prohibited substance in order to obtain similar or stronger pharmacological effects, thereby avoiding prosecution.

Regardless of source, commercial or clandestine, amphetamine-type stimulants (ATS) are emerging as a class of drugs that are widely abused in the world and pose a serious threat to youth.

Some of the most prevalent synthetic drugs of abuse are: amphetamine, methamphetamine, ecstasy, para-methoxyamphetamine, gamma hydroxy-butyrate, gamma butyrolactone, ketamine, rohypnol, LSD, phencyclidine.

2. Amphetamine

Description

From a chemical point of view all amphetamine-type stimulants are related to the ß-phenethylamin molecule (2-PEA). This molecule is the basic element of the body neurotransmitters (such as dopamine and adrenaline) that convey the neuronal information of the central and vegetative nervous system. Amphetamines generally cause strong physical and mental stimulation, keeping users awake and alert for many hours, and some amphetamines cause mood lift (euphoria). As a result of the fact that they increase wakefulness, various amphetamines have been used by the military, by pilots, truck drivers, and other workers to keep functioning past their normal limits.

Amphetamines are also used to treat Attention Deficit Disorder and may have the seemingly paradoxical effect of quieting and calming users. Common amphetamines include Dexedrine (d-amphetamine), methamphetamine; Ritalin, and Adderall (dl-amphetamine). Substantial amounts of pharmaceutical amphetamines are diverted from medical use to recreational and work-related uses. Amphetamine is produced in huge quantities in underground laboratories around the world.

The most common amphetamine derivatives currently known from the illicit drug market can be classified in the following three categories:

- **Non-ring substituted amphetamine derivatives:** Amphetamine, Methamphetamine, Ethylamphetamine, Dimethyl-amphetamine, PPMA, N-Hydroxyamphetamine, N-Hydroxy-methamphetamine, Phenethylamine (PEA), (+) Cathine, (-) Cathinone, Methcathinone, Amfepramone, and Amphetaminil;

- **Methylenedioxy-amphetamines:** MDA, MDMA, MDE, MDDMA, N-Hydroxy-MDA, N-Hydroxy-MDMA, MBDB, BDB, MMDA, FLEA, 6(2)-Cl-MDMA;
- **Ring and side-chain substituted amphetamines:** 2 C-B, 2 C-T, 2 C-T2, 2 C-T7, 2 C-C, 2 C-I, TMA-2, DOM, DOB, DOC, DOI, DOET, Diethoxybromoamphetamine (all 2,4,5-ring substituted orientation) and PMA (4-MA), DMA (2,5-DMA), TMA, PMMA, 4-MTA, AL and MAL (all other ring substituted orientation).

Common and brand names: Speed, Black birds, Black beauties, Candy, Christmas tree, Snow, Wake ups, Dex, Adderall, Dexamphetamine.

Chemistry

(±)-alpha-Methylbenzeneethanamine.

History

Amphetamine was first synthesized by the German chemist L. Edeleano in 1887 (originally named phenyl-isopropyl-amine).

In the 1930's amphetamines were first marketed as "Benzedrine" in an over-the-counter inhaler to treat congestion and in the late 30's, amphetamine was prescribed for the treatment of narcolepsy and ADHD (Attention Deficit Hyperactivity Disorder). Amphetamine use grew rapidly when amphetamines were distributed to soldiers during World War II. Now, in most countries prescriptions became required for possession.

Effects

- Positive
  - Increased alertness, motivation and talkativeness
  - Positive mood shift, sense of well-being.
- Negative
  - Increased aggressiveness
  - Paranoia
  - Dry mouth
  - Headache
  - Tachycardia, increased breathing rate and blood pressure
  - Rise in body temperature
  - Fever and sweating
  - Diarrhea or constipation
  - Blurred vision
  - Impaired speech and dizziness
  - Insomnia
  - Numbness
  - Irregular heartbeat (palpitations, arrhythmia)
  - Impotence/inability to achieve

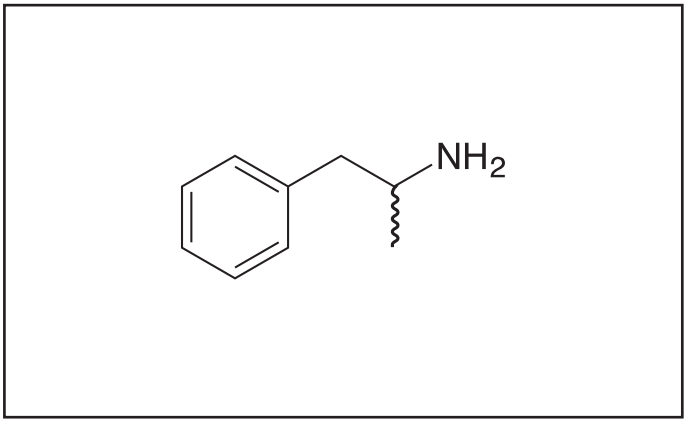

Figure 1 Amphetamine

erection in men (high dose or chronic use)
- Convulsions (high dose)
- Dry, itchy skin (chronic use)
- Acne, sores (chronic use)
- Pallor (high dose or chronic use)
- Psychotic episodes (rare except in overdoses or after chronic use).

• Neutral
- Reduced appetite (anorexia)
- Dilated pupils
- Flushing
- Loss of coordination
- Restlessness.

Problems

Manifestations of acute overdosage with amphetamines include restlessness, tremor, hyperreflexia, rapid respiration, confusion, assaultiveness, hallucinations, panic states, hyperpyrexia, and rhabdomyolysis. Fatigue and depression usually follow the central stimulation. Cardiovascular symptoms include arrhythmias, hypertension or hypotension, and circulatory collapse. Gastrointestinal symptoms include nausea, vomiting, diarrhea, and abdominal cramps. Fatal poisoning is usually preceded by convulsions and coma.

Psychosis

Users of large amounts of amphetamines over a long period of time can develop an amphetamine psychosis, which is a mental disorder similar to paranoid schizophrenia. The psychosis is manifested by hallucinations, delusions, and paranoia. Bizarre, sometime violent behavior is exhibited by those with amphetamine psychosis. Symptoms often disappear within a few weeks after discontinuing the use of the drug.

Overdose

Individual patient's response to amphetamines varies widely. While toxic symptoms occasionally occur as an idiosyncrasy at dosages as low as 2 mg, they are rare with doses of less than 15 mg; 30 mg can produce severe reactions, yet doses of 400 to 500 mg are not necessarily fatal. In rats, the oral LD 50 of dextroamphetamine sulfate is 96.8 mg/kg.

Neurotoxicity

Neurotoxicity with D/L amphetamine (most of which is prescribed as medications) is not well documented, but at very high doses and frequencies, neurotoxicity does occur in mice and rats.

Therapy

Medical treatments include the use of antidepressant agents such as imipramine, desipramine, amitriptyline, dosepin, trazodone or fluoxetine (Prozac). These affect serotonin (the neurotransmitter in the brain that deals with both depression and drug craving). Sedatives such as Dalmane, chloral hydrate, Librium, phenobarbital or even Valium are used, very carefully, on a short-term basis to treat anxiety or sleep disturbance problems. Antipsychotic medications such as Haldol, Thorazine, and others are also used to buffer the effects of unbalanced dopamine. In addition to treating the physical

and psychological aspects of craving, treatment providers should stress on group counseling and peer pressure for compulsive amphetamine users, as these forms of therapy work well for this population.

Effects of use during pregnancy

It is possible for babies of mothers who use amphetamines to be born with:

- cardiac defects
- cleft palate
- birth defects
- addiction and withdrawal.

3. Methamphetamine

Description

Methamphetamine is an addictive stimulant drug that strongly activates certain systems in the brain and is available in both prescription and street forms. Methamphetamine is chemically related to amphetamine, but the central nervous system effects of methamphetamine are greater. Both drugs have some limited therapeutic uses, primarily in the treatment of obesity.

The drug is relatively easy to synthesize, which has contributed to its widespread use. On the street, it is generally found as an odorless, white or off-white, bitter-tasting powder, though it is also found in pills, capsules and larger crystals. It is frequently snorted, but is also used orally, smoked, and injected.

Common and brand names: Meth, Speed, Crystal, Glass, Crank, Tweak, Yaba, Desoxyn.

Chemistry

Powder methamphetamine is the hydrochloride salt form, which is strongly hygroscopic (absorbs water from the air quickly).

The HCl salt is smokable as is Crystal meth. "Crystal Meth" or "Ice" refers to methamphetamine grown into crystals. Although many people believe that Crystal Meth is the freebase form of methamphetamine HCl, this is not true. Methamphetamine is smokable in its normal HCL form, but taking the time to grow it into crystals makes it easier to smoke. Meth in visible crystals (rather than powder) is likely to be more pure as it is difficult to grow crystals from impure material. Methamphetamine freebase is oil and is uncommon on the street.

History

First synthesized in 1887, methamphetamine is made from the

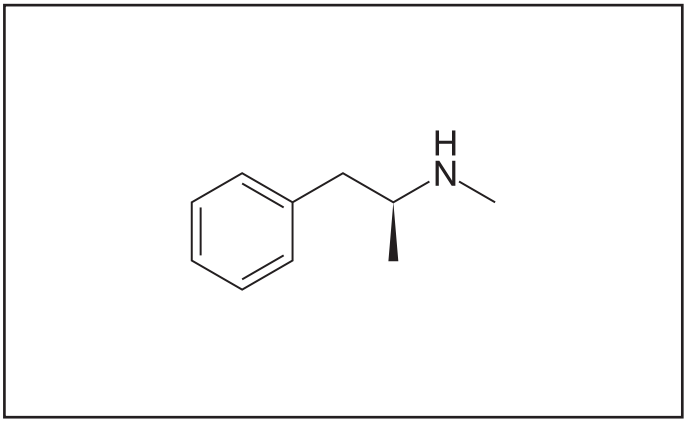

Figure 2 Methamphetamine

drug ephedrine (an organic substance used as a medicine in China for hundreds of years). In the 1930s it was sold in USA as a nasal spray for treatment of inflammation of nasal passages (ephedrine is still sold for this purpose) and as treatment for narcolepsy (sudden sleep disorder). During World War II, it was used by both sides to improve soldiers' performance. This became a major problem in Japan after World War II as they experienced the first known epidemic of methamphetamine abuse. In 1970, the Controlled Substances Act (USA) regulated the production of methamphetamine. Today, much of the methamphetamine available on the street is illicit and produced in clandestine laboratories in the United States.

Effects

- Positive
  - Increased energy and alertness
  - Decreased need for sleep
  - Euphoria
  - Increased sexual drive.
- Negative
  - Moodiness and irritability
  - Anxiousness and nervousness
  - Aggressiveness
  - Panic, suspiciousness and paranoia
  - Involuntary body movements
  - False sense of confidence and power
  - Aggressive and violent behavior
  - Severe depression, suicidal tendencies.
- Neutral
  - Excessive talking
  - Weight loss
  - Sweating
  - Visual and auditory hallucinations (hearing voices).
- Effects of habitual use
  - Fatal kidney and lung disorders
  - Possible brain damage
  - Permanent psychological problems
  - Lowered resistance to illnesses
  - Liver damage
  - Stroke.

Problems

Methamphetamine use generally increases the heart rate, blood pressure, body temperature, and the rate of breathing of the user. Chronic use can lead to what is called "Amphetamine Psychosis", resulting in paranoia, auditory and visual hallucinations, self-absorption, irritability, aggressive and erratic behavior, and picking at the skin. This can be magnified by lack of sleep, which often accompanies heavy use of methamphetamine.

Methamphetamine is an anorexant. This is considered a benefit for many light users, but in regular or heavy users can lead to malnutrition. Methamphetamine is also believed to be neurotoxic.

Addiction

Methamphetamine causes significant tolerance, as well as psychological dependence. This combination can be particularly bad because the user is likely to have strong cravings for more methamphetamine, while at the same time being unable to reach a satisfactory high. Withdrawal from high doses can produce severe depression (Table 1, Table 2, Table 3 and Table 4).

Overdose Effects:
Vomiting, headache, dizziness, cold sweats, shivering, etc. may result from too high dose of methamphetamine.

Neurotoxicity
Methamphetamine is toxic to dopaminergic and serotonergic neurons in rodents; however, little data are available on the toxic effects of methamphetamine on human brain.

Table 1 Oral Methamphetamine Dosages

Threshold	5 mg
Light Stimulation	5-15 mg
Common	10-30 mg
Strong (some rushing)	20-50 mg
Onset : 20 - 70 minutes (depending on form and stomach contents) Duration : 3 - 5 hours Coming Down : 2 - 6 hours Normal After Effects : up to 24 hours	

Table 2 Insufflated (Snorted) Methamphetamine Dosages

Threshold	5 mg
Light Stimulation	5-15 mg
Common	10-40 mg
Strong (some rushing)	30-60 mg
Very Strong	50 + mg
Note: doses for street meth or frequent use may be higher	
Onset : 5 - 10 minutes Duration : 2 - 4 hours Coming Down : 2 - 6 hours Normal After Effects : up to 24 hours	

Therapy
Analogously to Amphetamine therapy. (See above)

Effects of use during pregnancy
It is possible for babies of mothers who use amphetamines to be born with:
- cardiac defects
- cleft palate

Table 3 Smoked Methamphetamine Dosages

Threshold	5 - 10 mg
Light Stimulation	10-20 mg
Common	10-40 mg
Strong (some rushing)	30-60 mg
Very Strong (rushing)	50 + mg
Note: doses for street meth or frequent use may be higher	
Onset : 0 - 2 minutes Duration : 1 - 3 hours Coming Down : 2 - 4 hours Normal After Effects : up to 24 hours	

Table 4 Injected (IV) Methamphetamine Dosages

Threshold	5 mg
Light Stimulation	5-10 mg
Common	10-40 mg
Strong (some rushing)	30-60 mg
Very Strong (strong rushing, intense euphoria)	50- 100 mg
Note: doses for street meth or frequent use may be higher	
Onset : 0 - 2 minutes Duration : 1 - 3 hours Coming Down : 2 - 4 hours Normal After Effects : up to 24 hours	

- birth defects
- addiction and withdrawal.

4. Ecstasy (MDMA)

Description

MDMA is one of the most popular recreational psychoactives, most commonly sold in the form of "ecstasy" tablets. It is known for its empathogenic, euphoric, and stimulant effects, and has also been used in psychotherapy.

MDMA or "ecstasy" is a "psychedelic amphetamine" that has gained popularity over the past 20 years because of its ability to produce strong feelings of comfort, empathy, and connection to others. Usually, it comes in tablet form, but it is also sold in capsules or as powder. It is usually used orally and rarely snorted. MDMA use is closely tied to the underground rave (and dance club) scene throughout the world, but has also been widely used by therapists as an adjunct to psychotherapy. Because of the fact that MDMA is so popular and goes well with dance parties, its demand usually exceeds its supply especially at any given location on any given night (Fig. 3). This creates an opening for unscrupulous individuals to sell virtually anything as "ecstasy". While "ecstasy" is the popular name for MDMA, the functional definition of ecstasy is any pill represented as MDMA on the street. Ecstasy pills are notoriously unreliable in content, more than most other street drugs.

Usually they contain either caffeine, ephedrine, amphetamines, MDA, MDE, DXM or (in rare cases) DOB and do not necessarily contain MDMA or any psychoactive substance. This problem has led to the development of simple MDMA testing kits that may help users find out what is the content of a pill.

Common and brand names: Ecstasy, E, X, XTC, Rolls, Beans, Adam.

Chemistry

3,4-methylenedioxy-N-methamphetamine (MDMA) is a synthetic chemical that can be derived from an essential oil of the sassafras tree.

History

The methylenedioxy-derivatives of amphetamine and methamphetamine represent the largest group of designer drugs. The most frequently used compounds are 3,4-methylenedioxy-methamphetamine (MDMA-ecstasy) and 3,4-methylenedioxy-amphetamine (MDA), first synthesized in 1910 (MDA) and 1914 (MDMA), respectively, to be used as an appetite suppressant. At the end of the 1960s, non-medical (recreational) use appeared in the USA, and in the middle of the 1980s in Europe. A number of related compounds have been synthesized, including derivatives with one or more substituents (methoxy, methyl, halogen or sulphur), attached at different positions to the phenylring of amphetamine or methamphetamine in order to bypass the legal regulations and to produce more potent substances. A report from 1998 shows that 0.5-3% of the adult European population, mainly young people, has used ecstasy.

Effects

- Positive
  - Extreme mood lift
  - Increased willingness to communicate
  - Increase in energy (stimulation)
  - Ego softening
  - Feelings of comfort, belonging, and closeness to others
  - Feelings of love and empathy
  - Forgiveness
  - Increased awareness and appreciation of music
  - Neurotically based fear dissolution
  - Sensations bright and intense.
- Negative
  - Inappropriate and/or unintended emotional bonding
  - Tendency to say things you might feel uncomfortable about later
  - Difficulty concentrating and problems with activities requiring linear focus
  - Short-term memory scramble or loss and confusion
  - Muscle tension
  - Erectile dysfunction and difficulty reaching orgasm
  - Increase in body temperature, hyperthermia, dehydration

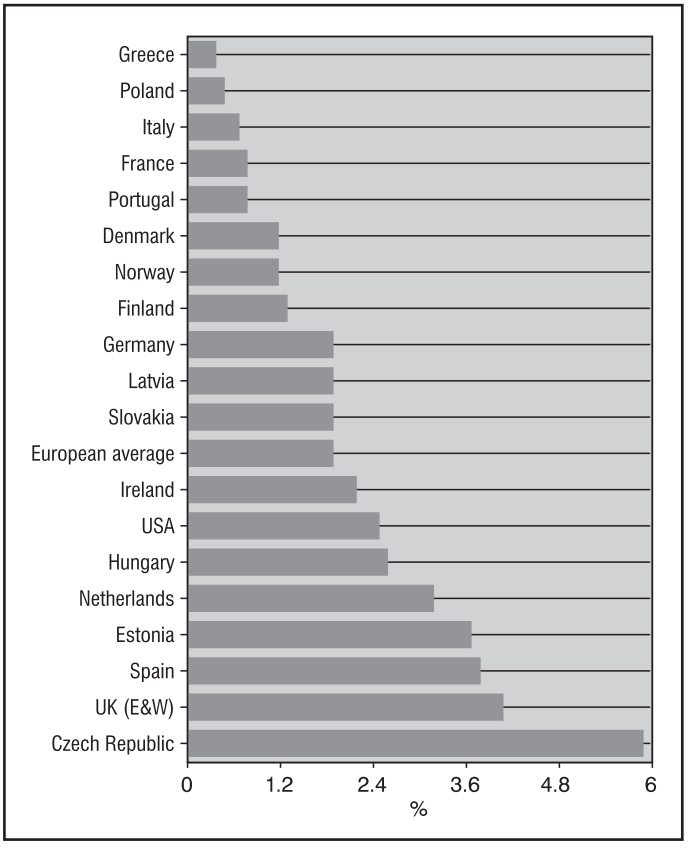

Figure 3 Recent use of ecstasy among young adults (15-34 years old) in Europe and USA

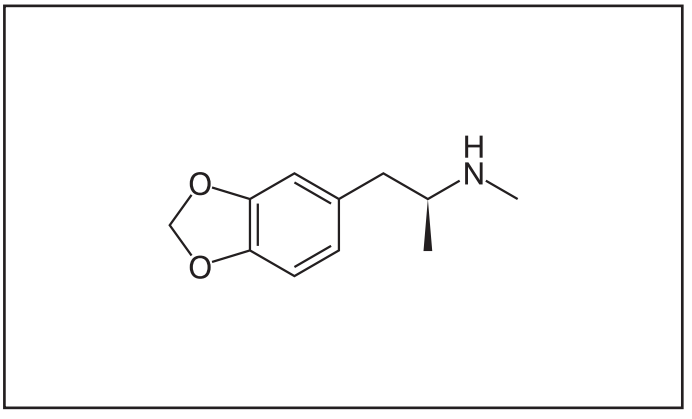

Figure 4 Ecstasy (MDMA)

- Hyponatremia
- Nausea and vomiting
- Headaches, dizziness, loss of balance, and vertigo
- Sadness on coming down, sense of loss or immediate nostalgia
- Post-trip Crash - unpleasantly harsh comedown from the peak effect
- Hangover the next day, lasting days to weeks
- Mild depression and fatigue for up to a week
- Severe depression and/or fatigue (uncommon)
- Possible strong urge to repeat the experience, though not physically addictive
- Possible psychological crisis requiring hospitalization
- Possible liver toxicity (rare)
- Possible neurotoxicity (controversial)
- Small risk of death approximately 2 users out of 100,000 have extreme negative reactions resulting in death.

• Neutral
- Appetite loss
- Visual distortion
- Rapid, involuntary eye jiggling (nystagmus)
- Mild visual hallucinations (uncommon)
- Moderately increased heart rate and blood pressure (increases with dose)
- Restlessness, nervousness, shivering
- Change in body temperature regulation
- Upwelling of unexpected emotion, emotional lability
- Strong desire to do or want more when coming down.

Problems

One of the primary problems with MDMA is the low quality of street ecstasy. Street ecstasy, especially pressed pills, is often mixed with a wide range of adulterants that can cause a variety of negative side effects both unpleasant and dangerous. MDMA is a known neurotoxin, but how damaging it is to use is very controversial and quite complex.

Another possible difficult situation arising from MDMA use is the release of emotions, which the user may be unprepared to deal with. This could include confronting past episode of abuse, re-experiencing painful memories, encountering emotional crises, or unearthing previously unrecognized feelings either alone or while in conversation with friends and loved ones. In these situations, therapists suggest the user should try to remain calm and avoid fighting the feelings.

Addiction

MDMA has the potential to be psychologically addictive. Individuals who use it regularly may find they have an increased desire to continue using it. There is a short period of tolerance after MDMA use. Using MDMA two days in a row is likely to lead to a greatly diminished experience the second day, though spaced 7 or more days apart, this effect is lessened. Some users report noticing reduced effects for up to 2 or 3 weeks after initial use.

"Loss of Magic"

Many users report that their enjoyment of MDMA seems to decrease as total lifetime usage increases. Some users report that Ecstasy "loses its magic" with as few as 10 experiences, while others have reported hundreds of uses before the empathic qualities fades or disappears.

Increased Negative Effects

Most users stop taking Ecstasy because of either an increased awareness or an actual increase in negative side effects during use, a reduced quality of the high, and increases in the post-MDMA depression and day after hangover.

Increasing Dosage

Most users report that when using more than once a month, or merely over increased total lifetime use, they need to increase the dosage in order to get positive effects with MDMA. Increased dosage is associated with increased side effects, hangover, and week-after depression (Table 5).

Neurotoxicity

There is an ongoing debate about the possible neurotoxicity of MDMA. Most experts now agree that MDMA is neurotoxic, but there is little agreement on what the consequences of this toxicity are. There is some evidence of changes to the brain in those who use MDMA heavily and/or frequently and a few studies have shown reductions in memory and increases in depression and anxiety. However, these studies have not been completely verified and debate continues.

Table 5 Oral MDMA Dosages

Threshold	30 mg
Common for small or sensitive people	50 - 75 mg
Common for most people	75 - 125 mg
Common for large or unsensitive people	125 - 175 mg
Required by few (side effects increase)	200 + mg
Onset : 20 - 70 minutes (depending on form and stomach contents) Duration : 3 - 5 hours Normal After Effects : up to 24 hours	

Therapy

There are no specific treatments for MDMA abuse. The most effective treatments for drug abuse and addiction are cognitive behavioral interventions that are designed to help modify the patient's thinking, expectancies, and behaviors, and to increase skills in coping with life's stressors. Drug abuse recovery support groups may be effective in combination with behavioral interventions to support long-term, drug-free recovery. There are currently no pharmacological treatments for dependence on MDMA.

5. Paramethoxyamphetamine (PMA)

Description

PMA is a strong psychedelic, which may cause dangerous overheating of the body. PMA has been sold in ecstasy tablets, and has led to dangerous and fatal hyperthermia in some users. It is an amphetamine derivative similar to MDMA but more lethal even in smaller doses. More than 50 mg may be fatal. PMA producers sometimes use the same imprinted logos on PMA that are used on MDMA tablets in order to market the product as MDMA to users, resulting in fatalities from overdose or mixing of the drug with MDMA.

Common and brand names: 4-MA, Death, Mitsubishi Double Stack, often sold as Ecstasy.

Chemistry

It is synthesized starting from anethole (the flavor compound of anise and fennel).

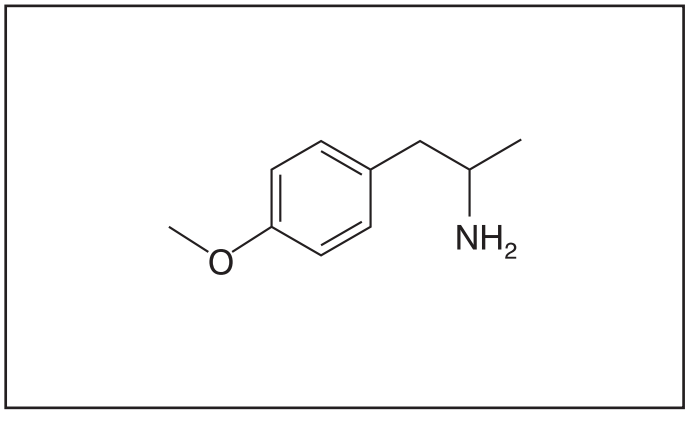

Figure 5 P-methoxyamphetamine

History

Paramethoxyamphetamine (PMA) was first produced by a Canadian laboratory in 1973. In that year alone, the drug was associated with nearly a dozen deaths in both Canada and the United States. Then the drug disappeared until the mid 90s. At that time, six people in Australia died after taking what they thought was ecstasy. A later investigation found that the victims had various amounts of PMA in their systems, sometimes combined with ecstasy, amphetamines, or prescription drugs. In the early 2000s PMA made its way back into Canada and the United States. It also showed up in Europe, mainly in Austria, Denmark, and Germany.

Effects

- Positive
  - Increase in energy (stimulation)
  - Minor visuals.
- Negative
  - Muscle spasms
  - Increased blood temperature
  - Increased blood pressure
  - Increased body temperature (fever)
  - Increased pulse rate
  - Labored breathing
  - Nausea and vomiting
  - Convulsions, coma and death.
- Neutral
  - General change in consciousness (as with most psychoactives)
  - Pupil dilation
  - Erratic eye movements.

6. Gamma Hydroxybutyrate (GHB)

Description

GHB is a naturally occurring component of human cells and of wine. It is used most commonly in the form of a chemical salt (Na-GHB or K-GHB), which is taken as a depressant with effects quite similar to those of alcohol. These salts are powders but are most often mixed with water for recreational use. GHB is more commonly used as a recreational intoxicant like alcohol, as a sleep-aid, or as a supplement by body-builders. One of the major concerns with GHB is that the recreational dosage range is narrow and even small overdoses can cause temporary unrousable unconsciousness (a type of coma) and large overdoses can be life-threatening. There are two other chemicals which are used as GHB equivalents: 1,4-butanediol and gamma butyrlactone.

Common and brand names: G; Sodium Oxybate.

History

GHB was developed in the early 60s as a human anesthetic, but was discontinued due to unwanted side effects. Its use as a sleep aid and body building supplement in the 80s and as a recreational psychoactive in the 90s led to it being scheduled in USA in March 2000.

Effects

As with alcohol and many other substances, the onset of GHB will be affected by how much and how recently one has eaten. Generally this will be between 10-20 minutes.

The primary effects of GHB last approximately 1 ½ hours. For many people there is an additional period of time (1-2 hours) of more subtle effects. Some recreational users consume GHB in a manner similar to alcohol, sipping it slowly over an evening rather than drinking a full dose all at once. In this case the duration will be longer as the period of ingestion is stretched out over time.

Chemistry

GHB is most commonly produced by combining gamma butyrolactone and a strong base such as sodium hydroxide (lye). These two substances react chemically and form the unique chemical GHB.

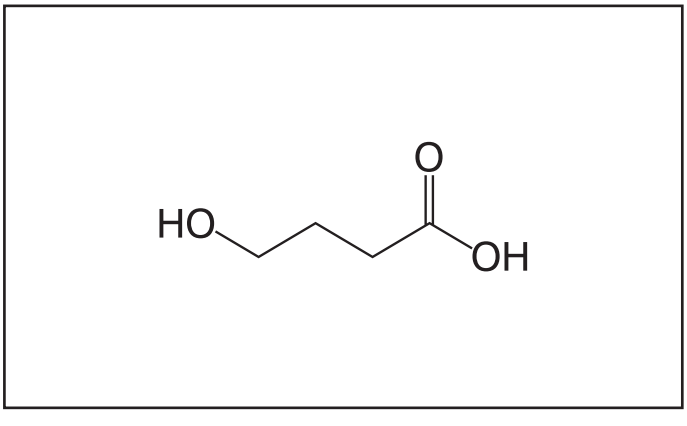

Figure 6 Gamma-Hydroxybutyric acid

The effects of GHB at recreational doses are physically quite similar to those of alcohol. At lower doses the effects include relaxation, reduction of social inhibitions, decreased motor skills, mood lift and other effects similar to mild alcohol intoxication. At higher recreational doses effects can include dizziness, difficulty focusing the eyes, positive mood changes, increased appreciation of music, dancing, and talking, slurring of speech, nausea, and grogginess. The line between high recreational dose and overdose can be a narrow one. At the overdose level, individuals may experience unconsciousness, extreme dizziness, disorientation, and vomiting. During higher overdoses (poisonings), users may experience unconsciousness, convulsions, vomiting, and potentially depressed breathing.

Problems

Unfortunately, GHB has a few prominent problems which, in combination, can be quite dangerous. The difference between a recreational dose and a mild overdose (temporarily unrousable sleep) can be as little as 1-2 g (the equivalent of a single dosage unit). Combining GHB with alcohol can lead to overdoses at even lower levels. In addition, because GHB generally comes in liquid form and because the concentration of this liquid is difficult to determine, it is relatively common for people to accidentally take a larger dose of GHB than they think they are taking.

At higher overdose levels, GHB can produce both unconsciousness and vomiting. This can be an extremely dangerous combination. Vomiting while laying unconscious on one's back can lead to aspiration (inhalation) of the vomit which can cause suffocation and damage to the lungs.

The DEA reports over 60 GHB related deaths in USA over the past 5 years, about 2/3 of these are poly-drug mortalities while 1/3 are GHB only.

Another problem associated with GHB is the issue of rape and assault that goes along with chemicals, which can be added to drinks and given to unsuspecting victims.

Addiction

The addiction potential of GHB is not well known, but it appears that GHB can be both physically addicting and mentally habituating for a small percentage of users. There is data that withdrawal symptoms last for several days following repeated daily use. These symptoms include a strong desire to repeat the experience, difficulty sleeping, vertigo, and worrisome chest pains.

7. Gamma Butyrolactone (GBL)

Often found in industrial cleaners, GBL is the precursor chemical for the manufacture of GHB. In addition, it has been marketed as a nutritional supplement in health food stores. GBL is synthesized by the body to produce GHB. Ingestion of GBL often causes a severe physical reaction, usually through the violent regurgitation of the fluid. GBL increase the effects of alcohol, and

can cause respiratory distress, seizures, coma, and death.

8. Ketamine

Description

Ketamine is a dissociative anaesthetic, developed in the mid '60s, used basically for veterinary anaesthesiology. Although ketamine is not used medically on humans much because it induces psychedelic episodes in patients, it is still used for some limited human applications because it does not depress breathing or circulation. Ketamine is used recreationally primarily as a snorted white powder and for therapeutic and psychedelic use it is often injected intra-muscularly (IM).

Active Ingredients: ketamine hydrochloride.

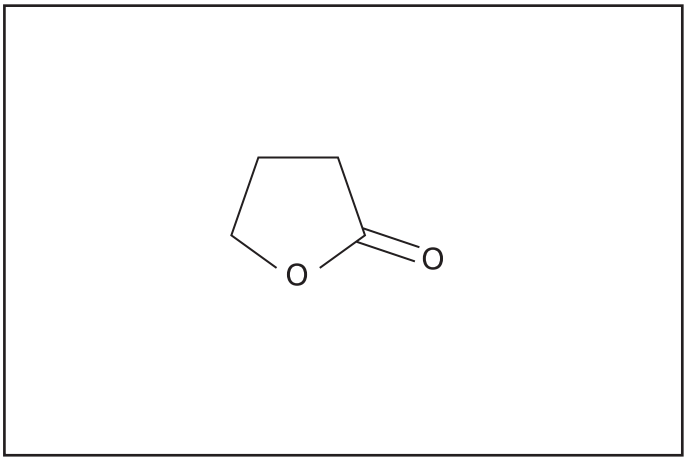

Figure 7 Gamma-Butyrolactone

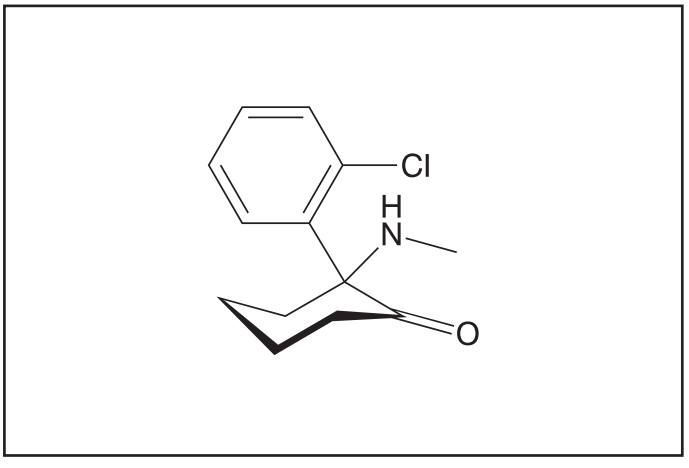

Figure 8 Ketamine

Common and brand names: Ketamine, K, Special K, Ketaset, Ketalar, Vitamin K, Lady K.

History

Ketamine was first synthesized in 1962 by Calvin Stevens at Parke Davis Labs while searching for PCP anaesthetic replacements. He named it "CI581". In 1965 Ketamine was discovered to be a useful anaesthetic and was first used recreationally by Edward Domino, who coined the term "dissociative anaesthetic". Ketamine was used for anaesthesia because it suppresses breathing much less than most other available anaesthetics, but in the 70s patients began to report unwanted visions under its influence. In 1978, John Lilly published his book "The Scientist" and ketamine popularity grew through the 1980s until in 1995 the DEA added ketamine to its "emerging drugs list". In 1998 and 1999, ketamine was lumped by media and legislators with GHB as a "date rape drug" and a "club drug" and

was emergency scheduled by the DEA (USA) in 1999.

Effects

Intra-muscular injection (I.M.) ketamine generally takes 1-5 minutes to take effect. Snorted ketamine takes a little longer than 5-15 minutes. Depending on how much and how recently one has eaten, oral ketamine can take between 5 and 30 minutes to take effect. The primary effects of ketamine last approximately 30-45 minutes if injected, 45-60 minutes when snorted, and 1-2 hours if used orally.

Its effects range (at lower doses) from mild inebriation, dreamy thinking, stumbling, clumsy, or "robotic" movement, delayed or reduced sensations, vertigo, sometimes erotic feelings, increased sociability, and an interesting sense of seeing the world differently to (at higher doses) extreme difficulty moving, nausea, complete dissociation, entering complete other realities, classic Near Death Experiences (NDEs), compelling visions, black outs, etc. Ketamine is also known for being more psychologically addictive/compelling than most psychedelics.

Problems

Negative physical effects can include dry mouth, respiratory problems and nervousness/racing heart. Many people also experience nausea and/or vomiting on ketamine, which can obviously be a problem when taking an anaesthetics or sedatives. Supervision of higher dose ketamine experiences by a sober sitter can help ensure that an unconscious participant does not have problems with vomiting and/or breathing. Two psychological difficulties which seem to come up for those who use ketamine regularly are paranoia and egocentrism. There are many reports of regular users starting to see patterns and coincidences in the world around them which seem to indicate that they are somehow more important or integral to the world than others. This same sense of the world focusing on the user can also feed into a sense of paranoia.

Addiction potential

Ketamine has the potential to be both physically and psychologically addicting. Individuals who use it regularly may find it difficult to stop.

9. Rohypnol (Flunitrazepam)

Rohypnol, as a sleep aid is produced in Europe and is available by prescription in many countries. Capable of producing extreme lethargy and significantly reducing recall capability of the brain; it has been often mentioned in relation to numerous date rapes. Abuse of rohypnol is generally episodic use among teenagers and young adults as an "alcohol extender" and disinhibitory agent, most often in combination with beer.

10. Lysergic Acid Diethylamide (LSD)

Description

LSD is the best known and most researched psychedelic. It is the

standard against which all other psychedelics are compared. It is active at extremely low doses and is most commonly available on blotter or in liquid form.

LSD is one of the most commonly used "psychedelic" or "hallucinogenic" substance. It comes in a variety of forms, but is virtually always taken orally. Today, LSD is most commonly found in the form of small squares of paper called blotter (full sheets of paper are decorated with artwork or designs, perforated, then soaked in liquid LSD solution and dried). Other forms include pills, gelatine sheets or shapes (pyramids, cubes, etc), liquid, liquid sugar cubes, and powder. Blotter is most common because it is easily produced, easily concealable and the format allows for few adulterant chemicals.

Common and brand names: LSD (Lyserg-Saeure-Diaethylamid in German), acid, cid, L, blotter, tabs, LAD, doses, trips, microdots (small pills).

Chemistry

d-lysergic acid diethylamide (LSD) is a synthetic chemical derived from ergot alkaloids

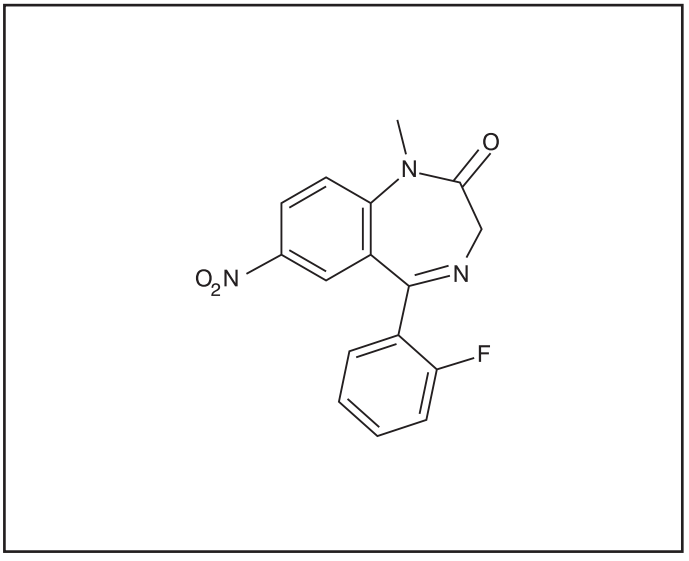

Figure 9 Flunitrazepam

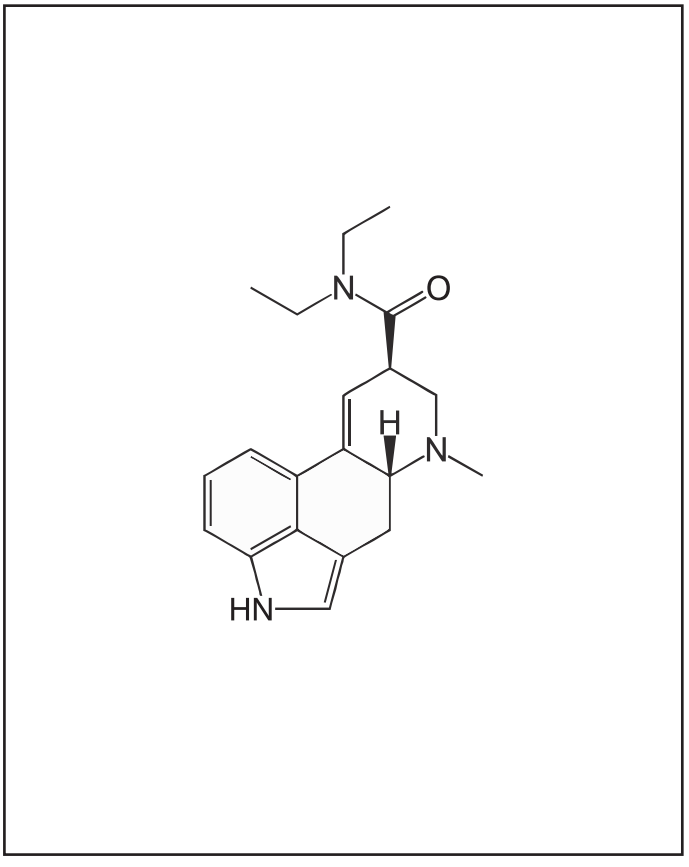

Figure 10 LSD

which are produced by the ergot fungus which grows on rye.

History

LSD was first synthesized in 1938 and discovered to be psychoactive in 1943. It became popular in the '60s and was made illegal in 1967. It has been widely available on the black market since that time.

Effects

Depending on how much and how recently one has eaten, LSD generally takes 20-60 minutes (though sometimes as long as 2 h) to take effect. The primary effects of LSD last for 6-8 hours. For many people there is an additional period of time (2-6 h) where it is difficult to go to sleep and there is definitely a noticeable difference from everyday reality, but which is not strong enough to be considered "tripping".

In the beginning stages of onset, LSD is likely to cause a sort of indefinably feeling similar to anticipation or anxiety. There is often a slight feeling of energy in the body, an extra twinkle to lights, or the feeling that things are somehow different than usual. As the effects become stronger, a wide variety of perceptual changes may occur; non-specific mental and physical stimulation, pupil dilation, closed and open eye patterning and visuals, changed thought patterns, feelings of insight, confusion, or paranoia, and quickly changing emotions (happiness, fear, giddiness, anxiety, anger, joy, irritation).

Problems

LSD can precipitate strong, temporary changes in an individual's experience of life and reality. Even in low doses, it is a powerful psychoactive that can be significantly affected by experiences, set and setting. Recent experiences, especially strong ones, can have a substantial effect on a trip. Physically or psychologically unsettling events in the days before an LSD trip can blossom into more serious distress and trauma while tripping. It is important to be prepared for the possibility of encountering difficult or frightening mental states.

Addiction

LSD is quite unlikely to lead to addiction in most people. There is no physical addiction or withdrawal after heavy use, although people can and do become mentally habituated to LSD as with any substance. There is a short period of tolerance after LSD use. Using LSD two days in a row is likely to lead to a diminished experience the second day, though spaced 3 or more days apart, this effect is nearly non-existent.

11. Phencyclidine (PCP)

Description

Phencyclidine is a synthetic chemical in the dissociative anesthetic class. It is perhaps best known by the media hype it received in the late 1970's portraying it as a extremely dangerous chemical causing madness, psychotic reactions, and super-human strength. It is found in a variety of forms including crystals/ powder, tablets, and liquid. Recently it

seems to be available on the underground market most commonly as cannabis joints, regular cigarettes or cannabis leaf dipped in liquid PCP and usually marketed as something else, seldom as "PCP".

Common and brand names: PCP, Phencyclidine, Crystal, Angel Dust, Rocket Fuel, Wet, Water, Fry, Amp, Embalming Fluid.

Chemistry

Phencyclidine (PCP) is a synthetic chemical.

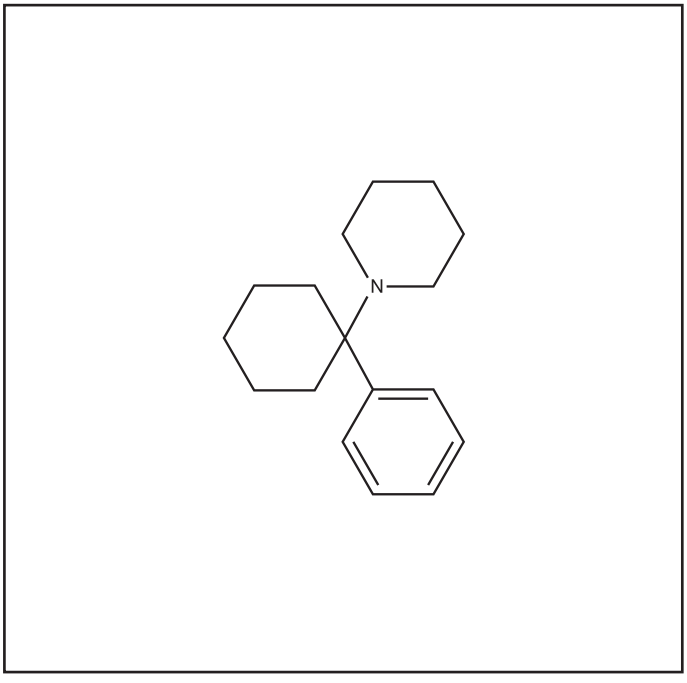

Figure 11 Phencyclidine

PCP is used in very small quantities with 5-10 mg considered an average dose.

History

PCP was first synthesized in 1926 and began being investigated as a human anesthetic in the mid 1950's by Parke Davis. It was marketed as a human anesthetic for two years under the name "Sernyl" before being withdrawn from the market due to hallucinations experienced by patients under its influence.

References

1. Reitox national reports (2004)
2. USA: SAMHSA, Office of Applied Studies, National Survey on Drug use and Health, 2003 (www.samhsa.gov) and (http://oas.samhsa.gov/nhsda.htm#NHSDAinfo)
3. 2005 EMCDDA statistical bulletin. Based on Reitox national reports (2004)
4. http://en.wikipedia.org/wiki/

Module 3.5
Misuse and abuse of legal drugs

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Key messages

- A legal drug is not necessarily safe or non-addictive;
- Sometimes, those who are addicted to prescription medications go from doctor to doctor to obtain the drug of abuse. "Doctor shopping" can be particularly dangerous because it prevents any one doctor from knowing the patient's medical history or what medications have been taken;
- There are different types such as drugs that are both legal and freely available (such as alcohol and nicotine) are among the most often abused;
- Other drugs (such as sedatives and tranquilizers) are available by prescription and are considered safe for medical purposes, but they are highly addictive, even at prescribed dosages.

Contents

1. Alcohol

Alcohol is a drug. It depresses the central nervous system similar to the way general anesthetics do, but it has some major differences from anesthetics. Because alcohol is almost completely metabolized in the body, its effects cannot be controlled. The dose that would be effective as surgical anesthesia is not much lower than the dose that causes respiratory arrest and death.

How alcohol affects the body?

Alcohol is absorbed primarily through the small intestine and stomach. The rate of absorption depends on the type of alcoholic beverage consumed and the amount of food and water in the stomach. Alcohol requires no digestion and is absorbed unchanged into the bloodstream. Although it contains usable calories, alcohol itself cannot be stored or converted into fats or protein. In fact, it prevents other calories from being burned and may even reduce the body's metabolic rate.

Once alcohol is absorbed, it remains in the bloodstream until it is metabolized. Over 90% of that metabolism occurs in the liver. A very small percentage is normally excreted unchanged through the breath, skin and urine.

Intoxication and driving

We metabolize the equivalent of 1½ drink per hour. Even after one drink (30 g of hard liquor, 1 beer, 1 glass of wine), driving ability is impaired. Depending on the size and weight of the person, drinking more than that amount rapidly causes serious impairment of the ability to drive safely.

Driving while intoxicated is illegal in all legal jurisdictions. Each country has its own laws regarding the allowable Blood Alcohol Concentration (BAC). Many countries have settled on .08 as the legal BAC limit, while others use the less restrictive .10 limit. The reason that this level is widely accepted is that most people become impaired enough at this level to be dangerous while driving. As a rough guide, an average 75 kg male reaches a .08 BAC level after consuming four drinks in an hour, and about 60 kg female reaches it after consuming three drinks in an hour. This is a rough estimate and not to be used as an actual guideline. Individuals vary significantly.

2. Prescription narcotics

Narcotics are used to control chronic or severe pain. Like alcohol or sedatives, they depress the central nervous system and have mood-altering effects. Narcotics are highly addictive and must be used carefully in a well-controlled manner.

Abuse of prescription narcotics usually involves pills prescribed to treat pain. Because narcotics have cough suppressant effects, they are used in cough syrups, so this is another form that is abused. The risk of using narcotics is that people without a history of addiction can become addicted in several weeks. Sometimes, patients begin with the

prescribed dose and go on to use more than the prescribed dose. Some individuals who are addicted to prescription narcotics make frequent trips to many different doctors and hospitals to get a supply of the drugs. Others find that their doctor is not properly supervising and authorizes refills repeatedly, allowing them to slip into addiction.

Methods of use
Prescription narcotics are generally taken orally.

Types
Opiate narcotics are among the most commonly abused narcotics. Codeine, methadone, and morphine (from which heroin is derived) are examples. All pain-relieving narcotics, including Percodan, Vicodin, and Percoset are very addictive.

Effects on the central nervous system
Narcotics induce an "opioid analgesia" by altering the perception of pain at the spinal cord and brain. They also affect emotional responses to pain. Opioids have stimulating effects as well because they block inhibitory neurotransmitters. Repeated use of these drugs can cause long-term changes in the functions of the nervous system.

Intoxication
Addiction is a major risk with prolonged use (over 2-3 weeks) of narcotics. Even moderate doses of some narcotics can result in a fatal overdose. When increasing doses of narcotics, the person may first feel restless and nauseous and then progress to loss of consciousness and abnormal breathing. Other risks include withdrawal symptoms that may last for months.

Life risks
Many prescription narcotic drugs are particularly addictive and cause extremely unpleasant withdrawal syndromes. Use by pregnant woman can adversely affect the fetus. Methadone infant withdrawal is especially severe.

Withdrawal
Withdrawal from prescription narcotics can be painful and unpleasant, especially when the drugs have been used at abusive levels. Medical detoxification is recommended.

Symptoms can include the following:
- Running nose
- Sweating
- Muscle twitching
- Muscle pain
- Headache
- Irregular heart beats
- Nausea and vomiting
- High blood pressure
- Fever
- Insomnia
- Dehydration.

3. Tranquilizers / sedatives

Tranquilizers and sedatives are prescribed to treat anxiety disorders and sleep disturbances. These drugs have a depressant effect on the central nervous system and work similar to alcohol.

Types

Tranquilizers can be divided into two categories. The major tranquilizers are also known as anti-psychotics and are used to control psychotic mental illness. Examples include Haldol, Thorazine, Navane, Prolixin, Mellaril, and Trilafon. The minor tranquilizers decrease anxiety, encourage sleep, and also act as an anesthetic. This class of tranquilizers includes the popular benzodiazepines. Minor tranquilizers include Halcion, Xanax, Ativan, Valium, BuSpar, and the antidepressant Anafranil.

Sedatives are specifically designed to induce drowsiness or sleepiness. They include barbiturates such as Nembutal, Seconal, Amytal, and Phenobarbital (Luminal).

Methods of use

These drugs may be swallowed or injected.

Effects on the central nervous system

Tranquilizers and sedatives depress functioning of the central nervous system, but the specific way depends on the drug. Many of them, such as the benzodiazapines, work through "release from inhibition" on those areas of the brain that limit activity of the central nervous system. In other words, they indirectly facilitate the action of certain brain areas to promote calmness or sleepiness. Barbiturates seem to have direct depressant effects on brain areas that regulate wakefulness and alertness, and they also act directly on nerve cells in the spinal cord.

Intoxication

Sedative intoxication can resemble alcohol intoxication (including hallucinations, delusions, and memory disorders), and it also has some of the more severe effects like delirium and seizures.

Other symptoms include:

- Reduced mental alertness
- Reduced attention span
- "Floating" sensations
- Depressed heartbeat
- Depressed breathing
- Sleepiness and drowsiness
- Shakiness or unsteadiness
- Confusion and disorientation.

Life risks

Studies show that recovery from sedative-hypnotic addiction is particularly difficult, with up to a 50% relapse rate during the 5 years following inpatient detoxification and high associated suicide rates. Sedatives in particular are unsafe in overdose and have been associated with many deaths because they depress respiratory function.

These drugs of abuse are prescription drugs. Individuals frequently obtain them by going to more than one doctor with the same complaints. Even at prescribed doses, these drugs can cause dependence.

Withdrawal

Withdrawal syndromes depend on the specific drug, but may last for weeks.
Some common withdrawal symptoms include:

- Agitation
- Disturbed sleep

- Irritability
- Convulsions
- Nightmares.

4. Soma

Soma (Carisoprodol) is a prescription muscle relaxant for reducing certain types of pain and muscle tension. It is rarely prescribed for medicinal purposes, but it is frequently abused and is scheduled as a controlled substance in some states. Soma can be fatal in overdose.

Soma produces sedating effects through the central nervous system and is chemically similar to the sedative Miltown. It crosses placental barriers and can transfer from a pregnant woman to an unborn fetus. It also appears in the breast milk of mothers who use it.

Soma's potential for causing addiction is well known. People can become addicted to soma and similar drugs even when these drugs are the prescribed treatment. Others deliberately use soma to enhance the effects of alcohol or other drugs.

Methods of use

Soma is taken orally in pill or tablet form.

Effects on the central nervous system

Soma acts directly on the central nervous system rather than directly on skeletal muscles. The drug seems to interrupt neuronal communication with the spinal cord and certain areas of the brain, resulting in sedation and altered perception of pain. The main effects of this drug may result from its general sedating effect.

Intoxication

Side effects of using soma include:

- Agitation
- Depression
- Dizziness
- Sleepiness
- Facial flushing
- Fainting
- Headache
- Insomnia
- Poor coordination
- Nausea and vomiting
- Rapid heart rate
- Shaking and tremors
- Stomach problems.

Life risks

Soma can cause dizziness, drowsiness, and other symptoms of sedative intoxication, making driving under the influence of the drug dangerous. Persons taking soma for medical reasons should be aware of the addictive properties of this drug.

Withdrawal

Withdrawal symptoms include:

- Abdominal cramps
- Headache
- Insomnia
- Nausea
- Chills.

5. Cough preparations

Many cough preparations, especially cough suppressants, contain codeine or

dextromethorphan (DXM). Codeine and other opiates are very effective cough suppressants, but they are addictive. DXM, a powerful psychoactive drug, is particularly addictive. Cough syrup abusers can obtain the drug from their doctors by complaining about coughs and other cold symptoms. Ingredients in many cough preparations are considered to be dangerous in combination with other drugs, particularly antidepressants (including SSRI medications and MAO inhibitors), antihistamine allergy medications, and Yohimbine.

Addicts commonly point to three reasons for using cough syrup:

- It is legal (and therefore more acceptable);
- It is low-cost or free; and
- It is seen as being safer than other drugs of abuse.

Methods of use

Some addicts drink cough syrup undiluted or mixed with sodas. Others soak marijuana joints with the syrup. In some cities, an underground black market has developed for selling syrup. DXM can also be extracted from cough preparations and taken orally, injected, and occasionally freebased.

Types

Examples of cough preparations include Drixoral Cough Liquid Caps, Robitussin AC, Dectuss, Phenergan with Codeine, Phensedyl, and Pherazine with Codeine.

Effects on the central nervous system

DXM exhibits cough-suppressant functions by activating specific opioid receptors (sigma opioid receptors) in the central nervous system. In this sense, DXM functions like ketamine or PCP. The sigma opioid receptor has been implicated in many of the symptoms of schizophrenia. DXM also affects receptors in the part of the brain called the cerebellum, which plays a role in coordinating movement.

The involvement of cerebellum receptors may account for reports of peculiar reactions to movement among persons abusing cough syrup.

Intoxication

Cough syrup abusers use the drug to obtain a marijuana-like high with occasional auditory hallucinations and pleasurable reactions to movement.

Other less desirable effects depend on the dose taken:

- Depression
- Dilated pupils
- Dissociation
- Dizziness
- Fever
- Hallucinations
- High blood pressure
- Hot and cold flashes
- Impaired judgment
- Memory disturbances
- Nausea and other gastric disturbances

- Panic attacks
- Psychotic episodes
- Rash
- Sexual dysfunction
- Sweating
- Tachycardia.

Life risks

Aside from the risk of addiction, cough syrup use is associated with increased fatigue, poor coordination, constipation, urinary retention, and other problems. Overdose deaths have been reported. As mentioned above, DXM may be particularly dangerous in combination with other medications or substances, including:

- "Non-drowsy" antihistamines (allergy medications) such as Claritin, Seldane, or Hismina;
- MAO inhibitors (a certain class of anti-depressant);
- The herb Yohimbe / yohimbine;
- SSRI antidepressants, such as Desyrel or Serzone.

Any of these substances in the system at the same time as DXM can be fatal!

Withdrawal

Withdrawal from cough syrups can cause a range of unpleasant and dangerous symptoms, depending on the content dosage of the preparation. DXM withdrawal is characterized by depression and difficulties with thinking and memory.

Warning signs

A person who is addicted to cough preparations may:

- Buy cough preparations at different stores
- Frequently purchase over-the-counter cough preparations.

6. Prescription amphetamines

Doctors prescribe amphetamines for different medical purposes such as appetite control in weight loss programs, narcolepsy, and hyperactivity disorders. Amphetamines were once used in inhalers for allergies and asthma, but this practice was banned because of the toxic effects of amphetamines. Ritalin, Cylert, and Adderall are among the best-known forms of prescription amphetamines. These drugs are used to treat hyperactivity or attention deficit (known as ADHD or ADD) in children, adolescents, and adults. Amphetamines, which "speed up" normal people, have a calming effect on those with hyperactivity or attention-deficit disorders. On the street, amphetamines are also called speed, bennies, eye openers, lid poppers, pep pills, and uppers.

Types

The commonly used prescription amphetamines include Ritalin, Cylert, and Adderall.

Methods of use

Prescription amphetamines can be swallowed in pill or tablet form or injected.

Effects on the central nervous system

Ritalin and Cylert stimulate the central nervous system by blocking the reuptake

of the neurotransmitter dopamine in the synapse. This has the general effect of increasing the amount of dopamine available for action in the central nervous system, creating a generalized stimulating effect. The drug's direct impact on dopamine systems may also have an indirect effect on another neurotransmitter serotonin. The effects on serotonin may be calming.

Adderall stimulates the release of a third neurotransmitter norepinephrine, which has a stimulating effect on the central nervous system. It may also increase available levels of serotonin. At higher doses, Adderall stimulates the release of dopamine. The effect on the dopamine system may contribute to the addictiveness of the drug.

Intoxication

Prescription amphetamines have pleasurable, elevating effects that make them drugs of choice for many people. They produce increased mental and physical energy and mild to moderate euphoria. Tolerance to amphetamines develops rapidly, which means that more are needed to get the same effect.

When abused, these drugs have the same kinds of effects as illicit street drugs, including:

- Irregular heartbeat
- Stomach upset
- Talkativeness
- Euphoria
- Sleep deprivation
- Restlessness
- Confusion
- Paranoia
- Irritability
- Aggression
- Heart attack
- Hallucinations
- Death.

Life risks

Prescription amphetamines are generally safe if used as prescribed by a physician.

Withdrawal

Withdrawal from amphetamines is similar to withdrawal from cocaine. Signs and symptoms include depression or irritability, fatigue, oversleeping and overeating, loss of memory, and confused thoughts.

7. Over the counter drugs

Many drugs available over-the-counter (OTC) can be addictive to different degrees. In fact, some of them are commonly used as ingredients in the production of illicit drugs. For example, cough and cold medications are used to produce illegal versions of amphetamines. Others may be used directly, such as mouthwashes and diet aids, because they contain drugs that produce pleasurable effects. Although these drugs have negative effects, people ignore those effects in an attempt to get the high that the drugs produce.

Some addicts and alcoholics may resort to over-the-counter substitutes when trying to quit their original substance of abuse. For example, an alcoholic might give up alcohol but start abusing

mouthwash or cough syrups. These kinds of substitutions are part of the cycle of chemical addiction.

Methods of use
Over-the-counter drugs are taken by various means, but they usually are orally ingested.

Types
Over-the-counter drugs that can be abused include alcohol, caffeine, antihistamines, decongestants, cough syrups, pain relievers, mouthwashes, sleeping aids, and diet aids.

Withdrawal
The presence of withdrawal symptoms depends on the individual drug.

8. Nicotine

Nicotine, which is a stimulant drug, is one of the leading causes of death in the world.

Types
- Chewing tobacco
- Pipes
- Cigars
- Cigarettes.

Methods of use
Tobacco can be smoked in a rolled cigarette or cigar or in a pipe. It can also be chewed.

Effects on the central nervous system
Nicotine is a stimulant that has a very rapid effect on the central nervous system. It can reach the brain within 8 seconds of smoking a cigarette. Structurally, nicotine resembles a naturally occurring chemical messenger in the brain: a neurotransmitter acetylcholine. Acetylcholine governs many essential body functions such as heart rate, circulation, learning, and memory. Because nicotine is so similar to acetylcholine, it is able to mimic acetylcholine actions in the brain, leading to stimulating effects on all of those body functions. At the same time, nicotine stimulates increases in another neurotransmitter dopamine, which stimulates the dopamine receptors in the brain's pleasure center to create a feeling of pleasure or euphoria.

Intoxication
Nicotine intoxication generally happens quickly because smoking is a highly effective delivery process. Nicotine goes straight to the lungs, where it is absorbed by the blood, sent to the heart, and pumped into the arteries and brain. Its effects on the body may include:
- Muscle twitching
- Weakness
- Rapid breathing
- Rapid heartbeat
- Abdominal cramps
- Elevated blood pressure
- Depression
- Confusion, agitation.

Life risks
About 45% of all smokers will die of a tobacco-related health problem. Nicotine use has decreased among adults, but it

has been increasing among teenagers and children. Nicotine is an addictive drug that can cause tolerance, dependence, and symptoms of withdrawal. The tars in tobacco, not the nicotine, cause the cancers that frequently develop in the lungs, throat, and other organs of chronic smokers. Cigarette smoke contains carbon monoxide, which prevents oxygen from attaching to red blood cells that carry it through the body. Chronic smoking causes carbon monoxide poisoning, which can damage the heart and brain.

Withdrawal

Physical withdrawal symptoms include irregular heartbeat, digestive problems, irregular body temperature, and intense cravings. Psychological symptoms include irritability, anxiety, and sleep disturbance. Cravings for nicotine can last for days, weeks, or years after a person stops smoking.

References

1. www.wikipedia.com/misuseoflegaldrugs
2. www.egetgoing.com/drugs/ldrugs.asp
3. www.rxlist.com/drugs.
4. Goodmans and Gilmans-Book of pharmacology.

Module 3.6
Polydrug use

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Key messages

- Polydrug use occurs when two or more drugs are used at the same time or on the same occasion;
- Mixing drugs can also occur when the manufacturer combines two different drugs in order to achieve a specific effect to save money. This often results in users combining drugs unintentionally;
- The combinations of drugs identified in mortality and overdoses provide indications of particular risks associated with drug combinations;
- It is well known that polydrug use is more difficult to treat than single drug use.

Contents

- Polydrug use depends on a variety of factors:

- demographic and social
- availability and price
- desired effect and outcome of use
  previous experience

Figure 1 The nature of polydrug use

1. The nature of polydrug use

The nature of an individual's polydrug use is dependent on a range of factors, including demographic and social characteristics, drug availability and price. In addition, previous experiences with drugs through psychiatric or medical treatment appear to influence an individual's polydrug use behaviors (Fig. 1).

2. What is polydrug use?

The broad definition of "polydrug" is the use of more than one drug or type of drug by an individual – consumed at the same time or sequentially. In its broadest terms, polydrug use is defined as the use of an illegal drug plus another legal or illegal drug. In Europe, the concept of polydrug use dates back to the 1970s. However, considerable differences exist in the substances included in the time frames. Differences appear to depend on the survey data available and on the perceptions of risk associated with particular substances or combinations. The substances included are usually the main illegal drugs, alcohol and medicines. Energy drinks are sometimes included and tobacco is included in France. Time frames for consumption range from a six-hour period to ever experienced during an individual's lifetime.

According to the broad definition, all illegal drug users would be defined as polydrug users as they almost always use alcohol and/or tobacco at some time in their life. Even when polydrug use is defined according to the more narrow range of "illegal drugs", the combinations and patterns of use vary so much that there is little value in adopting a standard definition. For the purposes of addressing general concerns about polydrug use in the EU, the acute risks for health are a main focus.

There is general consensus that polydrug use has four main functions: it maximises effects, balances or controls negative effects and substitutes sought after effects. Information about the functions of combining particular drugs is based on descriptions by users of attempts to have, and prolong, pleasurable experiences. The substances that are used depend on local availability, fashion and local prescribing practices where they include medical drugs prescribed to drug users in treatment (in Germany, France, Ireland and the United Kingdom) (Fig. 2).

3. Reasons for polydrug use

The reasons why individuals become involved in polydrug use warrant close examination because they inform treatment planning. Individuals typically engage in polydrug use in order to (Fig. 3):

- enhance effects of other drugs: CNS depressants enhance or potentiate other CNS depressants, such as alcohol and heroine, hence increasing risk to the person using these drugs;
- counteract effects of other drugs: speed, to counteract effects of alcohol;
- provide a substitute for preferred but unavailable drug: alcohol, BZDs or speed when heroin is in short supply;
- conform to normative ways of using drugs: alcohol and cannabis used simultaneously may be considered normal behaviour. Conforming to social norms may only result in occasional experimentation by large numbers of young users. Nevertheless, harm minimization strategies should be delivered at every opportunity;
- counteract the unpleasant effects of drugs from different classes:
  - depressants used to get to sleep after an amphetamine binge;
  - risk of unpredictable reactions;
- self-manage the withdrawal from a drug by the use of another drug: BZDs and alcohol/heroine.

- Becomes a concern in terms of its relative risk
- Generally associated with hazardous or harmful use of more than one drug
- Appears to be "the norm" amongst many drug using groups
  - many of whom rarely limit use to one drug, or
  - who use a primary drug along with a range of other drugs
- Is highly prevalent among subjects of drug treatment services

Figure 2 Polydrug use

- Enhance effects of other drugs
- Counteract effects of other drugs
- Provide a substitute for preferred but unavailable drug
- Conform to normative ways of using drugs
- Counteract the unpleasant effects of drugs from different classes
- Self-manage the withdrawal from a drug by the use of another drug

Figure 3 Reasons for polydrug use

4. Polydrug combinations

Many people deliberately manage polydrug combinations. Regular drug users are frequently experienced in working out drug effects and how to

balance the desired and unwanted effects (Table 1).

Table 1 Drug combinations used by recreational drug users in the same night

Alcohol and cannabis	50.6 %
Alcohol and ecstasy	11.9 %
Alcohol and cannabis and ecstasy	10.4 %
Cannabis and ecstasy	8.4 %
Alcohol and cocaine	7.8 %
Cannabis and ecstasy, alcohol and cocaine	7.8 %
Cannabis, alcohol and cocaine	2 %

4.1 Sedatives and alcohol

Taking alcohol and sedatives (tranquillizers and sleeping pills) together increases the effects of both drugs and severely affects co-ordination and performance. At high doses, this combination is linked to many cases of people dying from overdoses every year.

4.2 Cocaine and alcohol

This mix is converted in the body to a cocaethylene. Cocaethylene is more toxic than either drug alone. It can seriously affect your heart and has been a contributory factor in many cocaine related deaths.

4.3 Heroin and alcohol

Taking heroin (or any other opiate - type drugs e.g. morphine) with alcohol, increases the risk of going into a coma-like state and even death.

4.4 Ecstasy and alcohol

Alcohol dehydrates the body, as ecstasy does. This makes organs such as the liver, kidneys and heart work harder to cope with the effects of the drugs. In addition to causing possible damage to these organs, such a mix can lead to coma and even death.

4.5 Ecstasy and cocaine

Taking two strong stimulant drugs together may double the stimulation that the user feels, but it also puts extra physical strain on the body. As neither drug quality is tested, it is impossible for the individual to know how much of each drug they have actually taken.

4.6 Heroin and cocaine

Cocaine can speed up the heart immediately, but as the effect of the cocaine wears off, the heroin kicks in and slows down the heart. The result is that the heart rhythm can become erratic and could result in a heart attack.

4.7 Cannabis and stimulants

This combination offsets cannabis sedation and increases the pulse.

4.8 Cannabis and alcohol

The use of cannabis together with alcohol leads to increased intoxication and impairment.

5. Health risks

The combinations of drugs identified in mortality and overdoses provide indications of particular risks associated with drug combinations (Fig. 4) (See Module 2.3 Acute poisoning with substances of abuse).

Health risks associated with combinations of psychotropic substances depend not only on the pharmacological properties and amounts of the substances consumed but also on a range of individual characteristics and social and environmental factors.

- Whilst it is difficult to overdose on benzodiazepines alone, the combination of a large dose of benzodiazepines and a large dose of alcohol or an opiate drug such as heroin or methadone may be fatal.
- When ecstasy is used with alcohol, health risks increase because alcohol impairs thermal regulation and increases dehydration.
- When cocaine is combined with alcohol, the combination may be more directly toxic to the heart and liver than either cocaine or alcohol alone. Alcohol is often present in cocaine cardiac deaths.
- The combined use of different stimulants, including energy drinks, can lead to sympathetic hyperactivity that may result in impaired thermal regulation and cardiac functioning.

Figure 4 Examples of drug combinations considered high risk

In the context of "early-warning systems", there is growing concern about the potential mixture of psychoactive substances in tablets sold as ecstasy, which, despite the lack of intention on the part of users, may constitute polydrug health risks. For example, in Denmark during 2001 a range of 10 to 32% of tablets analysed contained more than one active substance. These tablets primarily contained MDMA and PMA, PMMA, MDE and MDA (See Module 3.4 Synthetic drugs). In France, two thirds of an analysed sample of tablets sold as ecstasy contained MDMA combined with other active ingredients – mostly medicaments.

6. Fatal and non-fatal overdose

Results of toxicological analyses of fatal and non-fatal overdoses associated with illegal drug use are not widely available but those that are consistently reveal that most of the deaths are associated with the injecting of heroin combined with other drugs. A recent study of 153 drug users in the United Kingdom who had experienced non-fatal overdose found that more than one drug had been used in 111 (73%) of cases. In fatal overdoses, at least one other drug or alcohol is involved in over 50% of cases in the United Kingdom and up to 90% in Ireland. Benzodiazepines,

alcohol, methadone and cocaine are the substances most frequently found combined with opiates and a common explanation for the overdose in question was that these combinations had caused it.

7. Harms related to polydrug use

Polydrug users are more likely to have greater personality disturbances than users of a single drug. It is well known that a number of adverse health and social consequences may be experienced as a consequence of drug use. These may include harms such as poor nutrition, poor hygiene and criminal activity. Indirect consequences may include changed behavior and changes in priorities resulting from the drug dependence.

Polydrug use may also cause problems of intoxication which can be even more acute given unpredictable drug interaction and potentiating effects. There are also people who may experience dependence-related problems, despite of the fact that the number of these people is lower than the number of those experiencing intoxication and regular use-related problems (Fig. 5).

8. Treatment

There is little research on the effectiveness of the treatment of polydrug users. Nevertheless, it is well known that polydrug use is more difficult to treat than single drug use. Generally, the adjustment of treatment to each specific case contributes to treatment success and usually the focus is on behaviour rather than substances. However, in acute treatment and in withdrawal, polydrug use might be very relevant.

Managing withdrawal from polydrug use is complex and only clinicians with some experience in withdrawal treatment should attempt to manage polydrug users. Polydrug users attempting withdrawal from multiple drugs are likely to encounter greater difficulties than individuals withdrawing from only one drug class at a time. There is a considerable overlap in symptoms common to withdrawal from different drugs. Anxiety, dysphoria, disturbed sleep, lethargy, disturbed appetite and cravings are symptoms common to most withdrawal syndromes. Any overlap may result in an amplification of withdrawal symptom severity and this greater discomfort is likely to be associated

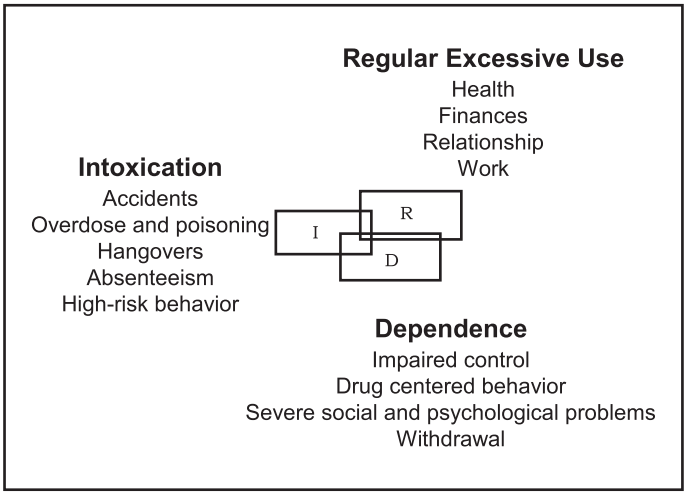

Figure 5 Harms from polydrug use

with poorer withdrawal outcomes. As a result, it is not always advisable to attempt to simultaneously withdraw subjects from different drug classes. For example, a person undergoing alcohol and benzodiazepine withdrawal simultaneously is more likely to suffer from seizures, acute brain syndrome or present with features of psychosis. Stabilization on one or more drugs while withdrawing from another should always be considered.

References

1. Clayton, 1986; Premier's Drug Advisory Council, 1996
2. ONS, 2000a and b; Farrell, 1989; Bennett and Higgins,1999; Strang et al., 1999; Taylor et al, 1996
3. Calafat et al. (1999)
4. Thorley, A. 1980, "Medical responses to problem drinking", The British Medicine Journal, pp. 2474-2482
5. Leccese et al. (2000); DrugScope (2001)

Module 3.7
Addiction in general practice

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Key messages

- Drug addiction is a significant menace of the society related with health problems;
- Treatment of addicted patients is important as it protects healthy people;
- General practitioners (GP) should know how to recognize the drug-addicted patient, to solve the medical problem of the patient, to inform the parents/relatives and to involve them in the problem;
- GP should recognise the effects of drug usage;
- GP should know the complications of long-term drug usage, as they impede clinical symptoms of patient.

Contents

- History of the patient
- Finding the etiology of the disease
- Correct diagnosis
- Removal of the cause
- Treatment

Figure 1 What is the aim of GP?

- To recognize the addiction
- To solve the medical problem of the patient
- To inform the parents
- To involve the relatives to the problem

Figure 2 Why GP should know?

- dry mouth, nausea, vomiting
- slow, weak breathing
- cold, clammy skin decreased appetite
- dizziness, tiredness, or light headedness
- muscle twitches
- myosis, no photoreaction

Figure 3 How we should know?

1. Introduction

Drug addiction is a significant social problem, which leads to severe health complications.

1.1 What is the aim of GP?

The aim of general practitioner is to find out the etiology of the disease, history of the patient, to diagnose correct, to remove the cause, and to give adequate treatment to the patient (Fig. 1).

However, when the patient is addicted it is difficult to make the diagnosis because drug usage complicates the symptoms and the patients usually deny drug use.

1.2 What GP should know about addiction?

The general practitioner should know how to recognize the addiction, to solve the medical problem of the patient, to inform the parents/relatives and to involve them into the problem (Fig. 2).

The most common symptoms that may occur in subjects, who use drugs, are dry mouth, nausea, vomiting slow, weak breathing cold, clammy skin, decreased appetite, dizziness,

tiredness, or light headedness, muscle twitches, myosis, and no photoreaction. These symptoms are non-specific and may be the initial clinical symptoms of some other disease (Fig. 3).

2. Complications of non-intravenous and intravenous drug addicts

Non-intravenous drug addicts are those, who take drug preparations per os or by inhalation, insufflation, smoking or oral intake. Taking these preparations leads to intoxication. The complications in drug addicts are associated with impaired immune response. Hypergammaglobulinemia of both IgG and IgM occurs in up to 90% of addicts. The reason for the immunologic changes is not clear but may reflect repeated antigenic stimulation from infections or from daily parenteral injection of foreign substances. Hypergammaglobulinemia in heroin addicts diminishes with methadone therapy. Heroin addicts and other injectors of intravenous drugs are at extremely high risk of HIV infection and AIDS. In communities where needles and syringes have been commonly shared, the spread of AIDS has become devastating.

Continuous drug abuse leads to intoxication, which is manifested by multi-organ failure (MOF):

- Primary multi-organ failure – when the acute poisoning affects several organs in its very beginning;
- Secondary (slow) multi-organ failure – when the intoxication affects only one "risky" organ or a part of the organism. Its functional insufficiency is the reason for failure in the functions of other organs and systems.

It is considered that MOF pathology in drug addicts is a result of changes in their immune system.

As a result of the interaction of the immune system with drugs or other chemical agents, immune suppression or immune potency may appear. Consequences of the suppressed immune function are: increased infection perceptivity and some forms of neoplasia.

The suppression of the immune response can be caused by some environmental factors – ionizing radiation, metals, and medicines.

- The development of different complications depends on the immune-competent cells.
- T-cells deficit leads to the development of virus and opportunistic infections (chicken pox, tuberculosis, listeriosis, aspergilosis, etc.).
- B-cells deficit is connected with severe bacterial infections (streptococci, Klepsiella, Neisseria, etc.).
- Damaged phagocytosis results in recurrent puss infections and chronic skin diseases.
- Deficit of the complement system results in recurrent infections with streptococci (Haemophilus influenzae, Neisseria meningitis).

Subjetcs prone to drug abuse are susceptible to virus infections and especially to HBV, HIV.

Immune system of drug addicts is weak because of the modification of cell mechanism for activation of leucocytes and lymphocytes and decrease in their phagocyte activity.

On the other hand, the suppression and stimulation of liver enzymes leads to the damaged liver biotransformational capacity. This can cause accumulation of active metabolites, abnormal concentration of toxins and interleukin production. In more than half of the cases of drug addicts, who have also hepatitis C, there are damages in the liver function: persisting infection, potentially contagious with possibility to progress to cirrhosis, liver failure and hepatocellular carcinoma.

Frequent infections in drug addicts lead to several complications. For example, an infection with mescaline resistant Staphylococcus aureus can cause severe glomerulonephritis by the release of bacterial super antigenes. Hepatitis C can induce membrane-proliferate glomerulonephritis. Cocaine can cause rhabdomyolysis, extreme hypertension and renal failure. The intake of ecstasy can also result in acute renal failure, electrolyte disbalance and malignant hypertension.

- Diagnosis of toxic substances:
  - serum
  - urine
- Immunological diagnosis of:
  - Hypergammaglobulemia
  - IgM, IgG

Figure 4 Laboratory diagnosis

- Addiction
- Decrease in the immunity
- Respiratory complications
- Heart related complications
- Neurological complications
- Kidney problems
- Neonatal abstinent syndrome

Figure 5 What complications can arise?

Drug abuse can lead to opiate induced asthma. Research on drug addicts using buprenorphine proves that. The alterations in organ function are reversible and could restore in about 45 days after drug stop acceptance stops (Fig. 4). Test of hematological markers provided the data with leucopenia accompanied by decrease in the lymphocytes and monocytes, increase in neutrophils, decrease in hematocrit.

3. Complications in intravenous drug addicts

Many complications of heroin addicted patients are related to the unsafe administration of drug, overdose, or risky behaviour, accompanying drug use. Common complications include pulmonary disorders, hepatitis, arthritic disorders, immunological changes, and neurological disorders (Fig. 5).

3.1 Overdose

Most drug addicts get into the emergency room after overdose intake (most often heroin). Heroin overdose produces suppression of the respiratory centre and respiratory failure. This life threatening condition can be cured by Naloxone in order to restore breathing after heroin, morphine or opioid poisoning (1 mg of Naloxone i.v. blocks the effect of 25 mg heroin). For buprenorphine intoxication treatment an overdose of 10-15 mg is needed. Other medication includes Naltrexon or Nalorphine (Fig. 6 and Fig. 7).

3.2 Pulmonary complications

Aspiration pneumonitis, pneumonia, lung abscess, septic pulmonary emboli, and

CNS Symptoms:
- Respiratory depression, intensive central cyanosis (bradipnoe 2-4/min)
- Sedation and drowsiness, unconsciousness up to coma
- Miosis
- Hypothermia
- Suppression of cough
- Suppression of pain
- Nausea and vomiting
- Euphoria or dysphoria
- Seizures

Periphery Symptoms:
- Cardiovascular: vasodilatation, hypotension
- Urinary tract: urinary urgency and retention
- Skin: urticaria from histamine release
- GI tract: constipation
- Uterus: decreased contractions

Figure 6 Opioid overdose symptoms

- CPR (cardiopulmonary resuscitation)
- Naloxone – bolus 2 mg I/V (0,4-2mg) to 10 mg (If no I/V access - sublingual, endotracheal, i/m), continous infusion
- In-patient monitoring at least 12 hours
- Heating

Figure 7 Opioid overdose treatment

- Pneumonia
- Lung abcess
- Septic pulmonary emboli
- Bronchospasm
- Atalectasis
- Decreased vital capacity

Figure 8 Complications related with lungs

atelectasis may occur. Pulmonary fibrosis from talc granulomatosis may develop when pills prepared for oral use are injected. Chronic heroin addiction results in a decreased vital capacity and from mild to moderate decrease in diffusion capacity. These effects are different from the pulmonary oedema that may occur acutely after heroin injection. Many opioid addicts smoke one or more than 20 cigarettes a day, that makes them particularly susceptible to a variety of pulmonary infections (Fig. 8).

3.3 Cardio-vascular disorders

Many physicians will encounter patients with cardiovascular problems related to recreational drug misuse. In addition to the problems posed by self-administration, massive overdoses may occur in individuals who attempt to smuggle illegal drugs by ingesting packets, which rupture in the gastrointestinal tract; inadvertent ingestion of recreational drugs by children has been reported. Successful management can be difficult, since many patients will be unwilling or unable to provide an accurate history. An awareness of the pathophysiological effects of these compounds is therefore an important aid to diagnosis.

Cocaine, ecstasy, and amphetamine share similar adverse effects on the cardiovascular system, related predominantly to activation of the sympathetic nervous system. Cocaine acts by inhibiting epinephrine reuptake in peripheral sympathetic nerve terminals as well as stimulating central sympathetic outflow (See Module 1.5 Cocaine characteristics and effects and Module 2.2 Cocaine cardiotoxisity). Circulating catecholamine concentrations can be raised as much as fivefold. Amphetamine and its derivative ecstasy produce indirect sympathetic activation by releasing epinephrine, dopamine, and serotonin from central and peripheral autonomic nervous system terminals, and serious cardiovascular complications have been well documented.

Sympathetic activation can lead to varying degrees of tachycardia, vasoconstriction, and unpredictable blood pressure effects, depending on the dose taken and the occurrence of coexisting cardiovascular disease. Hypotension as a result of a relative catecholamine depletion state, paradoxal suppression of the central nervous system (amphetamine), or acute myocardial depression (due to ischemia or a direct toxic effect of the drug) can occur.

Myocardial ischemia and infarction may be related to the raised catecholamine concentration causing an increase in oxygen demand, coronary artery spasm, platelet aggregation, and thrombus formation. Repetitive episodes of coronary artery spasm and paroxysms of hypertension may result in endothelial damage, coronary artery dissection, and acceleration of atherosclerosis. Paroxysmal increases in blood pressure can lead to aortic dissection or valvular damage, which increases the risk of endocarditis.

Cocaine and amphetamine have been associated with non-cardiogenic pulmonary oedema and a dilated cardiomyopathy. The adverse cardiovascular changes and sympathetic stimulation associated with these agents predispose to myocardial electrical instability and a wide range of tachyarrhythmias. The class 1 anti-arrhythmic properties of cocaine can impair cardiac conduction, precipitating conduction defects and brady-arrhythmias, including sinus arrest and atrioventricular block.

Morphine and its semisynthetic analogue heroin are the most commonly misused narcotic analgesics, accounting for almost half of drug related deaths. They act centrally to increase parasympathetic and reduce sympathetic activity, resulting in bradycardia and hypotension. Various bradyarrhythmias and tachyarrhythmias have been reported. Bacterial endocarditis, affecting mainly right sided cardiac structures, is a well known complication of intravenous narcotic misuse.

Non-cardiogenic pulmonary oedema (which may not develop until 24 hours after admission) can occur in heroin overdose.

All these drugs have important effects on cardiovascular function that significantly contribute to adverse events. Most adverse cardiac events occur in young adults and are potentially reversible. The key to diagnosis is a high index of suspicion, particularly when unexplained or unusual cardiovascular problems occur in association with central nervous system dysfunction, together with awareness of the pathophysiological effects of the drugs. There are no adequate randomised controlled trials to guide therapy, which is based principally on an understanding of the cardiovascular actions of the drugs, along with experience gained from observational studies (Fig. 9).

3.4 Liver complications

Viral hepatitis types A, B, and C may develop. The combination of viral hepatitis and the frequently high alcohol intake may account for the high incidence of liver dysfunction.

3.5 Musculoskeletal complications

The most common musculoskeletal complication is osteomyelitis, probably

- Endocarditis
- Non specific myocardial infact
- Rhabdomylosis

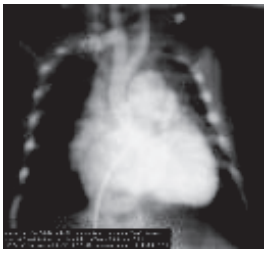


Figure 9 Heart related complications

due to hematogenous spread of organisms from unsterile injections. Infectious spondylitis and sacroiliitis may occur. In myositis ossificans (drug abuser's elbow), the brachialis muscle is damaged by inept needle manipulation, followed by replacement of the muscle bundle with a calcific mass (extra osseous metaplasia).

3.6 Addiction in pregnancy

The antennal care of the pregnant drug addicts or drug abusers has exactly the same aims as for the nondrug-abusers – to keep the woman in good health for her own sake, and to give her the best chance of delivering a healthy child. Not only the pharmacological effects of the drugs the mother uses, but also her lifestyle often complicates achieving these aims.

To start with, the diagnosis of pregnancy and hence the initiation of antennal care may be delayed because there is a high incidence of abnormal menstrual cycles and amenorrhoea during opiate administration, which often resolves when drug use is interrupted. Thus, it may happen that a woman who has become pregnant while temporarily abstinent assumes that her subsequent amenorrhoea is due to a resumption of drug-taking, and does not present to an antennal clinic until well into her pregnancy, when her increasing weight and enlarging abdomen become apparent. This late presentation may be particularly disadvantages for those living in poor environmental conditions, hygiene and with poor nutrition. However, once aware of their pregnant condition, many drug addicts do approach their GP or another agency for advice.

- Neonatal abstinant syndrome
- Inflammatory diseases of the infant
- Malformation
- Still birth

Figure 10 Risk and pregnancy

- Medical supervision
- AIDS test
- Test of hepatitis

Figure 11 What a medical practitioner can prescribe to a female patient?

The majority of pregnant drug addicts are dependent on opiates that cross the placenta and affect the foetus directly. Constantly exposed to these drugs, the foetus also becomes dependent on them and suffers from withdrawal if the mother

is deprived of her drugs. Obviously, if the mother injects drugs, the foetus is constantly exposed to the risk of infection and effects of unidentified adulterants.

Whenever possible, pregnant women should be encouraged to come into hospital at least for the initial assessment period and, in effort to engage all patients in treatment, clinic and in-patient units should be more flexible than usual and ready to make exceptions to their usual policies. After the birth the child is also put on methadone therapy so that to avoid the risk of distress syndrome development.

All pregnant addicts should be encouraged to be tested for HIV antibodies and for hepatitis. The woman will then be able to make an informed choice about whether or not she wishes to continue with the pregnancy.

The management of pain relief during the baby's delivery is another problem as normal doses analgetics are often insufficient for providing an effective analgesia, and on the other hand the foetus is not used to such high doses (Fig. 10 and Fig. 11).

Teratogenic effects

There is little evidence that drugs have teratogenic effect on the foetus especially LSD which produces chromosomal damage in human leukocytes. Cannabis is suspected of causing limb deformities. The impact or each type of drug hardly could be defined because most of the drug addicts use more than one type or do not know at all what type of drug they have exactly used in the first months of their pregnancy, which are most critical for teratogenic effect.

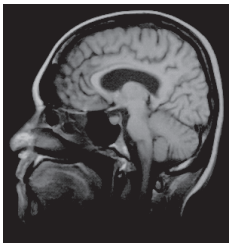
Low birth weight of the infant occurs frequently with children whose mothers are addicted – about 30 % do not respond to the gestation age. Low birth weight correlates with morbidity and mortality but it cannot be defined exactly whether it is due to drug effects or the lifestyle.

Neonatal abstinence syndrome

The reason for its development is the fact that opiates pass through the placenta and the foetus becomes dependent. After the birth the babies are hyperactive, irritable, nervous with tremor, and sometimes with convulsions. There might be troubles with the gastrointestinal tract attended by vomiting. The beginning of the abstinent syndrome usually appears in about 24 hours after the birth but with methadone-dependent mothers it may appear only after 72 hours or even later. Chlorpromazine is a medicine at first choice but it is used only if abstinent appearances get worse. Breastfeeding is contra-indicated if there is HIV or HBV, HCV infection, constant use of drugs.

3.7 Neurological complications

In heroin addicts, neurological disorders are usually non-infectious complications of coma and cerebral anoxia. Toxic amblyopia (apparently due to adulteration of heroin by quinine), transverse myelitis,



- Micro aneurysms
- Brain abcess
  - Subdural abcess
  - Epidural abcess
- Amblyopia
- Guillain-Barre syndrome

Figure 12 Neurological complications

- To encourage family members to support the patient
- Psychoanalysis of the patient
- Toxocological analysis of the patient

Figure 13 How a general practitioner can help?

various mononeuropathies and polyneuropathies, and Guillain-Barré syndrome may occur. Cerebral complications include those secondary to bacterial endocarditis (bacterial meningitis, mycotic aneurysm, brain abscess, and subdural and epidural abscesses), those due to viral hepatitis or tetanus, and acute cerebral falciparum malaria. Some neurological complications may be due to allergic responses to the heroin-adulterant mixture (Fig. 12).

References

1. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1290816
2. http://opiateaddictionrx.info/addiction/england/key1.html
3. www.blackwell-synergy.com
4. http://alcalc.oxfordjournals.org/cgi/content/full/38/6/597

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