DRUG ABUSE TREATMENT AND PREVENTION

STUDY MANUAL
FOR
MEDICAL STUDENTS AND YOUNG DOCTORS

Volume 1

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Training of Medical Students and
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CONTENTS

Chapter 1
Basic principles

Module 1.1
Drugs in general

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Key messages

- Animal models are useful;
- Addiction is a brain disease;
- Tolerance and dependence are normal physiological reactions;
- Consider quality of life.

Contents

1. Introduction

Various models followed one another and currently coexist in order to explain the maintenance of a chronic and compulsive consumption of a drug. The model of physical dependence was regarded for a long time as the explanatory model for the maintenance of addiction. In the twenties, it was recognized that an animal could be made dependent on morphine, but it had not been shown, that having morphine at disposal, they could be voluntarily made dependent. The hesitation of the animals to spontaneously develop the behaviours of self-administration of drug contributed to the spread of the idea that dependence was caused by a factor specific to the man and absent in the animal. Man could decide to consume the drug and found himself "punished" by the dependence. This model also deemed that animals were not a useful model in the study of addictions.

The development of self-administration techniques in animals allowed a clearer progress in the theoretical designs. However, the self-administration of a drug by the animals was in the major part explained by the existence of a physical dependence. The interruption of drug administration being associated with an unpleasant withdrawal syndrome, the maintenance of consumption was due to the existence of a negative reinforcement related to the interruption of consumption. However, in the maintenance of the chronic consumption of a drug, the physical dependence and the negative reinforcement associated with the interruption of consumption, did not explain the chronic and compulsive use of the drug. The self-administration behaviour was gradually associated with a conditioning in which drug acts as a positive reinforcement.

2. Reward pathway

Various authors contributed to highlighting the fact that we have a cerebral system associated with various motivational states. The cerebral mechanisms involved in the processes of opioid reinforcement are different from those involved in physical dependence.

Much evidence indicates that with regard to positive reinforcements, the dopaminergic system plays an important role, especially the méso-cortico-limbic system. This system is composed of various structures which include the tegmento-ventral area, the nucleus accumbens, the prefrontal cortex, the amygdala and the septum. Drugs, and in particular opioids, interfere with this system, and this can at least partly explain, the loss of control and the compulsive need to use drug.

Various studies (Stolerman, 1992; Nicoll, 1980) indicate the capacity of the opioids to interfere with dopaminergic transmission via the GABAergic system. Opioids could indeed inhibit the GABAergic neurons. This effect of opioids on the GABA system is associated with

a massive release of dopamine in the nucleus accumbens and other parts of the limbic system. Let us note however that dopamine is not the only element associated with the reinforcing capacity of opioids. Certain data indicates that the μ opioid receptor seems to be a key element in the reinforcing mechanisms of morphine. The μ receptor plays a central part in the reinforcing effects of the opioids whereas dopamine has only a modest role. Let us also note that the μ receptor is also involved in the reinforcing effects of other drugs and that conversely other systems are also involved in the modulation of the effects of opioids.

3. Consequences of the repeated use of drugs

The repeated use of drugs (e.g. opioids) leads to tolerance and a physical dependence.

Tolerance and dependence are classical physiological and non pathological adaptations, associated with the repeated use of various types of opioid agonists.

Dependence is particularly revealed when the chronic administration of opioids is stopped in an abrupt way or when an opioid antagonist is administered, inducing a withdrawal syndrome. Addiction is a disorder which is characterized by a compulsive use of drug and incapacity to limit the chronic use of drug.

The mechanisms underlying the transition between the occasional and controlled use of drug and the behavioural loss of control are still largely unknown.

4. Tolerance

Various classes of tolerance are described, innate tolerance and acquired tolerance, which itself is subdivided into subcategories.

4.1 Innate tolerance

Innate tolerance refers to a genetic susceptibility to a drug during its first exposure.

4.2 Acquired tolerance

Acquired tolerance is subdivided into various distinct types.

4.3 Pharmacokinetic tolerance

Pharmacokinetic tolerance refers to changes in the distribution or the metabolism of a drug after repeated administrations; it involves a modification of the concentration of drug at the site of action.

4.4 Pharmacodynamic tolerance

The pharmacodynamic tolerance refers to the adaptations within the systems affected by a drug and involves a decrease in the response.

4.5 Behavioural tolerance

Behavioural tolerance refers to behavioural changes in the response to a drug following repeated administrations. It is a form of compensation developed by learning the effects of a drug on behaviour.

4.6 Cross tolerance

Cross tolerance refers to the fact that the repeated use of a drug confers tolerance not only to the drug used but also on other drugs of the same category. The existence of an incomplete cross tolerance between the various categories of opioid agonists indicates the pharmacological complexity of the effects of the opioids.

5. Dependence and addiction

The mechanisms underlying the transition between the occasional and controlled use of a drug and the loss of control are still unclear. The border between dependence and addiction is not clear as many factors are involved. If dependence reflects a normal physiological mechanism, other factors contribute to make it evolve into a pathological state commonly called addiction. The emergence of the number of problematic opioids users made it possible to specify, that beyond a simple physiological adaptation, the development of addiction would imply individual vulnerability.

Considering the pharmacological actions of opioids, various adaptations take place in neurotransmission. These adaptations involve modifications in the response to the drug (e.g. tolerance, behavioural sensitization, etc.) and behaviour modifications. These physiological modifications underlie at least partly, craving and relapse.

From a behavioural point of view, the consumer associates the effects of the drug with subsequent changes at the emotional level, this is traditional conditioning. Moreover, the consumer learns how to use the product in an optimal way; this is an act of operative conditioning. The desire to want to attain a certain emotional state (e.g. euphoria) is consequently directed towards the research of the product (Heyne & Al, 2000; White 1996; Wolfgramm & Heyne, 1995). Positive reinforcement comes into play as the consumer seeks a situation according to the positive aspects that it brings to him.

From a behavioural point of view, the unpleasant feeling associated with the stop of the continuous use of the product (withdrawal syndrome) contributes to the maintenance of consumption. It is a negative reinforcement in which avoiding a situation leads to unpleasant sensations. Various studies also show that the genetic and environmental aspects (in particular stress) play a role in the development and the maintenance of addiction (Shaman & Al, 2000).

6. The opioid withdrawal syndrome

Neurobiologic aspects

The appearance of a withdrawal syndrome after the interruption of a chronic use of opioids is the principal physiological evidence of the existence of a physical dependence. The withdrawal syndrome is a series of signs following the interruption of chronic administration of an opioid agonist.

The available results indicate that no cerebral structure can by itself, be considered entirely responsible for the variety of the symptoms expressed at the time of withdrawal (Maldonado & Al 92, 96, Stinus & Al 1990, Tremblay & Charton 1981). However, various works indicates that the locus coeruleus plays an important role in the expression of the withdrawal syndrome (Torrecilla & Al, 2002; Akbarian & Al, 2002; Maldonado & Al, 1992; Nestler & Al, 1989). The locus coeruleus is the most important noradrenergic locus of the brain; it plays a fundamental part in the processes of activation and awakening.
With regard to the implication of the locus coeruleus during the withdrawal syndrome two hypotheses are considered:

The **external hypothesis** supposes the intervention of external factors to the locus coeruleus, in fact the release of excitatory amino acids. The administration of antagonists of the excitatory amino acids in the locus coeruleus would reduce the hyperactivity of this locus usually observed during naloxone opioid withdrawal precipitation (Rasmussen & Al, 1991; Akaoka & Aston-Jones, 1991). This release of excitatory amino acids would originate from the locus paragigantocellularis (Ennis & Aston-Jones, 1988; Rasmunssen & Aghajanian, 1989; Akaoka & Aston-Jones, 1991); a lesion of this locus involves a significant attenuation of the activation of the locus coeruleus during the precipitation of an opioid withdrawal.

The **internal hypotheses**, supposes that there is an intrinsic mechanism within the locus coeruleus (Kogan & Al, 1992; Aston-Jones & Al, 1997). This second hypotheses is however discussed insofar as various studies show the absence of an increase in the frequency of self-discharge of the neurons of the locus coeruleus on isolated cerebral tissues of animals treated with morphine. These data seem to indicate that there is no intrinsic mechanism within the locus coeruleus underlying the expression of opioid withdrawal. However, some data (Ivanov & Aston-Jones, 2001) indicate that the hyperactivity of the locus coeruleus induced by the withdrawal does not imply the release of neurotransmitters, but results from internal adaptations associated with the chronic administration with opioides. Potassium channels have been implicated in this phenomenon; however thorough studies will be necessary to specify this hypothesis.

7. Clinical description and mode of evaluation

7.1 Clinical description

The appearance of an opioid withdrawal syndrome occurs when the chronic administration of opioides is abruptly interrupted or when an antagonist is administered. Himmelsbach (1942) proposed the first relevant description of the manifestations of the withdrawal syndrome. Since then, other authors (Wang & Al, 1974; Zilm & Sellers, 1978; Handelsman & Al, 1987; Gossop & Al, 1987; Turkington & Drumond, 1989; Gossop 1990, Rosse & Al, 1998) have also been interested in clinical descriptions as well as with the standardized techniques of withdrawal evaluation.

7.2 Mode of evaluation

The scale of Wang (1974) remained a reference for the clinical and experimental protocols. However the variability of the symptoms of withdrawal, associated with the increasing availability of new opioids agonists, encouraged many teams to modify it. These successive modifications made the use of this scale confusing. Gossop & Al (1987) developed a standardized rating scale (32 items) of withdrawal. In order to facilitate and to integrate it in daily clinical practice, a condensed version was validated (Gossop 1990). This condensed version contains 10 items. This scale (Shorts Opiate Withdrawal Score SOWS) allows a reliable evaluation of the intensity of withdrawal (Farrel, 1994) and is useful for clinical applications and experimental purposes. In clinical practice the visual analogical scale is frequently used (Kindler & Al, 2000; Dirks & Al, 2002). This method is derived from the methods of pain evaluation, it makes possible to determine and quantify the intensity of withdrawal signs (Clement & Al, 2000).

The visual analogical scale is a small graduated plastic small rule. It comprises of a mobile cursor which moves with the hand. The small rule is used to help the patients experiencing withdrawal to express the intensity of their symptoms. The patient has to place the cursor for each symptom between "absence of symptom" and "extreme symptom" as often as that proves to be necessary (Hake, 2002).

8. Objectives of treatment

Each patient has individual characteristics, which specify the type of consumed substance, the quantity, the frequency, and also enable the evaluation of his mental and physical health. It is on the basis of this phase of evaluation that the therapeutic strategy and the objectives of the treatment will be set-up. The objectives could be as follows.

8.1 Abstinence or reduction in the frequency of the use of a substance

The ideal situation for the patients is generally to reach abstinence. However, for many of them, this request is not

easily realizable, particularly in the first phases of the treatment. Intermediate stages are often necessary before reaching abstinence. The reduction in the frequency and the quantity of consumption, substitution towards a less risky substance (e.g. methadone), and harm avoidance are possible alternatives (Weiss & Al, 1988; Marlatt & Al, 1993). The most important element is to incorporate the patient into a long-term process of treatment. Patients who wish to reach abstinence must be informed of the relapse risks and must accept the therapeutic programme in order to allow the maintenance of this abstinence and the early detection of signs of relapses (Strain & Al, 1994).

8.2 Reduction in the frequency and the gravity of relapses

An important stage in relapse prevention is the identification of the situations "at risk" and the capacity for the patient to develop alternative answers to these situations. These situations are craving (Wise, 1988) and certain situations associated with stress emergence (Brown & Al, 1995; Shaman & Al, 2000). A reduction in the frequency and the gravity of the relapses is often a realistic objective which makes it possible for the patient to improve his quality of life.

8.3 Improvement of psychosocial operation

The development of an addiction is associated with a degradation of the patient's health as well as with disturbances in his family relations, (Mlelland & Al, 1993; Mason & Al, 1998; Hatzitaskos & Al, 1999). The treatment must be also directed towards the re-establishment of the family and social relations, the reduction of impulsiveness and the regularization of the social condition. These aspects will contribute to optimize the chances of the patient to achieve the goals.

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Module 1.2

Pharmacological and biological aspects of drug addiction

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Key messages

- Former concept (valid for sedatives) – repetition of consumption -> tolerance -> increasing doses -> physical dependence;
- All addictive drugs share in common ability to induce activation and euphoria, at least during a part of the intoxication, and that is due to the activation of a dopaminergic mesocorticolimbic pathway called "reward system". As a consequence, the reinforcing effects of drugs increase over time, with a progressive loss of control of the consumption;
- These phenomena are amplified by the simultaneous exposure to stress factors;
- Even if described firstly with psychostimulants, sensitization was recognized for all the addictive drugs; furthermore, a cross-sensitization was demonstrated between all of them;
- Sensitization is poorly reversible, even after long-term cessation of consumption, probably due to a modification of gene expression in neurons;
- New conception of addiction. The repetition of consumption induces a progressive sensitization to the reinforcing effects of drugs. As a consequence, a loss of control of the consumption is more and more pregnant.

Contents

- Sedatives
  - Opiates
  - Alcohol
  - Benzodiazepine
  - Others
- Psychostimulants
  - Cocaine
  - Amphetamine
  - Methylen-dioxy-amphetamine
- Hallucinogens
  - Me scaline
  - Psylocibine
  - LSD
  - Cannabis
- Others
  - Nicotine
  - PCP
  - Others

Figure 1 Classification of substances leading to addiction

- Consumption
- Repetition
- Tolerance
- Increase of consumption
- Physical dependence

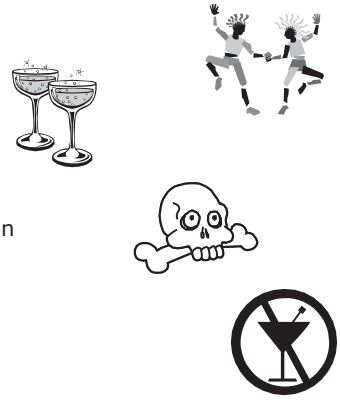

Figure 2 Classic model of addiction

"Contrary to sedative substances like alcohol, barbiturates and other opiates, psycho stimulants do not lead to physical dependence!"

Figure 3 "Classic" model of addiction was questioned

1. Classical concept: tolerance induced addiction

Various categories of drugs can lead to addiction, even if they differ in their pharmacological properties. An important issue was to identify the putative common mechanism of action of such different substances (Fig. 1).

Formerly, addiction was understood as a cascade of events: in summary, it was proposed that the repetition of consumption induced a progressive adaptation of brain circuits with a progressive decrease of the effects of drugs. This situation was called "tolerance"; as a consequence, people were supposed to increase their consumption to maintain the expected effect of drug. And, finally, as a consequence of such a massive consumption, a physical dependence could appear. The core phenomenon of addiction is supposed to be, in this model, the manifestation of physical dependence through a withdrawal syndrome when the patient tries to stop the consumption (Fig. 2).

However, if this model seemed to explain quite well the

addiction to sedative drugs like alcohol, barbiturates or opiates, this was not the case for other addictive substances like psychostimulants (cocaine and amphetamines). Thus, this "classic" model of addiction was questioned (Fig. 3).

2. Addiction without tolerance — psychostimulants

An important observation was the recognition that the reasons to consume addictive drugs are complex. For everybody, a primary reinforcement factor is present; it produces a feeling of stimulation and of pleasure. Later or in relation with environmental and/or personal problems, people can also consume drugs to relieve anxiety, depression or sleep problems. Finally, addicted patients can consume specific drugs to relieve withdrawal symptoms (Fig. 4).

2.1 Reward system

To illustrate the importance of primary reinforcing effects of drugs in the development of addiction, Fergusson et al. (2003) reported that the risk to become addicted to cannabis is clearly correlated with the positive effects of the drug at

- Primary factors: Euphoria, "Pleasure", "Stimulation", etc.
- Secondary factors: anxiolysis, antidepressor effect, effect on sleep, etc.
- Tertiary factors: control of withdrawal symptoms during abstinence

Figure 4 Positive reinforcement of consumption

New Zealand
Cohort of 198 persons who have used cannabis before the age of 16 traced between the age of 16-21
Relation of the effects of cannabis during the first consumption at the age of 16

Positive (high / happy / relaxed / did silly things / laughed a lot)
Negative (ill / frightened / passed out)

Risk of dependence at the age of 21.

symptoms +	risk
0	5.2%
1	8.5%
2	13.3%
3	19.9%
4	28.7%
5	39.1%

$p < 0.001$

symptoms -	risk
0	19.2%
1	31.3%
2+	22.7%

$p = 0.19$

FERGUSSON DM, HORWOOD J, LYNSKEY MTand MADDEN PAF
Early reactions to cannabis predict later dependence.
Arch Gen Psychiatry 60 : 1033 – 1039, 2003.

Figure 5 Early reactions to cannabis predict later dependence

- Induction of euphoria in the beginning of consumption can be observed in almost all substances which cause addiction
- The anatomical substrate of this activity is the activation of a mesocorticolimbic dopaminergic pathway, currently known as a "reward system"

Figure 6 "Reward system"

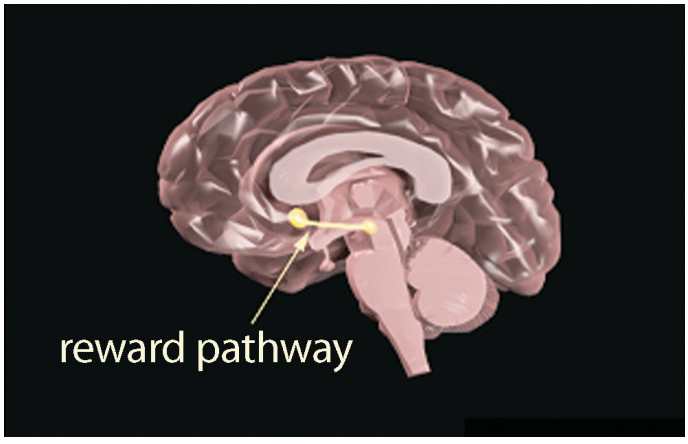

Figure 7 "Reward pathway"

DI CHIARA G and IMPERATO A. Drugs abused by humans preferentially increase synaptic dopamine concentration in the mesolimbic system of freely moving rats. PNAS 85, 5274-5278, 1988

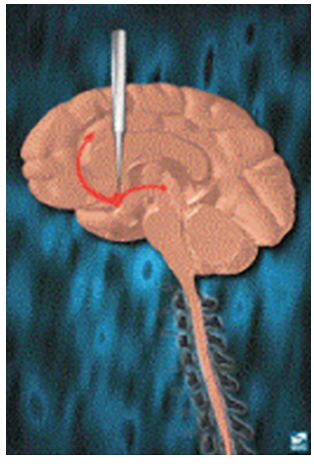

Figure 8 Drugs abused by humans preferentially increase synaptic dopamine concentration in the mesolimbic system of freely moving rats

- Increase in the quantity of noradrenaline and dopamine at the level of synaptic cleft.

  Noradrenergic system: responsible for awakening

  Dopaminergic system: responsible for the regulation of movements, and also for the "reward system"

Figure 9 Cocaine and amphetamine - mode of action

the beginning of consumption (Fig. 5).

For about 20 years, it was recognized all addictive drugs share in common this ability to induce activation and euphoria, at least during a part of the intoxication, and that is due to the activation of a dopaminergic mesocorticolimbic pathway called "reward system" (Fig. 6 and Fig. 7).

The crucial importance of this pathway was identified in microdialysis pioneer studies showing that all drugs abused by humans were able to increase the concentration of dopamine in the mesolimbic system of rodents (Fig. 8).

This is in accordance with what was already known for the pharmacological effects of psychostimulants (Fig. 9).

However, a key issue for the understanding of addiction was that no tolerance was reported if psychostimulants are consumed in a repeated way (Fig. 10).

2.2 Sensitization

In order to clarify this point, new studies were performed in animal models. The motor activation was observed during repeated administrations of cocaine or amphetamine. Tolerance was expected but, on the contrary, a progressive increase of the motor response was observed. This phenomenon was called "behavioural sensitization". This is a major point for the understanding of addiction, because this sensitization was recognized to reflect an increasing response of the reward system to drugs (Fig. 11).

As a consequence, dopamine receptors are more and more stimulated by addictive drugs. This has major implications such as the progressive modifications of intracellular second messengers and finally of gene expression due to an overstimulation of D1 receptors (Fig. 12).

As a consequence, long term modifications of neuro-transmission are induced through e.a. the release of increasing amounts of some neuropeptides (Fig. 13).

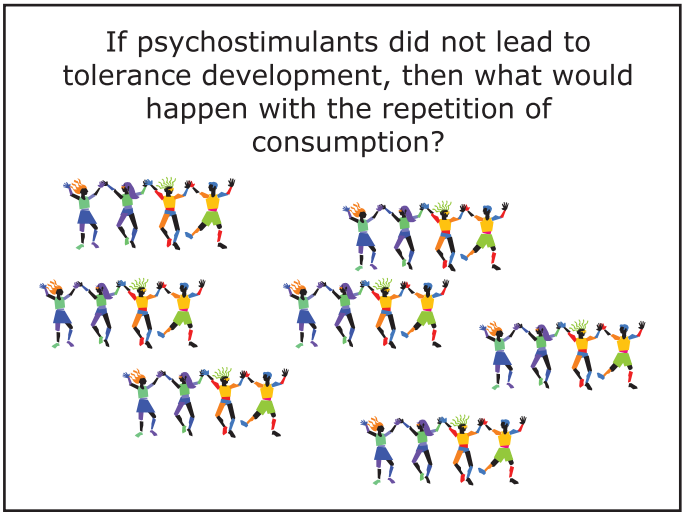

Figure 10 Repeated consumption of psycho-stimulants do not lead to tolerance development

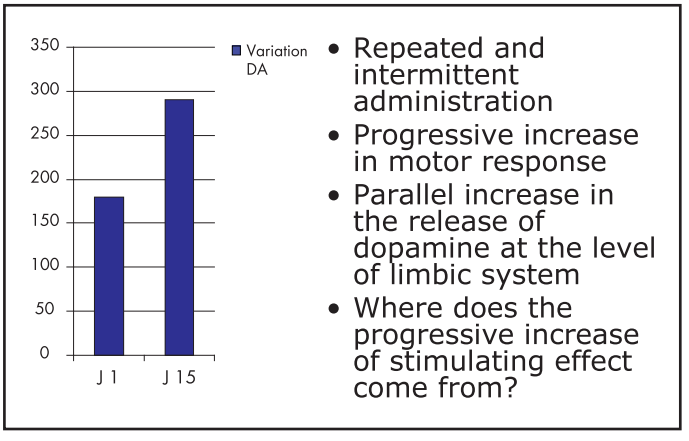

Figure 11 Psychostimulants - behavioural sensitization

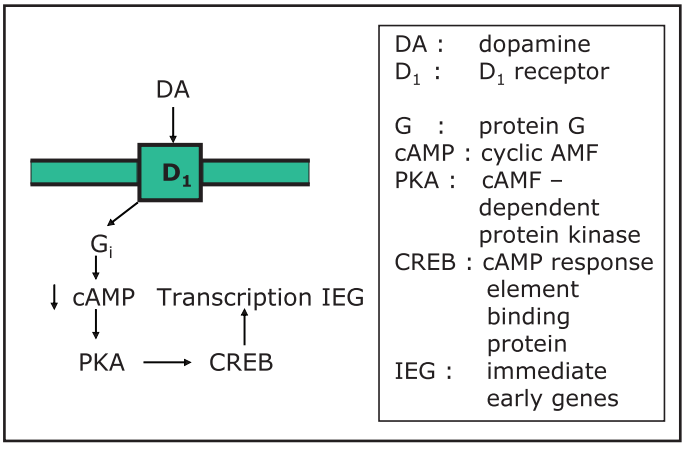

Figure 12 Effect of cocaine on genetic regulation

- Proto - oncogenes
  - c-fos
  - jun
  - ...
- Neuropeptides
  - somatostatine
  - VIP
  - tyrosine hydroxylase
  - prodynorphine
  - .....

Figure 13 Immediate early genes

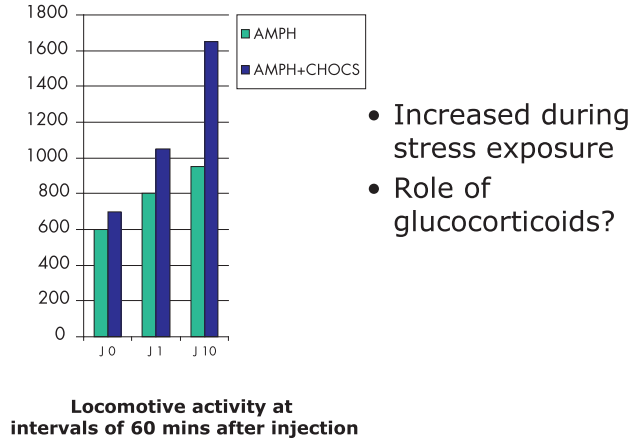

Figure 14 Psychostimulants - behavioural sensitization

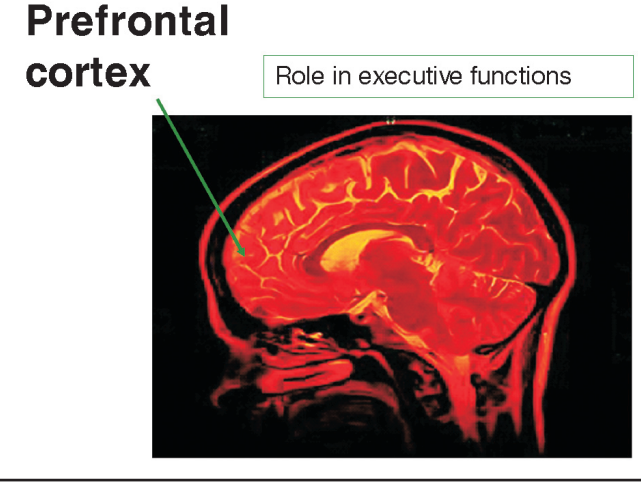

Figure 15 Role of prefrontal cortex in executive functions

2.3 The role of the stress: excitotoxicity – alteration of "executive functions"

Furthermore, this model permitted to identify a major drug-environment interaction. Indeed, it was shown in animal models that behavioural sensitization is amplified by the exposition to stress. The role of steroids is currently under discussion.

This is coherent with clinical reports that major life events are common boosters for addictive problems (Fig. 14).

It is also important to keep in mind that withdrawal manifestations are also stress factors and, therefore, an additional factor for the increase response of the brain to drugs in addicted people.

An additional consequence of the exposition to both stress and addictive drugs is a progressive alteration of the prefrontal cortex, probably through a mechanism of excitotoxicity mediated by excitatory amino acids (EAA). Many studies documented a decreased metabolic activity in this brain region in addicted patients. This decreased prefrontal activity was demonstrated to be responsible for an alteration

of what is called "executive functions" (Fig. 15).
Executive functions are all the cognitive abilities that make people able to cope with new environments, and to have goal-directed behaviours (Fig. 16).

3. Pharmacokinetics

It was also showed that pharmacokinetics parameters in addition to the pharmacodynamic properties of drugs are implicated in addictive processes. A key observation was made first with opiates, showing that they can be poorly addictive when given in steady-state conditions; on the contrary, persons become quickly addicted when they have consumed intermittently and especially when they are injected. This is the major difference between the situation of persons who are addicted to heroin and those who are involved in a maintenance program with methadone (Fig. 17).

In the same way, Volkow and Swanson (2003) reported that the addictive risk when giving methylphenidate (an analog to amphetamine) to children suffering from an attention deficit hyperactivity syndrome

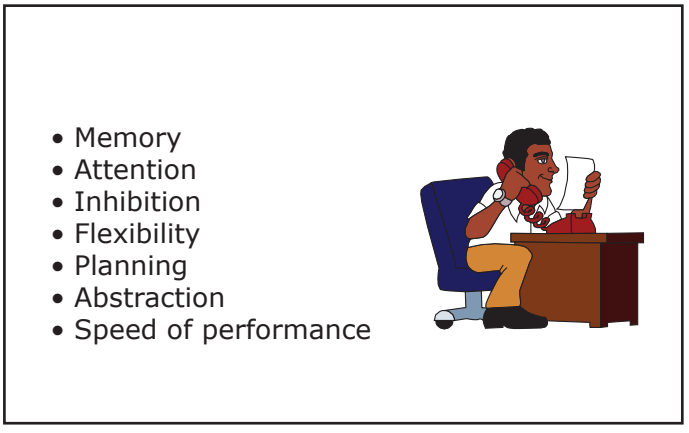

Figure 16 Long term use of psychostimulants

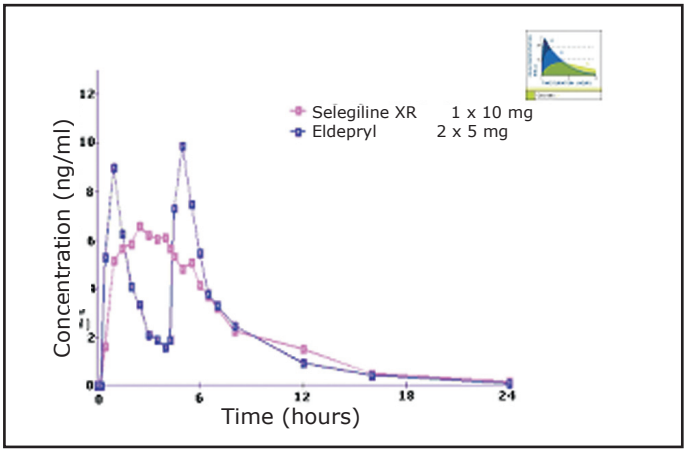

Figure 17 Pharmacokinetics

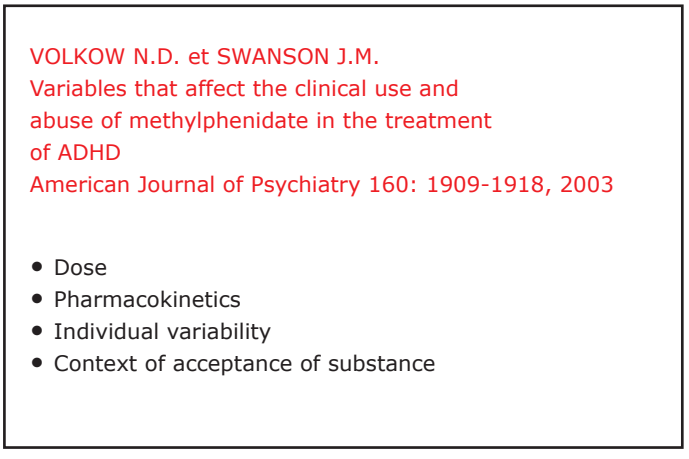

Figure 18 Variables that affect the clinical use and abuse of methylphenidate in the treatment of ADHD

(ADHD) is related mainly to the way the medication was consumed. The risk is low if a steady-state pharmacokinetic situation is reached, for example by using slow-released forms (Fig. 18).

Other discrepancies in the consequence of long-term effects of exposition to psychostimulants are also related to pharmacokinetic characteristics: when they are taken in a continuous way in the purpose of reducing appetite, tolerance appears progressively, and depression is common if patients try to stop the drug. If they are consumed in an intermittent way for there stimulating effects, behavioural sensitization and loss of control develop (Fig. 19).

To summarize (Fig. 20):

- Behavioural sensitization to drugs was first demonstrated by observing the increasing motor response to psychostimulants in animal models;
- This motor effect correlated with a progressive increase of dopamine-release in a mesocorticolimbic pathway currently popularized as the "reward system". As a consequence, the reinforcing effects of drugs increase over time, with a

- Continuous consumption: progressive development of tolerance and frequent appearance of withdrawal manifestations
  - Decrease of catecholamines and mostly dopamine
- Intermittent consumption: behavioural sensitization and loss of control of consumption
  - Increase in the release of dopamine during consumption

Figure 19 Long term use of psychostimulants

- Progressive increase of motor response during repetitive comsumption of psychostimulants
- Parallel increase in the release of dopamine in the «reward system» leading to increase of reinforcing properties of the products and loss of control over consumption
- Cross sensitization between all addictive drugs
- Sensitization increased by exposure to stress factors
- Irreversiblity after continuous consumption due to modification of gene expression?

Figure 20 Behavioural sensitization

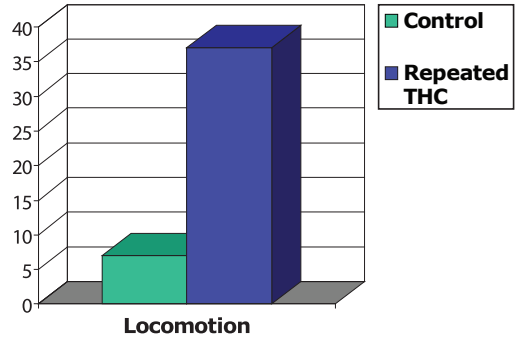

Figure 21a Cross-sensitization

progressive loss of control of the consumption;
- These phenomena are amplified by the simultaneous exposure to stress factors;
- Even if described firstly with psychostimulants, sensitization was recognized for all the addictive drugs; furthermore, a cross-sensitization was demonstrated between all of them.
- Sensitization is poorly reversible, even after long-term cessation of consumption, probably due to a modification of gene expression in neurons.

As an illustration of sensitization and cross-sensization, Cadoni et al. (2001) have shown that the motor response to tetrahydrocannabinol (THC) increased over time in rats and that response to THC was increased if the animal was previously sensitized to morphine. Similarly, the response to morphine was dramatically enhanced if rats were previously sensitized to THC (Fig. 21 a, Fig. 21 b and Fig. 21 c).

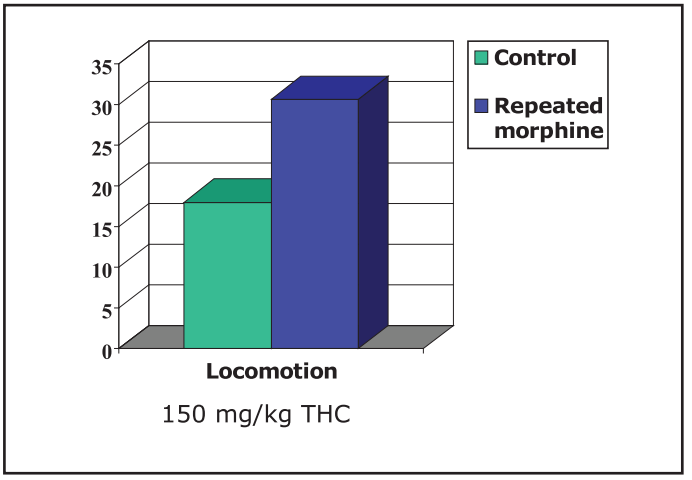

Figure 21b Cross-sensitization

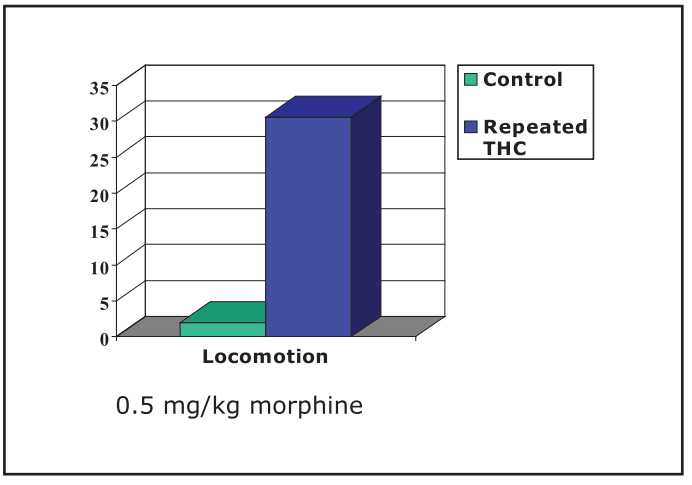

Figure 21c Cross-sensitization

- Tolerance in relation to possible sedative effect of the substance
- Sensibility in relation to stimulative (leading to euphoria) effects of the substance

Figure 22 Repeated consumption of toxicomanogenetic substances

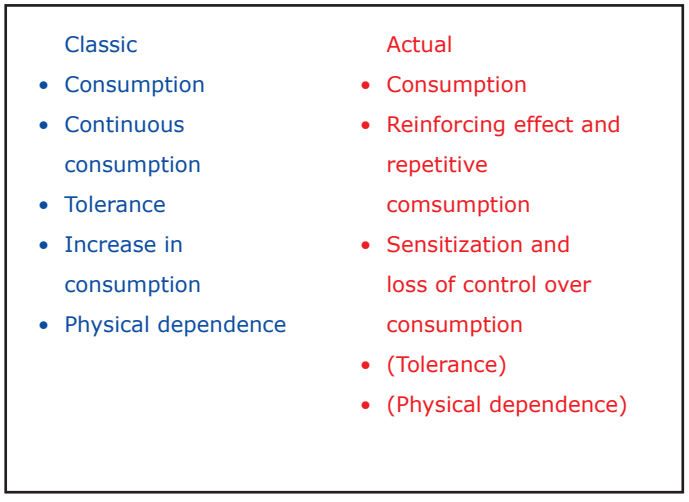

Figure 23 Models of addiction

manifestations, first euphoria and stimulation, and later sedation.

If the substance is consumed repetitively, there is a progressive sensitization toward stimulation and a tolerance for the sedative manifestations (Fig. 22).

As a conclusion, we moved to a new conception of addiction. The repetition of consumption induces a progressive sensitization to the reinforcing effects of drugs. As a consequence, a loss of control of the consumption is more and more pregnant. In addition, for drugs with sedative effects, the development of tolerance and physical dependence can also occur (Fig. 23).

4. Complex models of addiction – sedatives case

Therefore, we have to keep in mind that some addictive drugs have more than a single effect. For substances identified as "sedatives" like opiates and alcohol, there is a sequence of time-scheduled

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Module 1.3
Drug early detection, prevention and treatment

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Key messages

- Early detection needed;
- Clinical experience required;
- Role of associates;
- Detection is part of the treatment process.

Contents

1. Introduction

Detecting the problem of drugs is, in public health, an important but excessively complicated problem. Indeed, highlighting early problems is associated with several obstacles. The first obstacle is without any doubt the access to valuable information. The people likely to identify early drug-related problems (parents, teachers...) do not have up to date information on the topic. Great effort has been put into related web-based information and publications. However we will have to wait at least several years before we can see the effects of these efforts in the behaviours of teachers, parents etc. Another problem lies in the fact that highlighting early drug problems is also a "taboo". Indeed, few people dare to consider that certain problems of behaviours, school failure, etc are related to use/abuse of drugs.

One almost systematically gives up the idea of a problem of drug in preference to other "socially acceptable" causes. So even the well informed, general practitioners, teachers and parents hesitate to consider causes associated with drugs, because this field is stigmatised.

Apart from the lack of information and the problem of stigmatisation involved with psychotropic products, the early detection of drug-related problems is a field comparable with other fields of medicine. From a certain point of view, it is a very developed field. In this chapter we will elaborate on certain tools likely to help the clinician in his every day practice, however clinical experience is the best thing that clinicians can have to face drug-related problems. The every day confrontation with addicted patients is therefore the most important, in order to develop specific competence at this level.

2. Early detection

"Early detection" means highlighting the first clinical signs indicating a morbid tendency related to drugs. These morbid tendencies can appear during adolescence or even earlier. There are some common factors of vulnerability, however each case is to be considered as individually, even if the majority of the patients present identical pattern of problems.

Moreover, the majority of patients are slowly "progressing" in their addiction through stages. These stages can be organised in three categories: testing – non regular use – regular use. These three stages have three different underlying behaviours: the use, the abuse and the dependence. Whatever the physical criterion, it is essential to identify as quickly as possible drug-related problems before they go into the spiral of addiction.

The first "indicator" associated with drug-related problems are the persons acquaintances. It is indeed traditional to consider, from a clinical point of view, that the acquaintances are an

excellent indicator of the problems associated with the consumption of psychotropic substances. If they can feel the problems, it means that they already reached an important level. Therefore a dialogue with the acquaintances is of primary importance. In his daily routine, the clinician must therefore take care to gather the opinion of the close acquaintances of the patient. Thus, the wife/husband, the parents, teachers etc. are the many available resources who can help in better determining a possible problem. As we specified, suspecting a drug problem is sometimes badly accepted by the acquaintances, it will thus be important to approach this problem with precaution and delicacy.

It is also necessary to consider individual rights. Some people use or even abuse drugs and do not wish to be questioned by their acquaintances or their doctor. It is thus necessary to accept that the patient may refuse to admit a problem; there is sometimes a gap of several years between the initial evaluation and the acceptance of the problem, and between these two periods the situation has a tendency to worsen.

In the field of early-detection of drug abuse problems, two schools of thought co-exist. The first advocates the systematic evaluation of psychotropic problems amongst target populations and provides "indicators" of problems. Later these indicators are used to organise public health strategies. The second school considers that evaluation of problems in target groups is a waste of time, because it is not possible to predict which percentage is in need for treatment. This school advocates intervention instead of surveys.

An excellent example of this duality of approach relates to the problems of cannabis in Belgium. Several years ago cannabis use and abuse was identified in Belgium as a growing problem. However, the experts did not find an agreement on its dangerous effect on health. The lack of consensus on cannabis related health problems considerably delayed the development of therapeutic strategies at the national and regional levels. While some researchers tried to quantify the cannabis problem and argued on its potential side-effects, others opened a university-based clinic: "The Cannabis Clinic" (in Brussels). This centre provided information and medical check-ups. Eventually a great number of consumers came to this centre and psycho-medical anomalies were rapidly identified amongst the patients. Therefore "The Cannabis Clinic" helped to clarify the debate concerning the side effects of cannabis consumption while offering a possible option to those interested in their health.

3. Methods of detection

3.1 Acquaintances

As we already specified, the acquaintances remain one of the best signs concerning the existence of problems involved with psychotropic

use and abuse. Often, a spouse, a relative, a friend, takes part indirectly in the development of the problems. In the case of alcoholism one will speak about the Co-alcoholic. The entourage is conscious of the problems even before the patient think about coming to the hospital for help. A problem does not appear suddenly, it develops slowly and the entourage observes, often in silence. It is thus of primary importance to considerer the entourage, to question it, in order to obtain a maximum of information relating to the origin of the disorders and their development.

3.2 The clinical experience

The experience is acquired at the patient's bedside. The specialist develops over time a clinical skill which enables him to identify drug-related problems. There is no specific method, however attentive listening and good history taking should allow, even the absolute beginner, to detect certain signs predictive of a drug-related disorder.

3.3 Tests

There are many methods likely to highlight and to quantify a problem associated with psychotropic substances. Many tests indeed make it possible to quantify in a relatively adequate way a substance-related problem. However, these tests are not very useful for people who did not accept the fact that they have a problem. Denial is an important obstacle which very often makes the tests useless. The patients underestimate their consumption and the associated problems, therefore tests are sometimes useless.

4. Detection and treatment

It is important to specify that it is useless to propose detection if no treatment structure is available. In other words, the installation of specialized treatment centres is a stage which must precede problem-detection. If there are no treatment possibilities, it is of no sense to try to detect problems. The fact is "there are problems everywhere and there is a need for treatment centres everywhere". Detection is thus only one stage in the entire treatment process.

5. Conclusion

It does not matter the way we do it, but, the key point is to identify possible drug-related problems as soon as possible. This early identification will make it possible to set-up an efficient therapeutic program. Some competencies are necessary before being able to treat addicted patients. These competencies must include at least: 1) capacity to identify and quantify drug-related problems (via clinical experience, biological results, tests etc.); 2) capacity to propose adequate treatments according to the identified problems, and recognizing professional limits by re-orienting patients if necessary; and 3) ensure a regular follow-up for the patients.

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Module 1.4
Relapse prevention

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Key messages

- Relapse prevention is part of the treatment;
- Abstinence is the best option;
- Pharmacology and psychotherapy are needed;
- Relapse is part of the treatment process.

Contents

1. Introduction

Relapse prevention is an essential field in the treatment of people suffering from drug abuse or dependence. Indeed, it is not technically difficult to help a patient to interrupt his consumption, it is, however, excessively difficult to control his tendency to relapse. Relapse prevention must therefore be integrated in any programme of treatment. Even if a centre does not have the human resources to organize relapse prevention, it must work together with a structure likely to help the patients after the detoxification. Relapse prevention does not begin from the end of a treatment, it precedes the treatment. In other words, it is essential to evaluate what are the patients' plans after the detoxification, in order to have a good idea of the risks of relapse.

A large majority of the patients are persuaded that they can stop their consumption easily and that there's no need for assistance after their treatment. This clinical consideration is even more obvious with patients who benefit from ultra rapid detoxification. The desire to quickly stop their consumption is very intense but their desire for investing themselves into a program of follow-up is almost nonexistent. It is thus necessary to consider the patient's desire and motivation to invest himself into a programme of follow-up after detoxification.

This stage is initiated by approaching the patient with the concept of abstinence. It is necessary to consider the strategies needed to guarantee long-term success of the treatment. Furthermore, it will be necessary to propose certain ideas likely to be adopted, like directing the patient towards one or the other existing program. In the absence of a follow-up programme, a large majority of the treatment, in the short term, is associated with a high relapse rate.

Sometimes other approaches like the "quality of life" are preferred to the formal notion of abstinence. Thus the quality of life of the patient after his detoxification can be approached from a different angle which considers the relapse as an element of the treatment. The abstinence remains an essential element, but one does not limit oneself to try to maintain the patient in a state "without the product" but to help him to improve the general quality of his life.

Brewer and Streel for this reason proposed a model, which uses the analogy between the development of new skills without drugs with the learning of a new language. They propose an analogy between these two learning process where a set of variables must be controlled in order to guarantee an effective progression. Thus, anxiety, self-esteem, and many other elements must be considered in order to ensure constant progress and completion of the objectives.

Relapse prevention is the first step of a treatment and starts as soon as the therapeutic alliance is formed with

the clinical team. Then it will have to be planned during the treatment programme (weekly meetings, residential program after the cure etc.). Lastly, the prevention of relapses will have to be clearly defined and must integrate both short and long term objectives. These objectives will be regularly evaluated. The prevention of relapses can be achieved by pharmacological and/or psychotherapeutic support.

2. Abstinence

The abstinence is considered, after a period of abusive consumption or addiction, as the maintenance of a state free of the product which was problematic. Thus, an alcoholic, after his detoxification, must avoid consuming alcohol. He is, however, allowed to consume tobacco. The abstinence can concern one or more product. However, it must be decided in agreement with the patient. Indeed, it is useless to prohibit a patient, without using constraining methods, to abstain from a substance if he does not wish it. Some patients after a detoxification programme can use drugs in moderation. However, these cases are rare and abstinence should systematically be recommended to patients after their treatment.

3. The relapse

Relapse is often considered like a failure by the patients. However, relapse is an integral part of the therapeutic process. It confronts the patient with the difficulty of interrupting a regular consumption of psychotropic drugs. If controlled in an adequate way; the relapse can be used to identify the weaknesses of the patients and use them in the establishment of a new therapeutic program.

Each relapse must be clearly understood. Indeed, considering the context and the quality of life, it may happen that a patient has a weakness during his abstinence; he can use drugs one night, without jeopardizing all his previous efforts. Just like a patient who is on a diet and eats chocolate during a family celebration, the alcoholic patient, who drinks one glass, or more, on a precise occasion, and comes back to abstinence the following day, should not feel that his last efforts are destroyed. It is important to differentiate between such weaknesses and a relapse. Relapse must be regarded as the return to the state in which the patient was before the beginning of his treatment. Thus a small variation behaviour of is not a relapse.

4. Pharmacological assistance

Within the framework of a relapse prevention programme there are various pharmacological options likely to help the patient to overcome the craving, but also the consequences related to consumption such as the reinstatement of dependence. Two categories of pharmacological interventions are considered and are generally complementary. On the one hand the treatment which acts on the symptoms related to the abstinence

(anxiety, sleep disorder, craving etc.) and on the other hand, the drugs which protect the patient from a possible relapse. The first category is aimed at relieving the patient of the side effects of detoxification. The second category aims at protecting the patient by an effective blocking of the brain receptors. Thus, naltrexone, an opioid receptors antagonist, is used in order to prevent the reinstatement of dependence. If taken daily, naltrexone by blocking the opioid receptors prevents the opioid agonists from producing any effects. The patient thus benefits from a real chemical protection. Even if he uses drug, it cannot have an effect on him.

Thus, using this approach, a simple weakness does not involve a failure of the entire therapeutic process. All drugs of abuse produce their effect via specific receptors, thus the use of antagonists is limited to certain drugs.

5. Psychological assistance

Counselling forms the basis of the structure of a follow-up program. Patients can benefit from psychotherapeutic support encouraging resumption of responsibility. This support can be individual or collective and must deal with underlying psychological problems which remained silent when the patient used the drug. The best documented collective assistance is undoubtedly the AA groups. Other sub-sections also exist (e.g. narcotic anonymous etc.). The selection of an individual or collective psychotherapy must be decided in agreement with the patient. Some patients are more comfortable in an individual interaction, whereas others need the support that the group psychotherapy will bring to them. In all cases the psychological assistance must be considered as a complement to the global therapeutic program, and the different players (psychiatrists, social workers, etc.) must coordinate their efforts. This multidisciplinary approach is essential.

6. Conclusions

Relapse prevention is an essential element of the global therapeutic program. It must be initiated from the very first meeting with the patient in order to guarantee long term success of the detoxification programme. Relapse prevention is abstinence from the problematic drug and is based on the improvement of the quality of life. Pharmacologic and psychological assistance can be provided in order to support the patient in his efforts.

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Module 1.5
Cocaine characteristics and effects

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Key messages

- Cocaine is the second commonest illicit drug used and the most frequent cause of drug related deaths;
- Cocaine induces a sense of exhilaration by blocking the reuptake of the neurotransmitter dopamine in the midbrain;
- Its use is associated with both acute and chronic complications: neuro-psychiatric, cerebrovascular, cardiac, gastrointestinal, pulmonary, musculo-skeletal, dermatological genitourinary, and obstetric;
- Many cocaine users have little or no idea of the risks associated with its use;
- Patients, health care professionals, and the public should be educated about the dangers and the considerable risks of cocaine use.

Contents

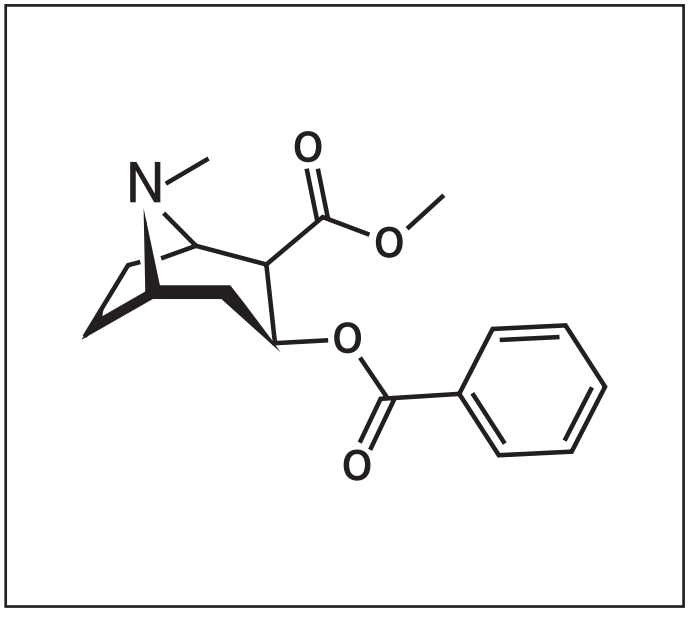

Figure 1 Cocaine, methyl (1R,2R,3S,5S)-3-(benzoyloxy)-8-methyl-8-azabicyclo[3.2.1] octane-2-carboxylate

"Regular cocaine use was associated with an increased likelihood of myocardial infarction in younger patients. Approximately 1 of every 4 nonfatal myocardial infarction in persons aged 18 to 45 years was attributable to frequent cocaine use." Qureshi AI, Suri FK, Guterman LR, et al. Circulation. 2001

"According to different sources 0.5-1.5% of all deaths in US are related to cocaine use" Goldfrank LR et al., Goldfrank's toxicologic Emergencies 2002

1. Introduction

Cocaine is the second commonest illicit drug used and the most frequent cause of drug related deaths.

Cocaine use is associated with both acute and chronic effects, related with loss of productivity, cardiac, cerebrovascular and other complications. Usually cocaine users have no idea of the risks associated with its use.

Cocaine is a powerfully reinforcing psychostimulant. It is a natural alkaloid, extracted from leaves of an Andean shrub, Erythroxylon coca, grown primarily in the Andean region of South America and to a lesser extent in India, Africa and Indonesia.

It has been distributed since many years as an odourless white powder of water-soluble cocaine hydrochloride (HCl) salt for nasal insufflation (snorting) or intravenous injection.

2. History

- Coca leaves have been chewed by South American Indians for many thousands of years to induce a mild and long-lasting euphoria. Coca is believed to be a gift from God;
- Spanish physicians reported the first European use of coca for medicinal purposes in 1596;
- The cocaine alkaloid was first isolated by the German chemist Friedrich Gaedcke in 1855;
- In 1859 Albert Niemann developed an improved purification process of coca extract. He named the alkaloid "cocaine";
- In 1879 cocaine began to be used to

treat morphine addiction;

- In 1884, William Stewart Halsted performed the first nerve block using cocaine as the anaesthetic; Halsted was cocaine addicted physician;
- In 1862 Merck started to produce cocaine for pharmacy;
- In 1886 Coca-Cola introduced cocaine containing laced syrup and caffeine (by John Pemberton); and a drink containing 60 mg of cocaine per serving (230 ml);
- By 1880, Parke-Davis sold a fluid extract containing 0.5 mg/mL of a crude cocaine (Fig. 3);
- In 1895, The Lancet reported a series of 6 deaths associated with cocaine use;
- Coca-Cola removed Cocaine from their formula by 1906;
- The Harrison Narcotics Act of 1914 banned non-prescription use of cocaine-containing products;
- In 1961 the Single Convention on Narcotic Drugs was signed in New York. It banned the production and trade of cocaine, cannabis and opium and its derivatives. It went into effect in 1964.

Figure 2 Publicity of French wine with cocaine in 1863.

Figure 3 Cocaine containing drops and syrups were popular in 19th century

In 1884 Sigmund Freud published the essay "Uber Coca," in which he advocated the use of cocaine in the treatment of asthma, wasting diseases, and syphilis. Freud also developed cocaine dependency.

Figure 4 Sigmund Freud and Cocaine

Former Tour de France winner Marco Pantani ("the Pirate") was found dead in the Italian seaside resort of Rimini

"The death of Marco Pantani was caused by acute cocaine intoxication"

Dr. Giuseppe Fortuni

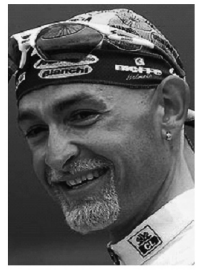

Figure 5 Cocaine and athletes

Cocaine formula - C17H21NO4
Molecular weight: 303.36.
It is available in two forms:

- Cocaine hydrochloride salt, which is prepared by dissolving the alkaloid in hydrochloric acid. It is water soluble powder; thermolabile (decomposes when heated). It can be taken orally, intranasally, or intravenously;
- Cocaine free base is manufactured by processing the cocaine with ammonia or sodium bicarbonate. It is a heat stable form, melting at 98°C, which allows it to be smoked. Cocaine free base is named "crack" because of the popping sound it makes when heated. Crack cocaine is considered the most potent and addictive form.

Biological half-life of cocaine is around 0.5 – 1.5 hours. Cocaine is metabolised to norcocaine, benzoylecgonine and ecgonine methyl ester by hepatic and plasma cholinesterase and also by non-enzymatic hydrolysis.

3. Chemical structure

Cocaine, beta-cocaine, benzoylmethyl-ecgonine.
Chemical name (IUPAC): methyl (1R,2R,3S,5S)-3-(benzoyloxy)-8-methyl-8-azabicyclo[3.2.1] octane-2-carboxylate

The excreted amount of nonmetabolized cocaine is relatively small.

4. Administration

Cocaine was applied as the hydrochloride salt in a 40 or 100 mg/mL solution as a local anaesthetic: in ear, nose and throat

surgery. The arrythmogenic potential of cocaine has led to the decline in its use as an anaesthetic.

Cocaine users administrate it by smoking, nasal insufflation, or intravenous injection.

It has been distributed as a water-soluble hydrochloride (HCl) salt for nasal insufflation (snorting) or intravenous injection ("mainlining"). Subcutaneous or intramuscular injections are rarely used because vasoconstriction slows the absorption.

Cocaine users typically smoke "crack" (basic cocaine) in a glass pipe. Cocaine is rapidly absorbed through the respiratory tract flowed by quick penetration into the brain; the effects appears in 0.5-3 minutes. Smoking cocaine delivers the substance to the circulation within seconds to minutes. Smoking of cocaine produces an almost immediate intense experience and will typically produce effects lasting 5-15 minutes.

Cocaine hydrochloride can be smoked to some effect but this is very inefficient as the powder tends to burn rather than vaporize.

Snorting (insufflation/ intranasal) is also popular. After nasal insufflation of cocaine powder, 2 concentration peaks are observed – after 10 and 45 minutes. The first peak is due to fast resorption, while the second peak is probably caused by secondary resorption in the gastrointestinal tract. Insufflation results in approximately 30 to 60% of the drug being absorbed. Compared to smoking, insufflated cocaine has slower absorption, but compared to ingestion, the absorption is faster.

Chronic use results in ongoing rhinitis and necrosis of the nasal membranes. Many users report a burning sensation in the nares (nostrils) after cocaine's anasthetic effects wear off.

Since cocaine hydrochloride is well absorbed through all mucous membranes, abusers may achieve a high blood concentration by means of intranasal, sublingual, intravaginal, or rectal administration.
Orally administered cocaine takes approximately 30 minutes to enter the bloodstream. Typically, about 30% (up to 60%) of an oral dose is absorbed. Maximum physiological and psychotropic effects are attained approximately 60

Table 1 Pharmacokinetics of cocaine according to the route of administration

ROUTE OF ADMINISTRATION	*ONSET OF ACTION*	*PEAK EFFECT*	*DURATION OF ACTION*
Inhalation (smoking)	*3–5 sec*	*1–3 min*	*5–15 min*
Intravenous	*10–60 sec*	*3–5 min*	*20–60 min*
Intranasal or other mucosal	*1–5 min*	*15–20 min*	*60–90 min*
Oral administration	*20-30 min*	*60 min*	*1-2 hours*

* adopted from Lange RA, Hillis LD. 2001

minutes after cocaine is administered by ingestion. General effects will persist for 1-2 hours depending on the dose.

"Mate de coca" or coca-leaf tea is a traditional method of consumption and is often recommended to treat altitude sickness. This method of consumption has been practiced for thousands of years by South American natives, particularly to reduce fatigue in messengers who made multi-day travels to other settlements.

Injected cocaine provides the highest blood levels of drug in the shortest amount of time. Upon injection, cocaine reaches the brain and produces an effect within 15-30 seconds, and the exhilarating rush that follows can be so intense that it induces some users to vomit uncontrollably. In a study of cocaine users, the average time taken to reach peak subjective effects was 3.1 minutes. The euphoria passes quickly.

An injected mixture of cocaine and heroin, known as "speedball" or "moonrock", is a popular and dangerous combination. The converse effects of the drugs mask the symptoms of an overdose.

Cocaine water soluble metabolites, including benzoylecgonine are excreted in the urine, which remains positive for cocaine metabolite within 48 – 72 hours, providing an indicator of recent cocaine use (about 80% of these metabolites are eliminated with urine over 24 hours).
Norcocaine is formed by an N-demethylation reaction, and represents less than 5% of the total quantity of cocaine metabolites.

It may mediate delayed effects of cocaine via enterohepatic recirculation. Cocaine metabolites can be found in hair and nails of cocaine users for up to several months.

The rate of metabolism depends on several factors: circulation, cholinesterase activity, duration of cocaine use.

5. Pathophysiology and mechanism of action

Cocaine is a strong CNS stimulant that interferes with uptake and metabolism of norepinephrine, dopamine, serotonin, and acetylcholine.

Cocaine also increases the release of catecholamines from central and peripheral stores.

Cocaine inhibits membrane permeability to sodium during depolarization and thus acts as a local anaesthetic by blocking the initiation and transmission of electrical signals.

The most important pharmacological actions of cocaine are blocking the initiation or conduction of the action potential following local application to a nerve and stimulating the CNS.

Cocaine acts as a powerful sympathomimetic agent. It blocks the presynaptic reuptake of norepinephrine and dopamine producing high level of these neurotransmitters at the post-synaptic receptors.

The significant effect of cocaine on the central nervous system is the blockage of the dopamine transporter protein (DAT), for this reason cocaine is called an inhibitor of a dopamine reuptake. Ventral tegmental area and the substantial nigra are regions rich in dopaminergic neurons (Fig. 6). The effects of cocaine on dopaminergic neuronal systems are suggested to be involved in producing euphoria and addiction.

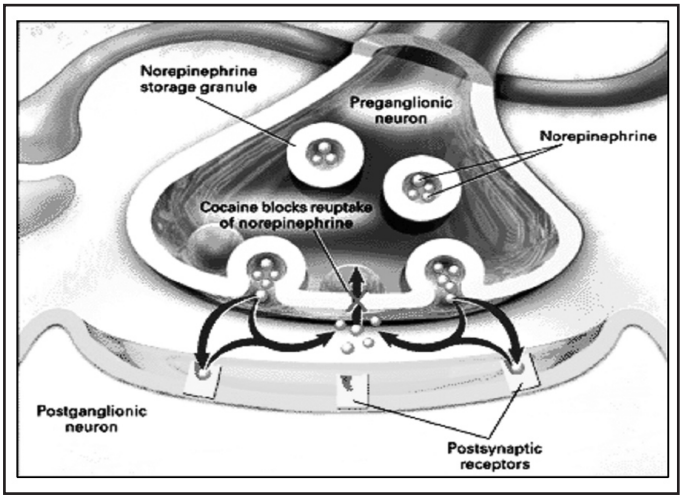

Figure 6 By blocking presynaptic reuptake of the neurotransmitters norepinephrine and dopamine, cocaine increases the quantity of neurotransmitters at the postsynaptic receptor sites.

The resultant activation of the sympathetic nervous system produces an acute rise in arterial pressure, tachycardia, and a predisposition to ventricular arrhythmias and seizures. Sympathetic activation also may result in mydriasis, hyperglycemia, and hyperthermia.

Acute cocaine administration increases extraneuronal dopamine and phosphorylation of dopamine- and cAMP-regulated phosphoprotein (M(r) 32 kDa) in striatal and cortical areas. It was found that novel palatable food consumption increases extraneuronal dopamine in the same areas.

The effects of cocaine on dopaminergic neuronal systems are suggested to be involved in producing euphoria and addiction.

Long-term use of cocaine leads to homeostatic dysregulation of dopaminergic signalling via down regulation of D1 receptors, leading to enhanced signal transduction. These decreased dopaminergic signalling may contribute to depressive mood disorders and sensitize this important brain reward circuit to the reinforcing effects of cocaine. The alterations in dopamine neurotransmission may be responsible for the development of compulsive use patterns.

Cocaine interferes with the uptake of norepinephrine and serotonin (5-HT), although it is less potent blocker of the norepinephrine transporter (NET) and serotonin transporter (SERT).

The stimulation of glutamate receptors (GLUR) plays a relevant role in the

development of behavioral sensitization to cocaine. It was observed that rats sensitized to cocaine presented a significant increase in the levels of GLUR1, NR1 and NR2B, in the nucleus accumbens, and of NR2B in the hippocampus compared to control animals. Cocaine sensitization is clearly dependent on NMDA receptor activity.

With regular use, moreover, neuroadaptive mechanisms result in development of tolerance, reverse tolerance (i.e., behavioural sensitization), and dependence.

When discovering long term effects of cocaine use in rats there was found increase of production of genetic transcription factors – activating immediate early genes (IEG), including ΔFosB. The altered gene activity change production of potentially many proteins; e.g. cyclin-dependent kinase-5 (CDK5), which promotes nerve cell growth and sprouting of new dendrites and dendritic spines (Fig. 7).

ΔFosB is naturally present in small quantities in the cells of the nucleus accumbens (NAc). Chronic administration of cocaine has recently been shown to increase ΔFosB in several brain regions, such as the frontal cortex and amygdala. The accumulations of ΔFosB are much smaller in these regions than those that cocaine causes in the NAc.

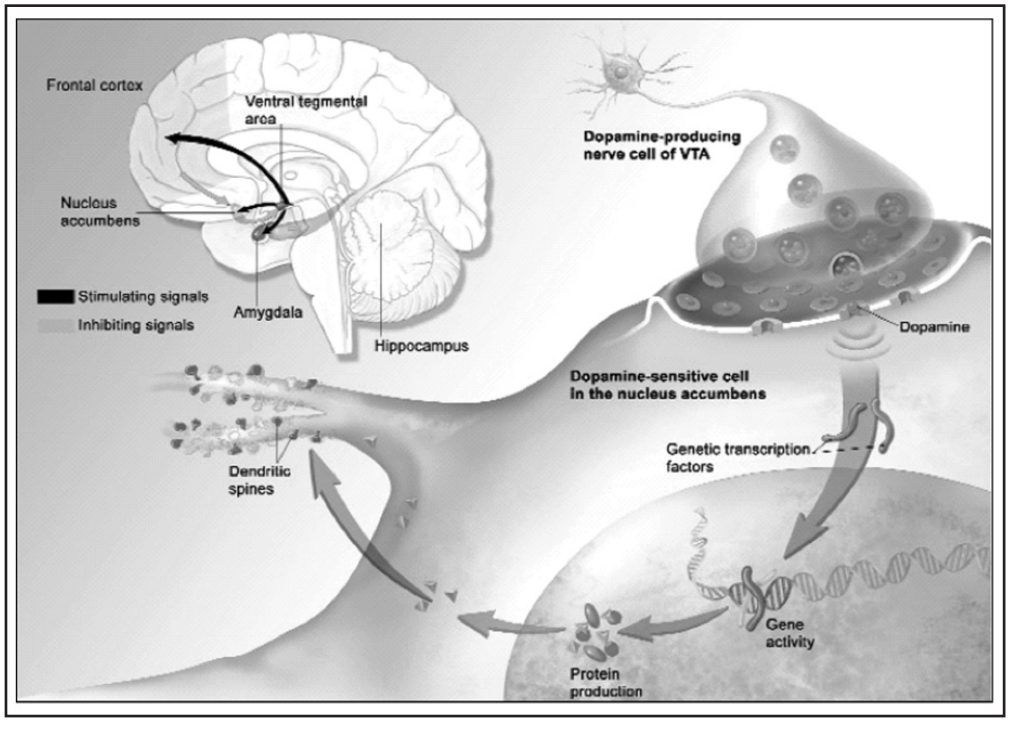

Figure 7 Short-term and the hypothesis for long-term effects of cocaine. (Nestler, E.J, 2005)

There is a speculation, that the presence of ΔFosB in the frontal cortex may contribute to the loss of frontal cortex control over cocaine urges that is seen in addiction.

On Figure 7 there is a possible explanation of cocaine effects. Cocaine causes euphoria in the short term and addiction in the long term via its effects on the brain's limbic system, which consists of numerous regions, including the ventral tegmental area (VTA) and nucleus accumbens (NAc), centres for pleasure and feelings of reward; the amygdala and hippocampus, centres for memory; and the frontal cortex, a centre for weighing options and restraint.

Cocaine causes the neurotransmitter dopamine to build up at the interface between VTA cells and NAc cells, triggering pleasurable feelings and NAc cellular activities that sensitize the brain to future exposures to the drug.

Cocaine affects the expression of numerous genes within the NAc, including some that influence the important neurotransmitter chemical glutamate and the brain's natural opioid-like compounds. An overstimulation of D1 receptors has major implications such as the progressive modifications of intracellular second messengers and finally of gene expression.

As a consequence, long term modifications of neurotransmission are induced through e.g. the release of increasing amounts of some neuropeptides. The time courses of cocaine-induced buildup of ΔFosB and cocaine-related structural changes (dendrite sprouting) suggest that these neurobiological effects may underlie some of the drug's short-term, medium-term, and long-term behavioral effects.

6. Tolerance, dependence and withdrawal effects

Cocaine is a powerfully addictive drug of abuse and an appreciable initial tolerance to the euphoric high may develop. Cocaine is psychologically addicting, particularly with heavy or frequent use, and possibly physically addicting as well. The short duration of effects is one reason leading to probability of addition.

As effects wear off, more drugs are frequently administered and a pattern of repeated use occurs. Following binge use of cocaine, the "crash" can last from 9 hours to 4 days and may consist of agitation, depressed moods, insomnia to hyper somnolence, and initial drug craving. Withdrawal symptoms can typically last from 1-3 weeks and may consist of alternating low and high drug craving, low to high anxiety, paranoia, dysphoria, depression, apathy, irritability, disorientation, hunger, fatigue, bradycardia, and long periods of sleep.

7. Effects of cocaine

7.1 Short term effects

Physiological: increased heart rate and blood pressure, increased body temperature, dilated pupils, increased light sensitivity, constriction of peripheral blood vessels, rapid speech, dyskinesia, nausea, and vomiting.

Psychological: euphoria, excitation, feelings of well-being, general arousal, increased sexual excitement, dizziness, self-absorbed, increased focus and alertness, mental clarity, increased talkativeness, motor restlessness, offsets fatigue, improved performance in some simple tasks, and loss of appetite.

Higher doses may exhibit a pattern of psychosis with confused and disoriented behaviour, delusions, hallucinations, irritability, fear, paranoia, antisocial behaviour, and aggressiveness.

Overdose of cocaine: convulsions, hyperthermia, and coma.

7.2 Long term effects

Psychological: addiction, irritability, mood disturbances, depression, agitation, nervousness, drug craving, paranoia, general CNS depression, fatigue, insomnia.

Physiological: Itching / picking / scratching, normal heart rate, normal pupils.

8. Complications

- Neuropsychiatric complications;
- Neurological: seizures, migraine, cerebral infarction, and intracranial haemorrhage;
- Cardiac: myocardial ischemia, coronary artery spasm, acute myocardial infarction (MI), atherosclerosis, myocarditis, cardio-myopathy, arrhythmia, hypertension, and endocarditis;
- Gastrointestinal: mesenteric ischemia or infarction, perforation;
- Pulmonary: pulmonary oedema, pulmonary infarction, and haemoptysis;
- Genitourinary and obstetric: renal and testicular infarction, abruptio placenta, spontaneous abortion, prematurity, and growth retardation;
- Musculoskeletal and dermatological: rhabdomyolysis, skin ischemia, superficial and deep venous thrombosis, and thrombophlebitis.

8.1 Neuropsychiatric complications

Neuropsychiatric complications occur in about 40% of cocaine users. Psychiatric disturbances include depression, suicidal ideation, paranoia, kleptomania, violent antisocial behaviour, catatonia, and auditory or visual hallucinations. Hallucinations occurring with cocaine intoxication can be simple or complex, affecting various sensory categories (e.g. visual, auditory, cutaneous, visceral, cenesthesic), and may be associated with delusions of persecution.

A moderate proportion of addicts develop panic attacks, which are different from primary panic attacks in that cocaine users frequently have psychosensory symptoms, infrequent agoraphobia, hypersensitivity to caffeine, untoward responses to antidepressants, partial improvement with alprazolam, and marked recovery with clonazepam or carbamazepine.

8.2 Convulsions and seizures

Convulsions occur in about 3% of cocaine users. Convulsions caused by cocaine can be generalized or partial, simple or complex.

Cocaine use is associated with seizures. They can be induced in some persons by small quantities of cocaine by different routes of administration. The majority of seizures induced by intravenous or crack cocaine are single, generalized, not associated with any lasting neurological deficits.

The multiple seizures induced by nasal insufflation of cocaine are associated with an acute intracerebral complication or use of other drugs. After intoxication has passed, these individuals do not require long-term anticonvulsant therapy. Seizures caused by cocaine use are associated with cerebral lesions or with interictal EEG abnormalities.

8.3 Cerebrovascular disorders

Cerebrovascular disorders include arterial and venous complications. Arterial complications include either ischemic or hemorrhagic strokes. Hemorrhagic events could be intraparenchymal or subarachnoid. When neurological symptomatic is present, the imaging diagnostics shows neurological abnormalities in almost 70- 80% of cases.

Haemorrhage occurs within a few minutes/or in the first hour, although it may occur within seconds of cocaine use or may lag cocaine use by as long as 10 hours. It occurs about twice more often than ischemia.

This corresponds well with the increased systolic blood pressure seen in these patients.

Ruptures of multiple mycotic aneurysms and large-vessel thromboses have been described.

8.4 Cardiac complications (see Module 2.2 Cocaine cardiotoxicity)

Cocaine use has been associated with both acute and chronic cardiovascular diseases. These include acute myocardial infarction, myocardial ischemia (both silent ischemia and ischemia associated with angina), and acceleration of the development of atherosclerosis, myocarditis, cardio-myopathy (both dilated and hypertrophic), arrhythmias, hypertension, aortic dissection, and endocarditis.

The risk of acute myocardial infarction is highest within the first hour after cocaine use and then rapidly declines. However, some reports suggest that myocardial

infarction can occur as early as minutes after cocaine administration or as late as a few days afterward.

There is no clear relation between the dose of cocaine and the occurrence of an acute coronary event. Myocardial infarction may develop in first-time users, occasional users, and long-term users. Electrocardiographic abnormalities occur in 90 percent of patients with cocaine-induced myocardial infarction and include ST-segment elevation, T-wave inversions, and Q waves. Measurement of cardiac troponin may be superior to measurement of creatine kinase in making the diagnosis.

8.5 Muscular disorders

In regions of the world with warm climates, cocaine-intoxicated patients in emergency rooms may show rhabdomyolysis. These patients have blood CK values exceeding 12,000 U/L. More than one third of these patients develop severe kidney insufficiency with hypotension, hyperpyrexia, disseminated intravascular coagulation, hepatic dysfunction, and CK values greater than 30,000 U/L. Dialysis is indicated in such patients.

The pathogenesis of rhabdomyolysis remains obscure and speculative.

Probably because of dopamine depletion, administration of neuroleptics in agitated long-term cocaine users can worsen the clinical picture and cause development of malignant hyperthermia. These patients should be treated with a dopaminergic agonist (e.g. bromocriptine) and not with neuroleptics.

8.6 Complications in pregnancy and newborns

Women using cocaine have higher number of spontaneous abortions, premature births, and placenta previa than nonusers. Babies born to these mothers exhibit significant depression in behaviour and response to stimuli. Intrauterine foetal growth may be retarded; microcephaly, small-for-date birth weights, convulsions, infarcts, cerebral haemorrhages, hypertonicity, motor restlessness, and absence of saccadic movements on oculovestibular stimuli are more common than in newborns of mothers who do not use the drug.

Congenital malformations are postulated to result from foetal ischemia during the first trimester, and occlusive stroke is a consequence of ischemia during the third trimester.

Respiratory anomalies in newborns are more noticeable during sleep. Severe respiratory difficulty syndromes and failures of the awakening mechanism have been documented. Sonography, CT scan, and MRI revealed cortical infarcts and midline congenital malformations in 15% of infants born to mothers who used cocaine.

9. Medical Care

Acute intoxication requires hospitalization for detoxification and management of acute neurovascular complications.
For long-term management, drug-dependence programs can be effective in decreasing drug use by behavioural interventions. Cognitive behavioural therapy can be effective in decreasing craving for the drug.

Patients require follow-up for neurological complications.

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Module 1.6

Toxicity and abuse of anabolic androgenic steroids

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Key messages

- The use of anabolic androgenic steroids (AAS) has increased substantially over the past two decades;
- There are several classes of steroids (more than 100 different forms) that were developed to achieve a remarkable anabolic effect, to promote muscle growth, increase lean body mass, and stimulate fat loss;
- There are many adverse effects of AAS use;
- In men these include: testicular atrophy, decreased testosterone production, gynecomastia, hypertension, fluid retention, tendon injuries, sleep disorders, etc;
- In women: decreased breast size, irregularities of the menstrual cycle, facial hair growth, fluid retention, hypertension, sleep disorders;
- The psychiatric effects: major mood disorders including depression and mania.

Contents

1. Classes of AAS

Anabolic steroids are synthetic analogues of testosterone. They promote muscle growth, increase lean body mass, and stimulate fat loss. Non-medical use of anabolic steroids and other substances has a long history of efforts to enhance athletic performance.

Anabolic androgenic steroids originally are designed for therapeutic purposes to provide enhanced anabolic (tissue-building) potency with negligible androgenic (masculinizing) effects (Fig. 1). AAS shift the nitrogen equilibrium to the positive side for better utilization of ingested protein and the increased retention of nitrogen. AAS compete for glucocorticoides receptors, resulting in an anti-catabolic effect by blocking the protein synthesis inhibition which physiologically occurs after exercises due to glucocorticoides liberation.

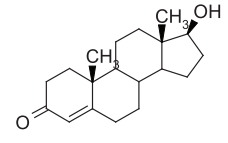
Anabolic Activity

- Development of muscle mass
- Reverse catabolic or tissue-depleting processes

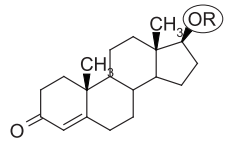
Androgenic Activity

- Growth and development of male sex organs
- Important for male sex drive and performance
- Development of secondary sexual characteristics
- Important role in spermatogenesis

Figure 1 Anabolic and androgenic activities



Testosterone (injectable)



Testosterone esters (injectable)

R = $COCH_2CH_3$ propionate
R = $CO(CH_2)_5CH_3$ enanthate
R = $COCH_2CH_2(C_5H_9)$ cypionate

Figure 2 Structure of testosterone and androgens, class 1

Over 100 different distinct AAS have been reported that vary in their chemical structure, their metabolic fate and physiological effects that could be classified as soluble and insoluble, injectable and oral preparations, and according to their chemical structure.

Three main classes of AAS have been described. The first class, is derived from esterification of the 17 β-hydroxyl group of testosterone propionate, cypionate, ethanate. Correspondingly, there are testosterone propionate (TP), testosterone cypionate (TC) and testosterone ethanate (TE) which are used primarily as injectable forms (Fig. 2). Esterification retards degradation and prolongs the duration of action after injection of the hormone by slowing its release into circulation.

Metabolism includes (Fig. 3):

- hydrolysis to testosterone;
- reduction to 5α-dihydrotestosterone (DHT)- an androgen with higher biological activity at brain androgen receptors (AR) than testosterone;
- aromatization to estrogens.

The second class of AAS androgen esters (Fig. 4) called 19-nor-testosterone derivatives (nor means a lack of a methyl group) includes: Nandrolone decanoate (Deca-Durabolin) and Nandrolone phenpropionate (Durabolin).

They are used primarily as injectable compounds. The substitution of methyl group for hydrogen atom at position C19 extends the half-life of this class of AAS beyond that contributed by esterification alone. It should be noted that nandrolone decanoate has reduced androgenic activity at the androgen receptor compared to dihydro-testosteron.

Metabolism includes:

- hydrolysis to testosterone;
- reduction;
- aromatization to 17β-estradiol, is the actions of their estrogenic metabolites at brain estrogen receptors.

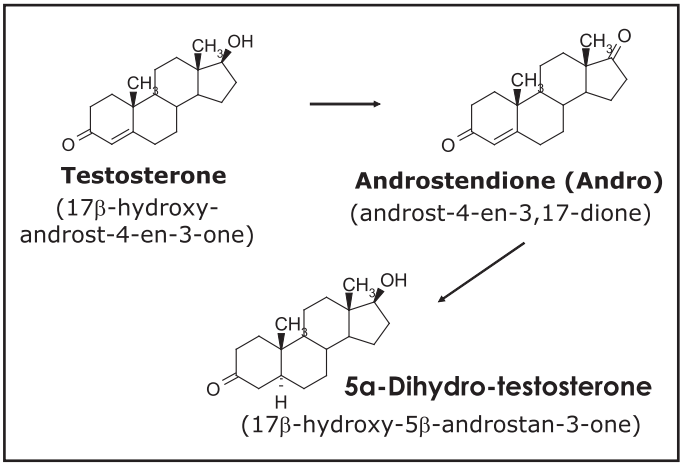


Figure 3 Metabolism of androgenic steroids

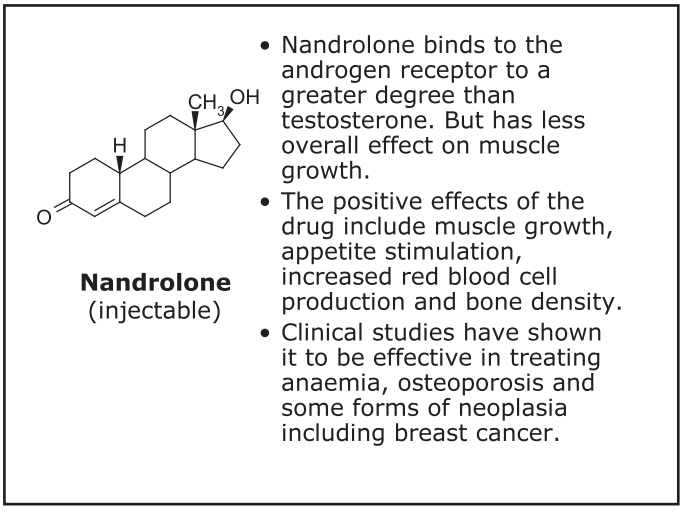


Figure 4 Nandrolone

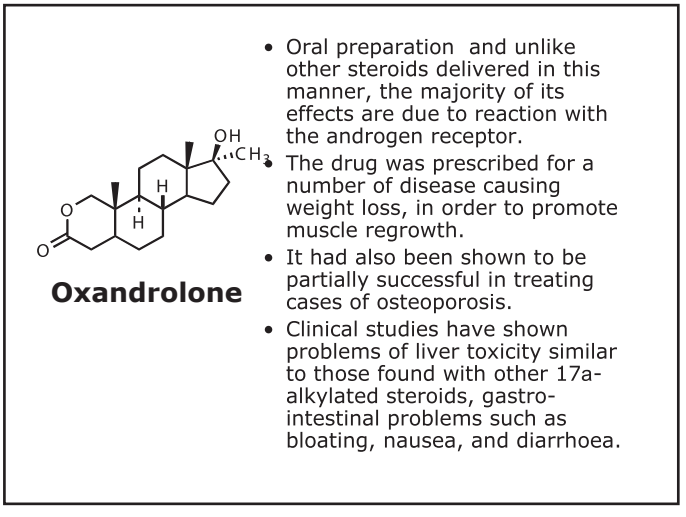


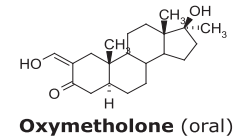
Figure 5 Oxandrolone

To the third class of AAS belong steroids that are alkylated at C17 (Fig. 5 and Fig. 6) such as 17α-methyltestosterone, oxymetholone, methandrostenolone, and stanozolol. The alkylation retards metabolism of these AAS, so they could be applied orally.

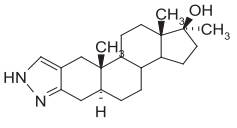
Metabolism: into dihydrotestosterone, 17β-estradiol, although other androgenic and estrogenic metabolites may be formed.

2. Mechanism of action

The diversity in the chemical nature and metabolic fate of the AAS provides these compounds with complex signalling capabilities along diverse pathways.



Oxymetholone (oral)



Stanozolol (oral)

- Unlike most injectable anabolic steroids, Stanozolol is not esterified. The drug has also an oral application and large bioavailability, due to a C17 a-alkylation which allows the hormone to survive first pass liver metabolism when ingested.
- Stanozolol has been used on both animal and human patients for successful treating of anaemia and hereditary angioedema.
- Ben Johnson was stripped of his gold medal in the 100 meter sprint at the 1988 Summer Olympics when he controversially tested positive for this drug after winning the final.

Figure 6 Oxymetholone and Stanozolol

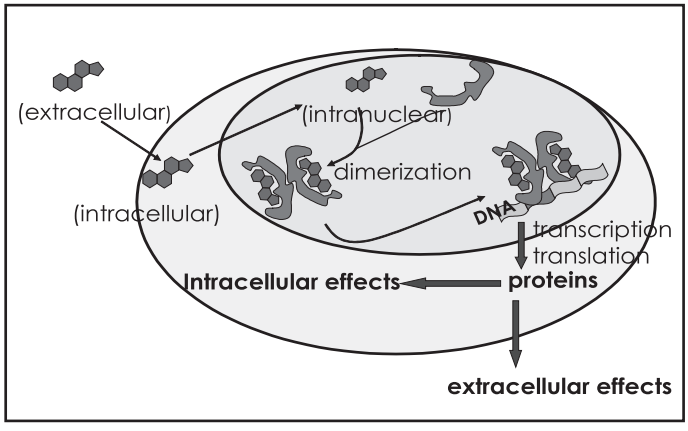


Figure 7 Overall mechanism of steroid hormone action

AAS are biologically active at the AR (Fig. 7). Since the AAS can be aromatized to estrogenic metabolites, ER – along with AR – signaling mechanisms could be involved in mediating the biological actions of AAS. The 17-alkylated AAS also bind to a non-AR/ER microsomal binding site, indicating that these synthetic steroids may also elicit rapid signaling via steroid receptors that are distinct from the classical nuclear receptors. AAS can elicit rapid changes in neuronal signaling via allosteric modulation of ion channels.

The diversity of metabolic effects depends on sex, age and developmental stage. One of the ultimate effects is an increasing protein synthesis. The effects are determined by the type and quantity of receptors and enzymes controlling steroid metabolism

in a given organ. The structure of androgen receptors appears to be identical in muscle and other organs. Anabolic steroids show an anticatabolic effect by improving utilization of protein and by inhibiting the catabolic effect of glucocorticoids. By increasing the athlete's aggressiveness, producing euphoria, or decreasing the athlete's sense of fatigue during training, AAS lead to gains in strength.

- Administration of AAS may occur through multiple routes and often in combination (stacking).
  - Intramuscular injection, orally, and in gels or creams that are rubbed on the skin.
- Self-administration is common and often occurs in a regimented pattern. User cycles may last between 4 and 12 weeks, with "off-cycles" occurring between using periods.
  - Athletes using AAS (doping) cycle during training and compete in the off-cycle in hopes of circumventing drug tests.
- AAS may be used in combination with accessory drugs and dietary supplements to maximize results.

Figure 8 Methods of AAS use

These psychological effects may allow a higher intensity and longer duration of training (Fig. 7).

3. Medication

"Steroids" refers to the class of drugs, which are available legally only by prescription. AAS were originally developed for the treatment of hypogonadal dysfunction in men, initiation of delayed puberty, and growth. They continue to be used today for these treatments. They are also prescribed to treat body wasting in patients with HIV/AIDS and other diseases that result in loss of lean muscle mass: chronic conditions including cancer, severe burns, anaemia, hepatic and kidney failure, breast cancer, and hereditary angioedema. Abuse of anabolic steroids, however, can lead to serious health problems, some irreversible.

4. Administration and doses

Anabolic steroids can be taken: orally, injected into the body, or rubbed in the skin in the form of a gel or cream (Fig. 8).

The "orals" are ingested tablets or capsules. The injectable forms are known as "oils" or "waters". The "waters" are short-acting forms: they work much faster and are eliminated much more quickly. The "oils" refer to the long-acting types. They are injected into a muscle, usually the buttocks, and the steroid is released slowly over time. Typically, these drugs are injected only a couple of times a week.

Doses taken by abusers can be 10 to 100 times higher than the doses used for medical conditions. The normal prescribed daily dose for medical

purposes usually averages between 1 and 5 milligrams. Some athletes, self-administers of AAS have been reported to use concentrations that reflect 10–100× therapeutic replacement doses of testosterone (10–400 mg/day) far exceeding medically recommended dosages. As the injectable forms are less hepatotoxic than oral, they are favoured by users. However, the oral preparations tend to be cleared more rapidly from the system and may be preferred when drug testing is anticipated.

4.1 Cycling, stacking, and pyramiding

AAS users frequently use a combination of oral and injectable drugs during 4- to 12-week cycles, sometimes in combination with other drugs such as stimulants, depressants, pain killers, anti-inflammatories, and other hormones. The simultaneous use of multiple steroid preparations is called "stacking," and the pattern of increasing a dose through a cycle is referred to as "pyramiding." They escalate steroid use by increasing the number of steroids or the dose and frequency of one or more steroids used at one time, reach a peak amount, and then gradually reduce the dose toward the end of the cycle.

Stacking and pyramiding are intended to maximize steroid receptor binding and minimize toxic side effects. The fact that these benefits have not been substantiated scientifically has not appreciably influenced dosing patterns. Many users "cycle," taking the drugs for 6 to 12 weeks or more, stopping for several weeks and then starting another cycle. It is not uncommon for athletes to cycle over a period of months or even years. They may do this in the belief that by scheduling their steroids intake, they can manipulate test results and escape detection.

4.2 Complex use of drugs

The use of accessory drugs in combination with AAS aiming to enhance anabolic effect, fat loss or reduce side effects of AAS: growth hormone (GH), human chorionic gonadotropin (HCG), insulin like growth factor (IGF-1), thyroxine and insulin as adjuvant anabolic agents has increased.

Of about 25% of the steroid users admit to the unsupervised use of both GH and insulin. The anabolic effects of GH on target tissues are not direct, but are the result of increased production of IGF-1 in the liver and peripheral tissues. Some of AAS users use recombinant injectable IGF-1 preparations. In addition to the effects mediated by IGF-1, GH is a powerful stimulant of lipolysis in central and peripheral adipose cells. The anabolic effect of insulin is manifested by an artificially induced hyperinsulinemic state that increases amino acid transport into muscles inhibiting protein breakdown and stimulating overall bulk protein synthesis. Long-term GH administration in normal individuals may lead to cardiac instability, hypertension, development of insulin resistance, and possibly type 2 diabetes.

Clomiphene, antiaromatases, and tamoxifen, are among the accessory drugs taken. Clomiphene and HCG are commonly used to reverse the endogenous testosterone suppression experienced by users, in an effort to "kick start" natural hormone production at the end of a steroid cycle and reverse testicular atrophy. Tamoxifen and antiaromatase medications block or alleviate the symptoms of gynecomastia that result from the aromatization of testosterone to estrogen. The unsupervised use of insulin, diuretics, stimulants, and thyroxine can precipitate a number of medical emergencies.

5. Effects

Anabolic steroid abuse has been associated with a wide range of adverse side effects.

AAS interfere with endogenous hormone levels, hormone metabolism and hormone signalling, thus producing variable effects. Some of them are reversible, when the user stops the AAS.

The best documented physiological effects are those on the liver, serum lipids and reproductive system. Increased

Figure 9 Signs and symptoms

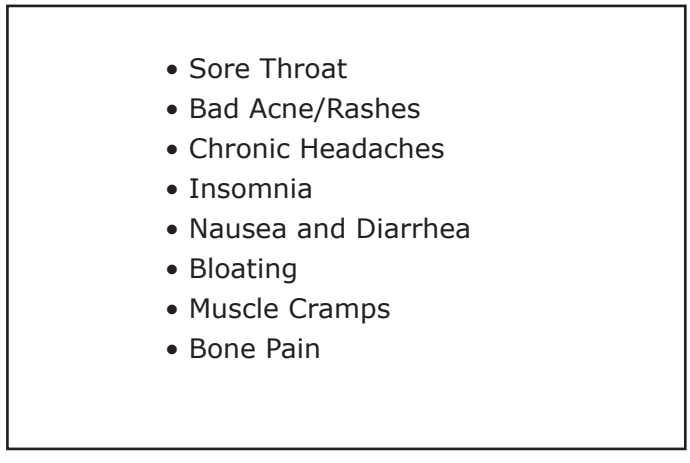


Figure 10 Short term physical effects

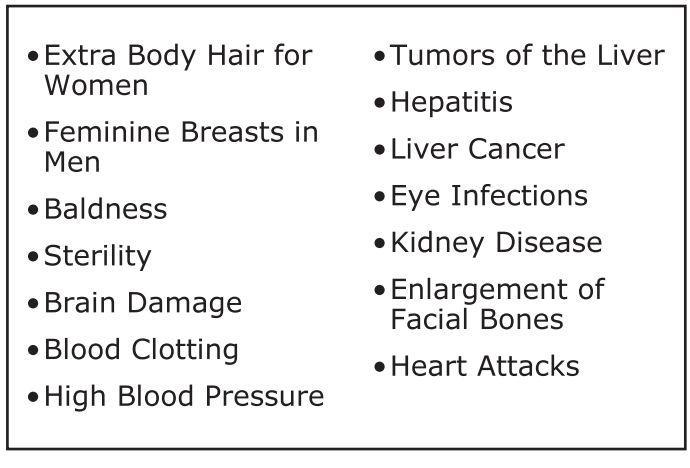
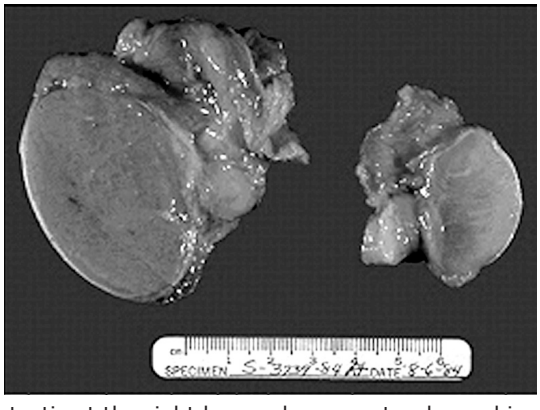


Figure 11 Long term physical effects

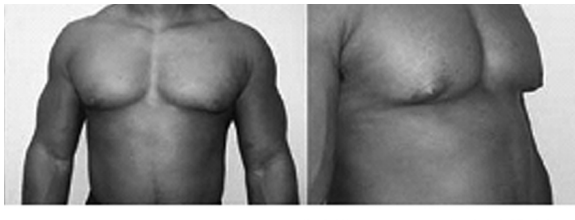
- Aggressive, and sometimes homicidal, attitude "Roid Rage"
- Chronic Depression
- Loss of Memory
- Excessive Sexual Arousal
- Loss of Interest, lack of concentration

Figure 12 Psychological effects



The testis at the right has undergone atrophy and is much smaller than the normal testis at the left. Use of anabolic steroids diminishes testosterone levels and leads to testicular atrophy that diminishes sexual function.

Figure 13 Testicular atrophy



The breast tissue excised from a male with gynecomastia.

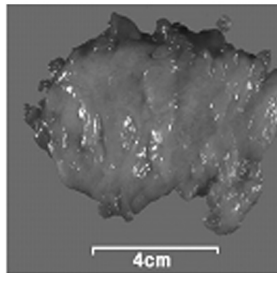


Figure 14 Gynecomastia

levels of irritability, aggression, personality disturbance and psychiatric diagnoses are among some of the adverse psychological effects of AASs (Fig. 9, Fig. 10, Fig. 11 and Fig. 12).

Steroid use decreases the glucose tolerance, while there is an increase in insulin resistance. These changes mimic Type II diabetes. These changes seem to be reversible after cesation of the drugs.

In the literature sleep apnea has been reported, which has been also associated with AS-induced increase in hematocrit, leading to blood stasis and thrombosis.

6. Complications in different organs

Steroid abuse disrupts the normal production of hormones, causing both reversible and irreversible changes.

6.1 Male reproductive system

AAS are derivatives of testosterone, which has strong genitotropic effects. In mature males, the body secretes 2.5-10 mg of testosterone each day to promote various

body processes. Steroid users often introduce up to an additional 100 mg of testosterone into the system daily. It leads to supra-physiological concentrations of testosterone or testosterone derivatives. When levels become too high, the body's own production of the testosterone is shut down. Via the feed back control, the production and release of luteinizing hormone (LH) and follicle stimulation hormone (FSH) is decreased. Prolonged use of AAS in relatively high doses leads to hypogonadotrophic hypogonadism, with decreased serum concentrations of LH, FSH, and testosterone. There are strong indications that the duration, dosage, and chemical structure of the anabolic steroids are important for the serum concentrations of gonadotropins. A moderate decrease in gonadotropin secretion causes atrophy of the testes (Fig. 13), as well as a decrease in sperm cell production. Oligo, azoospermia and an increased number of abnormal sperm cells have been reported in athletes using AAS, resulting in a decreased fertility. After stopping AAS use, the gonadal functions will restore within several months. In bodybuilding, where usually high dosages are used, after stopping steroid use, often HCGs are administered to stimulate testicular function.

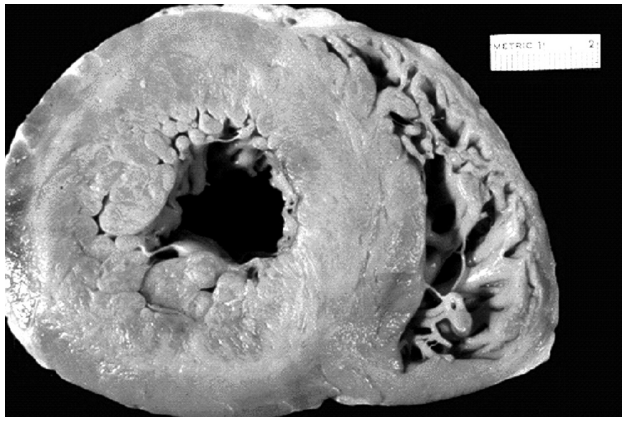
The effectiveness of this therapy is unknown. The various studies suggest that using more than one type of AAS at the same time ("stacking") causes a stronger inhibition of the gonadal functions than using one single AAS. Several cases have been reported in which the situation of hypogonadism lasted for more than 12 weeks.

A well known side effect of AAS in males is breast formation - gynecomastia (Fig. 15). Gynecomastia is caused by increased levels of circulating estrogens, which are typical female sex hormones. The estrogens estradiol and estrone are formed in males by peripheral aromatization and conversion of AAS. The increased levels of circulation of estrogens in males stimulate breast growth. In general, gynecomastia is irreversible.

AAS may affect sexual desire. Although few investigations on this issue have been published, it appears that during AAS use sexual desire is increased, although the frequency of erectile dysfunction is increased. This may seem contradictory, but sexual appetite is androgen dependent, while erectile function is not. Since sexual desire and aggressiveness are increased during AAS use, the risk of getting involved in sexual assault may be increased. There are some case reports suggesting a causal relationship between anabolic steroid use and the occurrence of Wilms tumor, and prostatic carcinoma.

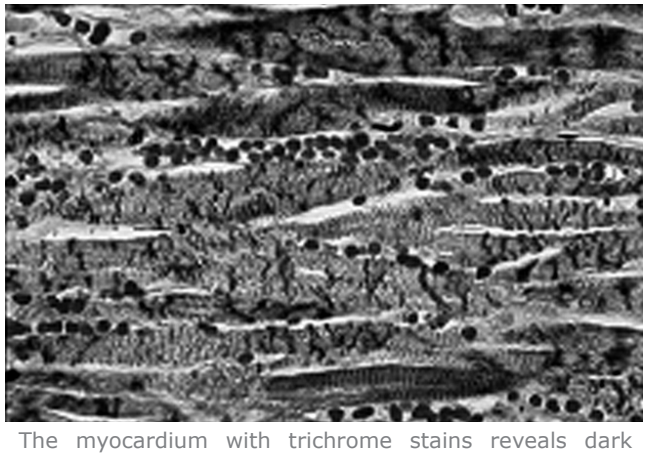
6.2 Female reproductive system

In the normal female body small amounts of testosterone are produced, and as in males, artificially increasing levels by administration of AAS will affect the hypothalamic-pituitary-gonadal axis. An increase in circulating androgens will inhibit the production and release of LH and FSH, resulting in a decline in serum levels of LH, FSH, estrogens and



Cardiac hypertrophy involving the left ventricle. Cardiac hypertrophy and myocardial fibrosis can occur with anabolic steroid use. Hypertrophic heart does not function well, diminishing performance and increasing the risk for sudden death.

Figure 15 Cardiac hypertrophy



The myocardium with trichrome stains reveals dark contraction bands indicative of ischemic changes following increased coronary artery response to catecholamine release with use of anabolic steroids. This has been observed in cases of sudden cardiac death with anabolic steroid use.

Figure 16 Myocardial fibrosis

progesterone. This may result in inhibition of follicle formation, ovulation, and irregularities of the menstrual cycle.

Other side effects of AAS use in females are increased sexual desire and hypertrophy of the clitoris. AAS use by pregnant women may lead to pseudohermaphroditism or to growth retardation of the female fetus, or even lead to fetal death. It is likely that the severity of the side effects is related to the dosage, duration of use and the type of the drug.

Additional side effects of AAS especially in women are acne, hair loss, withdrawal of the frontal hair line, male pattern boldness, lowering of the voice, increased facial hair growth, and breast atrophy. The lowering of the voice, decreased breast size, clitoris hypertrophy and hair loss are generally irreversible. Females using AAS may develop masculine facial traits.

6.3 Serum lipoproteins and cardiovascular system

Hypertension, ventricular remodeling, myocardial ischemia, and sudden cardiac death have each been temporally and causally

associated with anabolic steroid „use in humans...” Sullivan M. L., Martinez C. M., Gennis P., Gallagher E. J.
Steroid abuse has been associated with cardiovascular disease (CVD), including heart attacks and strokes, even in athletes younger than 30. No longitudinal studies have been conducted on the effect of AAS on CV morbidity and mortality. Most of the investigations have been focused on risk factors for CVD, and in particular the effect of AAS on blood pressure and on plasma lipoproteins. Although in most studies there was no difference in serum cholesterol and triglycerides between drug-free users and non-users, during AAS use total cholesterol tends to increase. Furthermore, HDL-cholesterol demonstrates a marked decline, well below the normal range. Serum LDL-cholesterol shows a variable response: a slight increase or no change. The response of total cholesterol seems to be influenced by the type of training that is done by the athlete. When the exercise is mainly aerobic, the increasing effect of AAS is counterbalanced by an exercise-induced increasing effect, which may result in a net decline in total cholesterol. The precise effect of anabolic steroids on LDL-cholesterol is yet unknown. It appears that AAS influence hepatic triglyceride lipase (HTL) and lipoprotein lipase (LPL). Androgens and anabolic steroids stimulate HTL, presumably resulting in decreased serum levels of HDL-cholesterol. High LDL and low HDL levels increase the risk of atherosclerosis, heart attack, and stroke. There are studies reporting elevated levels of homocysteine, another risk factor for CVD. Cardiac hypertrophy and myocardial fibrosis can occur with anabolic steroid use (Fig. 16). Steroids also increase the risk of thrombosis, blood clots potentially disrupting blood flow and damaging the heart muscle.

AAS cause fluid retention, which can lead to high blood pressure. No unanimity exists about the influence of AAS on arterial blood pressure. The response is most probably dose dependent. There is some data suggesting that high doses increase diastolic blood pressure, whereas low doses fail to have a significant effect on diastolic blood pressure. Increases in diastolic blood pressure normalize within 6-8 weeks after abstinence from AAS.

There is evidence that the use of AAS does elicit structural changes in the heart and that the ischemic tolerance is decreased after steroid use. Echocardiographic studies in bodybuilders, using AAS, reported a mild hypertrophy of the left ventricle, with a decreased diastolic relaxation, resulting in a decreased diastolic filling. Some investigators have associated cardiomyopathy, myocardial infarction, and cerebro-vascular accidents with abuse of AAS. Although the mechanisms responsible for the alteration of LV relaxation properties remain unclear, 2 mechanisms for the alteration of diastolic functions are discussed: blood pressure and structural alteration of the myocardium by the androgen receptor. It is important to realize that myocardium

is overstimulated to irregular growth by AASs, and the drugs may lead to cell disarray in the myocardium, as in hypertrophic cardiomyopathy.

6.4 Liver

AAS may exert a profound adverse effect on the liver. This is particularly true for orally administered AS. The parenterally administered AS seem to have milder effects on the liver. Testosterone cypionate, testosterone enanthate and other injectable AAS seem to have little adverse effects on the liver. However, lesions of the liver have been reported after parenteral nortestosterone administration, and also occasionally after injection of testosterone esters. The majority of the studies of AAS on liver function involve hospitalized patients who are treated for prolonged periods for various diseases, such as anemia, renal insufficiency, impotence, and dysfunction of the pituitary gland. In clinical trials, treatment with AAS resulted in a decreased hepatic excretory function. In addition, intra hepatic cholestasis, reflected by itch and jaundice, and hepatic peliosis were observed. Hepatic peliosis is a hemorrhagic cystic degeneration of the liver (blood-filled cysts), which may lead to fibrosis and portal hypertension. Rupture of a cyst may lead to fatal bleeding.Benign (adenoma's) and malign tumors (hepatocellular carcinoma) have been reported. There are rather strong indications that tumors of the liver are caused when the AAS contain a 17-alpha-alkyl group. Usually, the tumors are benign adenoma's, that reverse after stopping steroid administration. However, there are some indications that administration of AAS in athletes may lead to hepatic carcinoma. Often these abnormalities remain asymptomatic, since peliosis hepatis and liver tumors do not always result in abnormalities in the blood variables that are generally used to measure liver function. AAS use is often associated with an increase in plasma activity of liver enzymes such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (AP), lactate dehydrogenase (LDH), and gamma glutamyl transpeptidase (GGT). The increase in plasma levels of these enzymes reflect hepatocellular damage or at least increased permeability of the hepatocellular membrane. In longitudinal studies of athletes treated with AAS, contradictory results were obtained on the plasma activity of liver enzymes. In some studies, enzymes were increased, whereas in others no changes were found. When increases were found, the values were moderately increased and normalized within weeks after abstinence.

6.5 Musculoskeletal system

Rising levels of testosterone and other sex hormones normally trigger the growth spurt that occurs during puberty and adolescence and provide the signals to stop growth as well. When a child or adolescent takes anabolic steroids, the resulting artificially high sex hormone levels can prematurely signal the bones to stop growing with premature fusion of the epiphysis (growth center) of long bones.

Table 1 Possible adverse effects and complications of anabolic steroids*

Liver	Hepatocellular damage
	Peliosis hepatis
	Hepatocarcinoma, Hepatoadenoma
	Cholestasis
Reproductive	Oligo- or azoospermia
Males	Prostatic hypertrophy, Prostatic carcinoma
	Gynecomastia
	Testicular atrophy, Impotence
Females	Amenorrhea
	Uterine atrophy
	Teratogenicity
	Clitoromegaly
	Breast atrophy
Musculoskeletal	Early closure of physes in children (shorter adult height)
	Increased rate of muscle strains/ruptures
Endocrine (other than reproductive)	Decreased glucose tolerance
	Acne
	Hirsutism
	Integument
	Striae
	Male pattern baldness
	Edema
Larynx	Deepening of the voice
Cardiovascular	Decreased HDL cholesterol/ Increased cholesterol
	Increased blood pressure
	Thrombosis
Urinary	Wilm's tumor
Psychologic	Mood swings
Aggressiveness	Depression
Psychosis	Addiction
Immunologic (infectious)	Decreased IgA levels
Hepatitis B or C; HIV infection (if needles are shared)	**Withdrawal and Dependency Disorders**

* Adapted from. Landry GL, Primos WA Jr. Anabolic steroid abuse. Adv Pediatr. 1990; 37:185–205

6.6 Skin

In both males and females acne and increased oiliness are frequently reported, as well as hypertrophy of sebaceous glands, increased tallow excretion, hair loss, and alopecia, flushed or yellowish skin, bruising, even with small injuries, increased perspiration, pronounced stretch marks.

6.7 Infections

Many abusers who inject anabolic steroids may use nonsterile injection techniques or share contaminated needles with other abusers. In addition, some steroid preparations are manufactured illegally under nonsterile conditions. These factors put abusers at risk for acquiring threatening viral infections, such as HIV and hepatitis B and C. Abusers also can develop endocarditis, a bacterial infection that causes a potentially fatal inflammation of the inner lining of the heart. Bacterial infections can also cause pain and abscess formation at injection sites.

7. Behavioural problems. Anabolic androgenic steroids influence behaviour.

Case reports and small studies indicate that anabolic steroids, when used in high doses, increase irritability and aggression. Some steroid abusers report that they have committed aggressive acts, such as physical fighting or armed robbery, theft, vandalism, or burglary. Abusers who have committed aggressive acts or property crimes generally report that they engage in these behaviours more often when they take steroids than when they are drug free. A recent study suggests that the mood and behavioural effects seen during anabolic-androgenic steroid abuse may result from secondary hormonal changes. The association between anabolic steroids and aggression was tested by administering high steroid doses or placebo for days or weeks to human volunteers and then asking the people to report on their behavioural symptoms. To date, four such studies have been conducted. In three of these studies, high steroid doses did produce greater feeling of irritability and aggression than did placebo, although the effects appear to be highly variable across individuals. In one study, the drugs did not have that effect. One possible explanation, according to the researchers, is that some, but not all, anabolic steroids increase irritability and aggression.

An undetermined percentage of steroid abusers may become addicted to the drugs, as evidenced by their continued abuse despite physical problems and negative effects on social relations. Also, steroid abusers typically spend large amounts of time and money obtaining the drugs, which is another indication that they may be addicted. Individuals who abuse steroids can experience withdrawal symptoms when they stop taking steroids, such as mood swings, fatigue, restlessness, loss of appetite, insomnia, reduced sex drive, and steroid cravings. The most dangerous of the

withdrawal symptoms is depression, because it sometimes leads to suicide attempts. If left untreated, some depressive symptoms associated with anabolic steroid withdrawal are known to persist for a year or more after the abuser stops taking the drugs.

8. History

The beneficial effects on physical strength, after the subcutaneous administration of testisglycerol extracts, were already reported in 1872. The characterisation and synthesis of testosterone resulted in the Nobel Prize for chemistry in 1935 was performed by Butenandt and Ruzicka. In 1935 testosterone was synthesized by Charles Kochakian, and German soldiers were reportedly using it.

The current history of AS as abusable drugs began in 1954 among Olympic weightlifters. In 1956, Methandrostenolone was first marketed in the United States, clearing the way for the use of anabolics by U.S. athletes. At first, only world-class athletes in high-strength sports such as weight lifting abused anabolics. Among Olympic athletes, AS were a problem since 1964. Athletes and their trainers developed high dose, multiple-drug regimens that were not based on scientific research. As their reputation grew, anabolic abuse spread to other sports.

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Module 1.7
Alcoholism: clinical and therapeutic issues

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Key messages

- Alcoholism and other alcohol-related problems are worldwide;
- There are several categories of "drinking problems" excessive drinking, alcohol abuse and alcohol dependence (inability to control consumption; physical dependence with withdrawal symptoms);
- The early diagnosis is very important: it is based on biological markers and standardized questionnaires;
- Alcohol can also have major consequences if consumed by pregnant women: fetal alcohol syndrome;
- When treating alcoholism, it has to be considered as a chronic and relapsing disease;
- Four-step therapeutical strategy: introducing the patient to treatment, stopping drinking, prevention and control of lapses and relapses and return to a normal way of life;
- Detoxification is necessary, but is only a first step in the treatment;
- A relapse prevention strategy must be adapted to the specific problems of each patient;
- The goal of the treatment is to improve the quality of life of both the patient and his family.

Contents

In Belgium, in people over 18 years of age:
- More than 70% drink alcohol
- 20% have drinking problems
- 5% are dependent on alcohol

Figure 1 Epidemiology of drinking problems

Expected life duration in alcohol dependent persons:
52 years

Figure 2 Expected life duration

- More somatic problems in chronic consumers (cirrhosis, cancer, cardio-vascular diseases). More often in wine-producing countries (France, Italy, ...)
- More deaths related to abnormal behaviour (suicide, road accidents) in "binge" drinkers. More often in Nortern countries (Great-Britain, Scandinavia)

Figure 3 Reasons for the high mortality rate in alcoholic people

1. Epidemiology of drinking problems

Alcoholism and other alcohol-related problems are worldwide. In western countries, one can estimate that about 20% of adults compromise their health due to alcohol. Furthermore, 5% of adults are alcoholics with all the aspects of alcohol-dependence (Fig. 1).

Moreover, drinking alcohol is really dangerous if we consider that it restricts life expectation of about 25 years in people who become addicted (Fig. 2).

However, even if this reduction of life expectation is common in all countries, the reason for high mortality is not homogenous. In countries that are wine producers like France, Spain and Italy, mortality is mainly due to somatic complications in persons, who consume high amounts continuously. Whereas, in UK and Scandinavia, where binge drinking is more common, overmortality appears to be related more frequently to alteration of behaviour, thus inducing accidents, assault and suicide (Fig. 3).

By drinking problems, one means a lot of different clinical

situations. The first one is "excessive drinking", the situation of persons without any behavioural abnormality, but with a consumption inducing an increased risk of morbidity.

"Alcohol abuse" is characterized by repeated inability of a patient to control his consumption, even if he can otherwise stop drinking sometimes for a long period. "Alcohol dependence" is typical for alcoholism and will be described on the Figure 5. Finally, there exists a rare situation where people have major manifestations of inebriety after consuming only small amounts of alcohol beverage; this is commonly due to the activation of temporal epileptic focus by alcohol (Fig. 4 and Fig. 6).

Alcohol dependence is the final state of most patients with drinking problems. The key factor is the inability to control consumption. Furthermore, the addicted person has obsessional ideas about drinking. He has an overwhelming desire to drink (craving) and adapts his way of life to this. Finally, most alcoholics develop physical dependence characterized by the occurrence of withdrawal symptoms, if they try to stop drinking (Fig. 5).

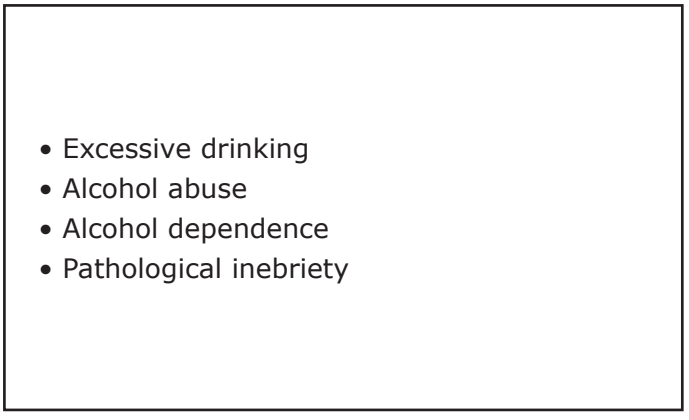

Figure 4 Drinking problems

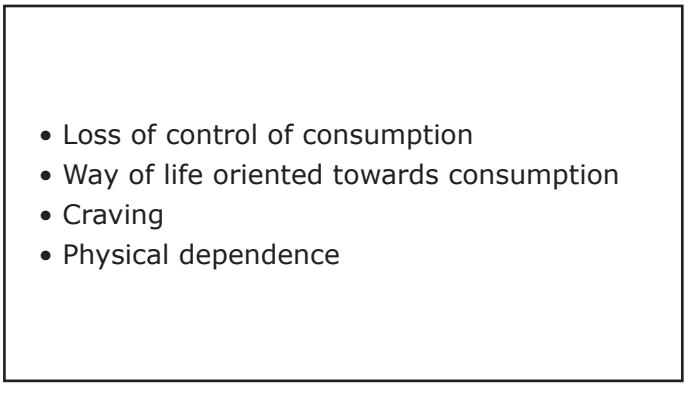

Figure 5 Alcohol dependence

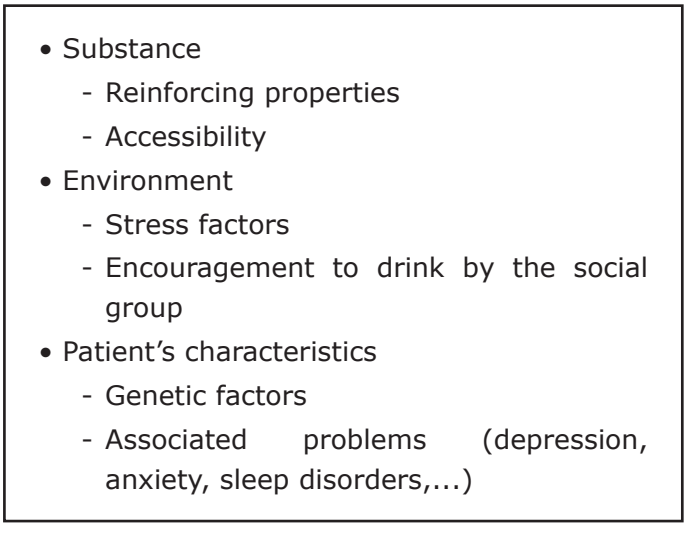

Figure 6 Causes of alcoholism

- High risk environment
- Family antecedents of alcoholism
- Previous dependence on other substances
- Psychological difficulties
- Sensation seeking
- Liking the taste of alcohol-containing beverages

Figure 7 Increased risk of alcoholism

- **Major complications of alcoholism**

  - Cirrhosis
  - Polyneuropathies
  - Cerebral atrophy
  - Compulsive drinking
  - Skid-row situations
  - ....

Figure 8 Alcoholism: late identification

- **Addition of non-specific problems**

  - Hypertension
  - Digestive problems
  - Psychological problems (depression, anxiety, sleep difficulties, ...)
  - Repeated difficulties at work
  - Problems with the family
  - Traffic accidents
  - Inebriation
  - Increased tolerance to alcohol
  - .....

Figure 9 Alcoholism: early recognition

2. Causes of alcoholism

Alcoholism is related to the interactions between the reinforcing properties of alcohol on the brain, environmental factors (stress factors) and personal factors combining genetic sensitivity to the effects of alcohol and the presence of associated problems like depression or anxiety (Fig. 6).

It is important to keep in mind that an increased risk of development of drinking problems can be sometimes recognized. Early detection is therefore important (Fig. 7).

Unfortunately, drinking problems are frequently recognized very late, at the moment of decompensation of major complications of alcoholism, such as cirrhosis, neurological problems, etc. (Fig. 8).

3. Special markers of early diagnosis

It is important to keep in mind that the physician can often diagnose drinking problems very early. The diagnosis of drinking problems has always to be considered when the patient presents in a repetitive way problems that are otherwise

non specific. If alcohol problems are suspected, specific markers have to be investigated (Fig. 9).

Biological markers for alcoholism do exist: like increased blood gamma glutamyl transpeptidase, carbohydrate deficient transferrin or mean corpuscular volume. However, those markers are not always specific to alcohol problems, and, furthermore, they can be negative in persons with otherwise major drinking problems. Therefore, it is also necessary to consider a way to question the patient about his alcohol consumption. Simple and direct questions like "Do you estimate that you have some problems with drinking alcohol?" can be effective. There are also standardized questionnaires that have been validated in general practice (Fig. 10).

The best known questionnaires are AUDIT and the very simple CAGE. It was demonstrated that answering "yes" to at least one question of CAGE permits to diagnose very accurately alcohol problems in most of the patients (Fig. 11).

- Biological markers (GGT, CDT, MCV)
- Specific questionnaires (CAGE, AUDIT)

Figure 10 Specific markers for alcoholism

- Have you ever thought of giving up alcohol use? **(C = cut down)**
- Has anyone made any unpleasant remarks about that so far? **(A = annoyed)**
- Have you ever felt guilty about having a drink? **(G = guilty)**
- Have you ever had a drink in the morning so that you could feel better? **(E = eye opener)**

Figure 11 CAGE questionnaire

- Small body size
- Mental retardation (most frequent cause in industrialized countries)
- Facial abnormalities
  - Microcephalia
  - Microphtalmia
  - Short eye clefts
  - Hypoplastic filtrum
  - Short upper lip
- No trigger dose!

Figure 12 Alcohol and pregnancy Foetal alcohol syndrome

Figure 13 Foetal alcohol syndrome

- Hepatic steatosis and cirrhosis
- Pancreatitis
- Hypertension
- Hyperlipidemia
- Myopathy
- Polyneuropathy
- Cerebral complications
  - Cerebellum atrophy
  - Wernicke-Korsakoff syndrome
  - …
- Etc.

Figure 14 Somatic complications of alcoholism

1. Introducing the patient to treatment
2. Stopping drinking
3. Prevention and control of lapses and relapses
4. Return to a normal way of life

Figure 15 Treatment strategies for alcoholic patient

4. Alcohol and pregnancy

Alcohol can also have major consequences if consumed by pregnant women. A foetal alcohol syndrome was described for years in infants of women with major alcohol problems. It is characterised by a combination of somatic and mental deficiencies. However, the full presentation of the syndrome is rare. More often, only some manifestations are present; the most frequent is mental retardation. We now know from animal and human studies that there is no safe trigger dose of alcohol consumption in pregnant women; the higher the consumption, the higher the risk of foetal alcohol syndrome, but, the risk only disappears by complete abstinence (Fig. 12).

In this baby, the characteristic facial abnormalities are present: small eyes, no philtrum and a very short upper lip (Fig. 13).

Alcohol is a small ubiquitous molecule that can interfere with all physiological processes. As a consequence, all parts of the body can develop problems related to alcohol consumption.

However, alcohol has not direct organotoxicity; its toxicity is related to indirect factors like excitotoxicity, lipid peroxidation, free radicals production and lack of thiamine (Fig. 14).

5. Treatment strategy of alcoholic patient

The treatment of patients with alcohol dependence is not easy and is often a long and difficult task. Alcoholism has to be considered as a chronic and relapsing disease. The way can be defined as a 4-step therapeutical strategy.

The first and not always easy task is to induce in the patient the desire to change something in his life and to understand that a lot of his problems are directly or indirectly linked to his alcohol consumption. When he begins to be aware of this, he will need help to stop drinking and afterwards to remain abstinent for a long time. The therapist, the patient and his family have finally to keep in mind that the aim of the treatment is to improve the quality of life and not only to modify the drinking habits (Fig. 15).

5.1 Four-step therapeutic strategy

Introducing an alcoholic patient to treatment is not an easy task. Often, it is even not possible to have direct contacts with the patient. In that case, the first task is to support the family and to give information about drinking problems and the modalities of treatment. Secondly, when it is possible to meet the patient, it is important not to do in the hurry, but first to assess the patient's situation according to a multiaxial model including, of course, not only the drinking habits, but also the medical, psychological and social situation of the patient. Finally, a motivating way of interviewing is useful, suggesting a link between the problems encountered by the patient and his drinking habits. This can make him to agree to modify something and to ask, for example, for detoxification. It is important to recognize this moment and to be active at this time to permit the patient to stop drinking (Fig. 16).

5.2 Prochaska and Di Clemente model

Model of cognitive change in addicted people: this progressive cycle of patient suffering from addiction was developed some years ago by Prochaska and Di Clemente. After a period of precontemplation ("I have no problem", the patient enter a situation

1. Supporting the family
2. Assessing the situation
3. Motivating interview with the patient
4. Waiting for a suitable moment for changing

Figure 16 Introducing the patient to treatment

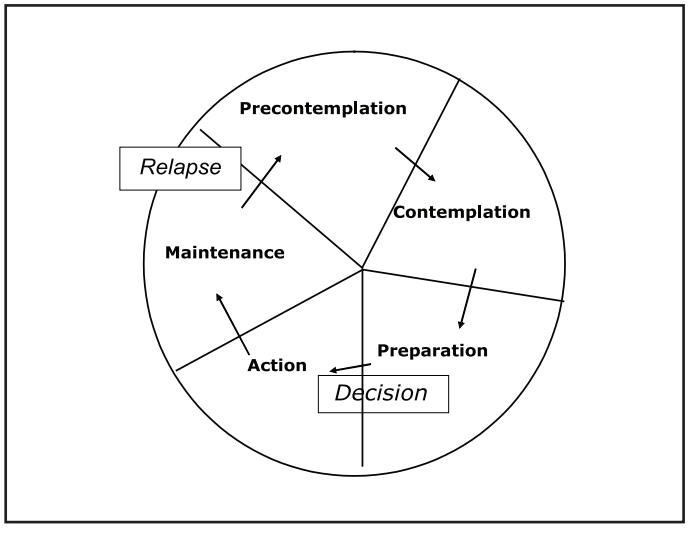

Figure 17 Model of cognitive change in addicted people (Prochaska et Di Clemente)

- First hours
  - Irritability, tremor, insomnia, nausea
- Day 2 - 4 : Delirium tremens
  - Disorientation, confusion, hallucinations
  - Autonomic disorders (t°, arterial tension, ...)
  - High mortality!
- Day 2 - 7 : Grand mal convulsions

Figure 18 Withdrawal syndrome

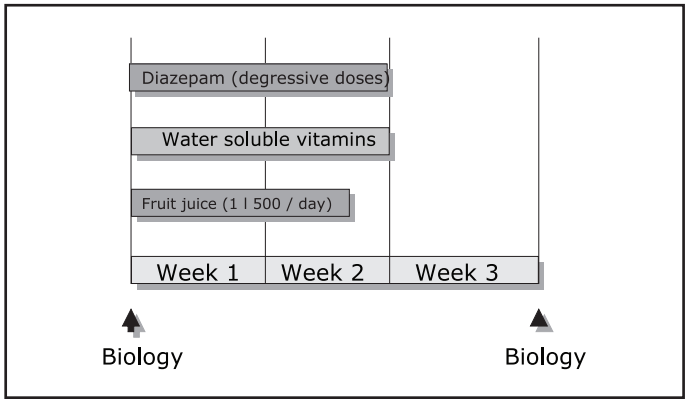

Figure 19 Detoxification schedule

of contemplation ("I have problems, but I don't know what to do"). The next step is preparation ("I know what is necessary to do, and I am thinking about"). It is then time for decision and for action ("I want to go to the hospital to stop drinking").

Finally, it is necessary to use strategies to prevent relapses, and, if they occur, to stop them as quickly as possible (Fig. 17).

5.3 Withdrawal syndrome

If the patient decides to stop drinking, it is important to inform him that he needs medication to prevent withdrawal symptoms. The latter can be dangerous and eventually cause delirium tremens and epilepsy (Fig. 18).

It is easy to prevent or to stop withdrawal manifestations. The most popular medication in this case is diazepam, a benzodiazepine. It has to be used immediately, starting with high dosage (20 to 100 mg the first day). This dosage must be tapered off progressively in about 2 weeks. It is also needed to give hydrosoluble vitamins complexes and beverages (fruit juices) during

this detoxification procedure (Fig. 19).

5.4 Detoxification

The first task in detoxification is to break the cycle of addiction by stopping safely physical dependence; this can be achieved easily by benzodiazepines given in a degressive way. This also gives the opportunity to assess the health situation of the patient according to a multiaxial algorithm and to organize a program to prevent relapse. Information to the patient and his family is needed; this also helps to reinstate communication between the patient, his family and, when possible, the workplace (Fig. 20).

5.5 Protracted withdrawal syndrome

It is important to keep in mind that, after the period of detoxification (usually 2 to 3 weeks), the patient is not completely cured, even if he is protected from specific complications of alcoholism. Originally, there was an agreement that a so-called "protracted withdrawal syndrome" existed, which interfered with the patient's quality of life. Until recently,

- Preventing pharmacodependence by diazepam
- Multiaxial assessment (bio-psycho-social)
- Giving information about the alcoholic disease and its treatment
- Organization of follow-up
- Reintroducing communication with family and workplace

Figure 20 During detoxification

- Recognition of a protracted withdrawal syndrome
- Unspecific clinical manifestations (asthenia, non characteristic depression and anxiety manifestations)
- Unknown pathophysiology
- No specific treatment

Figure 21 After detoxification, the protracted withdrawal syndrome: classical view

- Demonstration of a reduced frontal blood flow in all patients after withdrawal
- Associated with alteration of executive mental functions (all mental functions that are needed for decision and coping with new situations)
- Alteration of executive functions is closely correlated with the short-term risk of relapse
- In addition, major alterations of sleep patterns after detoxification (inducing fatigue)

Figure 22 Protracted withdrawal syndrome: our experience

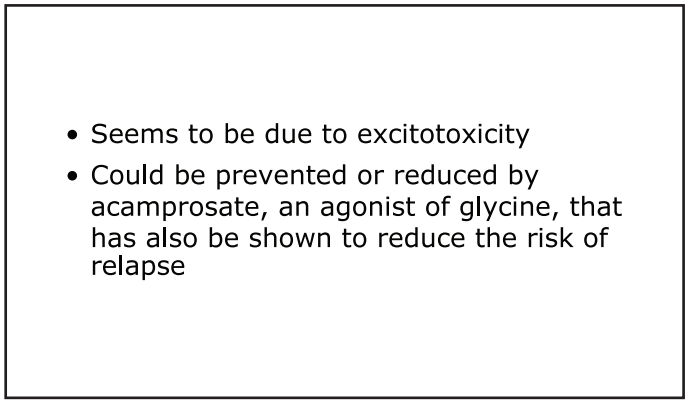

Figure 23 Protracted withdrawal syndrome

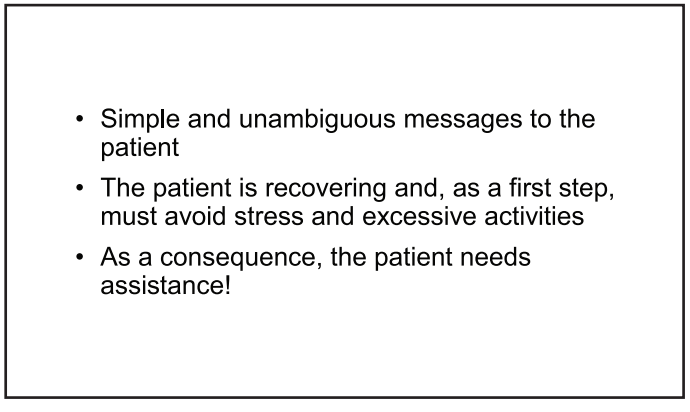

Figure 24 Protracted withdrawal syndrome: consequences for early follow-up

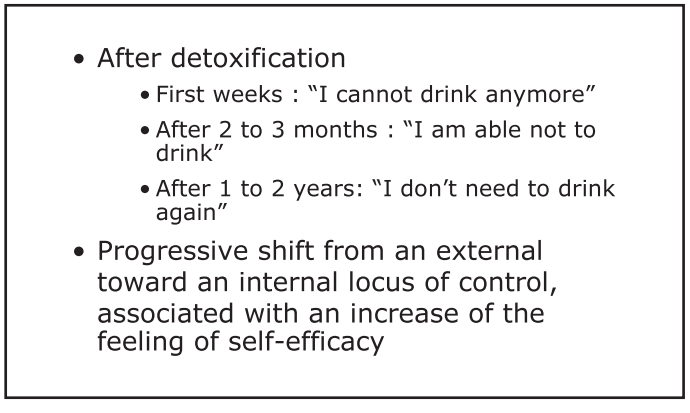

Figure 25 Cognitive evolution of abstinent patients

no known patho-physiological explanation or specific treatment was available (Fig. 21).

We studied this situation in our department and we observed that, immediately after detoxification, all patients presented a decrease in frontal blood flow resulting in an alteration of the executive functions. This is an important issue, because the intensity of this alteration is directly related to a risk of short-term relapse. Moreover, patients after detoxification always present a severe deficit in the quality of sleep, resulting in fatigability (Fig. 22).

To our knowledge, the best explanation for this protracted withdrawal syndrome could be excitotoxicity in selected brain regions, triggered by both ethanol intoxications and withdrawal manifestations. A recent publication suggests that this invalidating syndrome could be reduced or prevented by acamprosate, an agonist of glycine, that has also been shown to reduce the risk of relapse (Fig. 23).

In addition to medication, it is important to remember that patients in this situation have a reduced ability to cope with

stressful situations and also a reduced possibility to integrate complex messages. "You cannot drink" is a much more useful sentence than "Don't drink, but…" because those patients are unable to handle mental double-tasks (Fig. 24).

After detoxification, both patients and doctors must remember that the big majority of addicted people remain unable to control drinking. If they remain abstinent, it is important to note that most patients present a progressive modification of their cognitions about drinking. More and more, there is a shift from an external locus of control (I will not drink if I can avoid meeting this person, if I can sleep, if there is no stressful event…) to an internal locus of control (Whatever happens, I am able not to drink) (Fig. 25).

5.6 Relapse prevention

The most validated psychotherapeutical approach of relapse prevention is the cognitivo-behavioural one. Providing information, encouraging the patient, giving him feedback about his evolution (for example by using blood markers such as GGT), and helping him to find tools to control himself are the key points (Fig. 26).

- Basic principles
  - Providing information about drinking problems and treatments
  - Encouraging the patient
  - Feed-back
  - Development of autocontrol tools
  - Identifying persons implicated in follow-up

Figure 26 Cognitivo-behavioral relapse prevention

- Psychodynamic approach for some associated problems, but not directly effective in drinking problems
- Systemic support directed to "co-alcoholism"
- Supportive associations like AA

Figure 27 Psychotherapy

- Disulfiram (deterrent therapies)
- Acamprosate
- Antagonists of opioids (naltrexone)

Figure 28 Pharmacotherapy: drugs that can improve abstinence rate

- Alcoholism as a disease
- Detoxification is necessary, but is only a first step in the treatment
- Abstinence is needed for most patients after detoxification. A relapse prevention strategy must be adapted to the specific problems of each patient
- The goal of the treatment is to improve the quality of life of both the patient and his family

Figure 29 Treating alcoholism: main concepts

6. Conclusions

To summarize, it is possible to cure alcoholism if one considers it as a chronic illness with possible relapses. In most people, a medication-assisted detoxification will be necessary, but this is only the first part of the treatment.

In addition to cognitivo-behavioural psychotherapy, other techniques are available. Classical psychodynamic approach is usually not suitable. A systemic model can be used if it is directed towards the cohesion of family, and the recognition and correction of "co-alcoholic" behaviours of the partner. Finally, the support of the patient by self-help groups such as Alcoholics Anonymous (AA) is of great value (Fig. 27).

Medication can also help to stabilise the detoxified patient. The old disulfiram (ANTABUSE) remains useful; its efficacy is based on the awareness of the patient that simultaneous alcohol and disulfiram use results in severe physical manifestations and that it is necessary to avoid them. More recent medication is now available: acamprosate - an agonist of glycine and naltrexone (an antagonist of opioids) able to reduce craving (Fig. 28).

After detoxification, it is necessary to remain abstinent. However, it is important to keep in mind that abstinence is a tool not a goal. The true aim of treatment is to improve the quality of life of the patients and their families (Fig. 29).

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Module 1.8
Addiction and family

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Key messages

- The term "codependency" has been used on each of the three levels of its meaning: as a didactic tool, psychological concept, and disease entity;
- Codependency is a learned behavior. "What we live with we learn; what we learn we practice; what we practice becomes habit; our habits have consequences";
- Behaviors of codependent persons are based on their emotional feelings and on how they view their world;
- Because of the complexity of the problems typically experienced by codependent persons, an integrative approach to treatment may be optimal;
- The recovery process for drug addict and family members is simple to state, but takes time and efforts to change. "If nothing changes, nothing changes".

Contents

1. Codependency definitions

Codependency is professional term that appeares sometime in the late 1970s. It has been used on each of the three levels of meaning: as a didactic tool, psychological concept, and disease entity.

1.1 "Codependency" as didactic tool

When working with family members of chemically dependent and other dysfunctional families, codependency can serve as a useful didactic tool. The use of the word "codependency", once it is explained to family members helps to normalize feelings that are being experienced and allows family members to begin to focus on their own dysfunctional patterns of behavior. Family members can be helped to realize that they, also, have something from what they need to recover.

Mellody, Miller, and Miller (1989) define codependency as a state of "dis-ease" in which one's authentic self is either unknown or hidden, the result of which is low sense of personal worth, painful relationships with others, and internalized shame. Some traits of syndrome include:

- exaggerated sense of responsibility for others;
- intense need for approval;
- sustained difficulty in both identifying and expressing one's own feelings.

Schaef (1986) and Whitfield (1989) suspect that codependence is part of an addictive process and that codependents live in families with other codependents, compulsive (e.g. alcoholics, anorexics) and chronically ill people.

Codependency has been used to describe the dynamics of almost any dysfunctional relationship. Cermak (1986), O'Brien and Gaborit (1992) describes codependency as "potentially existing in relationships apart from those characterized by alcoholism or other substance abuse patterns". However, Carothers and Warren (1996) found no relationship between codependency in adults and the chemical dependency of their parents during their childhood years.

1.2 "Codependency" as psychological concept

Codependency also has value as a psychological concept used to describe and explain human behavior.

Codependency is overdependency on others. That is difficult to see, however, because the overreliant persons are not just being controlled by others. They are also attempting to control the very ones who are controlling them. Some codependent people may be depending too much on those whose behavior is neither inappropriate nor out of control.

Controlling and being controlled by others, characterizes those who are codependent.
Using constructs from Bowen's intergenerational FST, they propose the following explanatory definition:

Codependence emerges from dysfunctional relationship patterns that are primarily rooted in the intergenerational family emotional system. These patterns include: anxiety – binding mechanisms in the form of triangulation, fusion, compulsive or addictive behaviors; lack of awareness of feelings while focusing externally on another person, activity, or substance; lack of intergenerational individuation; difficulty with establishing desired levels of interpersonal intimacy or distance, and diminished sense of personal identity and authority.

Here are four definitions for codependency as psychological concept:

- "An emotional, psychological, and behavioral condition that develops as a result of an individual's prolonged exposure to, and practice of, a set of oppressive rules" (Robert Subby);
- "A set of maladaptive, compulsive behaviors learned by family members to survive in a family experiencing great emotional pain" (The Johnson Institute);
- "A stressful learned behavior associated with an unhealthy focus on the needs of others and/or attempting to take responsibility for the behavior of others" (Brian DesRoches);
- "We begin tolerating abnormal, unhealthy, and inappropriate behaviors. Then we go one step further, we convince ourselves these behaviors are normal" (Melody Beattie).

1.3 "Codependency" as disease

Codependency can also be considered as a psychological disorder or disease entity. Clinicians often refer to family members as experiencing the consequences of codependency or as being actively codependent. The charachterisics of this type imply that "a consistent pattern of traits and behaviors is recognizable across individuals and that these traits and behaviors can create significant dysfunction" (Cerman, 1986). According to Schaef, codependency is "a disease that has many forms and expressions and that grows out of a disease process that is inherent in the system in which we live". This disease process is "addictive process". The addictive process includes chemical dependency, sexual addictions, eating disorders, personality disorders, and sexism, as well as codependency. So codependency is preoccupation with the lives, feelings and problems of other people and is a unique disorder that exists independently of chemical dependency.
Whitfield (1989) defines codependency as "any suffering and/or dysfunction that is associated with or results from focusing on the needs and behavior of others". Codependency as a primary disease is complete with a pattern of symptoms, course, and treatment. Similarly, Friel and Friel (1988) view codependency as dysfunctional pattern of living originating both in one's family of origin and culture that leads to an arrest of identity development.

2. How does codependency look like?

Codependent people have countless ways of trying to manage others and their problems. They could be classified as follows:

2.1 The Caretaker

Caretakers try to do for others what they could and should do for themselves. They try to be the hero, eager to fix problems. They feel responsible to change other people's moods.
The codependent individual feels responsible for other people. They feel anxious and even guilty when others have a problem. They feel compelled to help these persons solve their problems. They anticipate the other's needs and feels angry when their help is not effective or rebuffed. The codependent is over committed, harried, pressured, feels safe when giving, but insecure when someone gives to him/her, goes out of her/his way to help others.

2.2 The Enabler

It is the one who bails others out of the consequences of poor choices. Rescuers "enable" rather than confront problems that others create. They cover for other's glaring mistakes and protect the addict from the consequences of his actions. Enablers will go as far as lying, making excuses, hiding there mistakes and giving alibis. They may secretly provide the drug abuser with money to buy alcohol or drug.

2.3 The Pleaser

Pleasers try to do or be what they think others want them to do or be. They are preoccupied with making others happy and not disappointing them. Pleasers readily agree with others in order to avoid confrontation.

2.4 The Helpless Victim

They don't just want to be helped; they want to be taken care of. They need others to take care of them. They manipulate others to feel sorry for them. Wanting others to be around them all the time, they absorb attention like a dry sponge. They control others through weakness. They discover that moralizing and making long sermons or pleading, begging the addict to stop, do not work. These attitudes tend to increase the sense of guilt in the addict.

2.5 The Intimidator

They leave the impression that they know it all. They use knowledge to control. They can be cordial and friendly, as long as others agree with them. But when crossed, they turn mean.

2.6 The Helper

The helper truly encourages the addict to acknowledge his or her illness and seek treatment. The helper learns all that he/she can about the illness and seeks to demonstrate to the drug user how counseling and self-help groups can

"make the problem better". The helper supports the drug user through the stages of recovery and appreciates his/her efforts to become drug-free.

3. Origin of codependency

Many codependent people grew up in homes where mother or father obsessively pleased or took care of others. They might have grown up with one parent who had a destructive addiction while the other parent made excuses or pretended the problem did not exist. Crothers and Wanner (1996) found correlations between adult codependency and paternal coercion, control, non-nurturnace, and maternal compulsivity. Spann and Fischer (1990) found codependency in adults negatively correlated with communication, satisfaction, and support in the family of origin and positively correlated with control and leisure activities.

Crothers and Warren (1996) state that codependency is associated with having had a codependent father or mother:

- Codependent adults may simply have learned codependent attitudes and behaviors from their parents through direct observation and modelling;
- Codependency may develop out of experience with codependent parents, whose external focus on their children and use of control, denial and rigidity within the family's relationships creates an environment in which their children are more likely than other children to model their parent's behavior.

Codependency is often found in a family environment which is constantly stressful. When a person compulsively uses food, drugs, alcohol, sugar, money, sex, work, or relationships, life becomes stressful. A codependent person having in a relationship with a compulsive person may develop an obsession to that relationship.

Because of the codependent's experience with needy persons, they come to trust nothing and no one. They dedicate their lives to taking care for others, while no one is there to take care of them.

But Fisher, Wampler, Lyness (1992) found that codependence was not predicted significantly by dysfunctional patterns in the family of origin.

4. What are the characteristics of codependency?

The generally accepted dynamic of codependency is as follows: codependent persons focus so much on what is happening with those around them and on trying to have some control over the lives of others that they lose touch with their own thoughts and feelings. As a result they use this control to gain a sense of fulfillment and emotional support from their intimate relationships with others. Codependent individuals also seek the approval of others in order to build their low self-confidence. Some of the primary characteristics of codependency are lack of autonomy, excessive involvement in caretaking for

the purpose of gaining emotional support, and low self-confidence (Cermak, 1986; Irwin, 1995).

Some authors recently have claimed that codependents do not need be in relationships with chemically dependent persons (Beattie, 1987). Other authors define codependency as an addiction in and of itself characterized by the uncontrollable urge to search "for other people or external objects for fulfillment of the self" (Whitfield, 1989). Whitfield characterises codependency as addiction of its own that arises from an individual's focusing so much upon the external environment that internal processes (e.g. emotions, desires) are forgotten or lost.

Cermak (1986) provides five major characteristics of codependency.

- The codependent displays a continual investment of self-esteem in the ability to influence or control feelings and behavior in the self and in others despite painful consequences;
- The codependent assumes responsibility for meeting the needs of others to the exclusion of his or her own needs;
- The codependent suffers anxiety in periods of intimacy or separation because of poor personal boundaries (Coleman & Colgan, 1987). Codependents may not recognize themselves as separate people with separate emotions and ideas. They are so externally oriented that they "take on" other people's emotions. Codependents do not know where they "end" and where others "begin". Codependents say they won't tolerate something from anyone, and then engage themselves in exactly that;
- The codependent enters into emotionally enmeshed relationships with personality disordered, drug dependent, and other compulsive people;
- The codependent can exhibit constriction of emotions, depression, hyper-vigilance, compulsions, anxiety, and excessive reliance on denial, substance abuse, stress-related medical illnesses, and/or primary relationship with an active substance abuser.

Crothers and Warren (1996) found that the manifestation of codependency is related to family of origin experiences such as unemployment, poor communication, violent conflict resolution strategies, lack of support and acceptance, control issues, feeling unloved or misunderstood, and lacking a safe environment to express feelings or problems. Compulsivity in fathers was not related to adult codependency, while compulsivity in mother was. Crothers and Warren (1996) find that loss of self is a major component or correlate of codependency.

Some authors describe other characteristics of codependent people:

- **Obsessive Compulsive Disorder**: Codependents worry that people are talking about them; they worry that

people are not talking about them; they never find any answers, they focus on other's problems; they spend money compulsively; eat or drink compulsively.

- **Controlling Behaviours:** Codependents try to control events and people through helplessness, guilt, manipulation, or domination. They are afraid to let people be who they are or let events happen naturally. They have lived in so many situations in which they had no control that they now try to control everything and get frustrated and angry when they cannot.
- **Dependency:** Codependents do not feel happy or content with themselves. They look to others to supply them their happiness or their needs. They equate love with pain and believe others are never, ever there for them. They need people more than they want them.
- **Poor Communication Skills**: Codependents blame, threaten, coerce, beg, bribe, and advise others. They do not mean what they say and do not say what they mean. They say everything is their fault. They believe their opinion does not matter and have difficulties asserting their rights or expressing honest emotions.
- **Sexual Problems:** They have sex when they don't want to. They try to have sex when they are hurt or angry, and refuse to enjoy it. They reduce sex to a technical act.

5. What are the feelings of codependent persons?

Codependents pay more attention to the feelings and desires of other people than to their own; they spend their time sharing the interests and hobbies of others at the expense of pursuing their own. Codependents sacrifice their own values to be close to others, they trust the opinion of others more than their own, and they believe that the quality of their lives depends on the lives of other people (Whitfield, 1989).

In general, codependents can be extremely responsible or irresponsible. They find it difficult to be happy, feel close to others, or have fun and be spontaneous. They are passive aggressive, feeling passive, hurt, helpless yet violent and angry. They laugh when they want to cry. They are ashamed of their families, of their relationships.

Behavior of codependent persons are based on their emotional feelings and on how they view their world. Family members usually experience the following anxieties when confronted with their relative's drug problems:

- **Fear:** Codependent people are grippe's with an inordinate amount of insecurity. The way they think and relate is motivated by a fear of disapproval, rejection, or anger. They think that something terrible is going to happen if they do not stay in control. Some codependents worry about what

others might do or think if they fail. Others, worry about what they might lose if they are not needed.

- **Shame and Guilty:** Their first response to the problem may be an effort to hide it.
- **Anger:** Throwing blame around is another common family response. Codependents ignore negative feelings, e.g. anger, because the reality of the situation becomes too painful.
- **Denial:** Parents deny that a member of their family has a drug problem even when there are faced with strong facts. Codependents ignore problems or pretend they do not exist. They stay busy to avoid thinking about things; they get confused, sick, depressed and visit doctors for a prescription. Many are workaholics.
- **Confusion:** Family members often feel at the mercy of conflicting emotions. While they strive to protect the user from harm or censure, they feel furious that he or she has been "so stupid".
- **Self-blame:** Some families often feel they are to blame for the situation and reproach themselves. Parents may feel they have failed.
- **Low self esteem and external referencing:** Codependents may respond only to external cues, not to internal feelings or perceptions. Codependents tend to come from troubled, dysfunctional families, and will deny this to the very end. They blame themselves for everything. But if someone else criticizes them, they get defensive and angry, not to mention self-righteous. Do not try to make compliment to a codependent; they feel "different" from the rest of the world. They love being the victim of sexual, physical, or emotional abuse, abandonment, neglect, and/or alcoholism. They feel like victims, carry lots of guilt and shame, and think their lives are not worth living.
- **Lack of Trust:** Codependents do not trust themselves, their feelings, their decisions, and other people. People with codependency need and depend on others too much. Something vital is missing inside them. Codependent people make others so important that their ultimate joy and fulfillment in life hinges on other's love, approval, and presence. They believe they cannot be happy unless others accept them, pay more attention to them, need them more, or become what they want.
- **Repression:** Most codependents repress their own needs, their own desires. They are afraid to let themselves be who they are and often appear rigid and controlled.

6. Help to family members

People who misuse drugs often live with their family. Often it is somebody else than the user who first seeks help. In almost all families where is a drug abuser, the family suffers from severe stress and conflict. Family members suffer because they do not understand the dynamics of drug dependence and therefore lack the necessary skills to

cope with the manipulative behavior of the drug-dependent person.

When a family member has a dependency, the whole family usually develops ways of coping with the problems associated with the dependency. Often, there is less communication: the family avoids talking about the issue, avoids expressing emotions, and may keep the addiction secret from the community. Some family members may take on some of the responsibilities abandoned by the addicted person.

A variety of strategies are available for helping family members of drug abusers:

6.1 Twelve-step recovery groups

Often, seeking outside help from a support group can help family members cope with what is going on in their family. It is important for them to realize that the addiction is not their fault. It is important to help codependent individuals to realize that they are not alone, to provide ongoing social support and the opportunity to learn more adaptive interpersonal skills, more effective coping skills.

6.2 Individual counseling

Family members need help to deal with confusing emotions such as love, hurt, disappointment and guilt which they experience on discovering a problem. The way in which parents respond has a major influence on whether drug–taking will stop or continue. Family counseling aims to help the situation and to enlist their support in achieving the recovery goals of the drug-dependent person. Family counseling aims to reduce the negative attitude or behavior and to enlist the whole family in the rehabilitation process.

6.3 Family therapy

Codependency is a learned behavior. But there comes a time when they must take responsibility for the way they have chosen to handle life. Codependent behavior is a coping mechanism used to escape negative feelings. Codependent tendencies may be countered by placing an emphasis on identifying and developing the unique characteristics, preferences, and needs of the codependent individual. As Earnie Larson states "What we live with we learn; what we learn we practice; what we practice becomes habit; our habits have consequences".

6.4 Psycho educational teaching

Family members can change a problem if they do not understand. They need to be able to recognize what dependency is, what it looks like, where it comes from, and what effect it has on themselves and others. They need to understand the addiction process.

Family members must recognize drug taking. The first step is to find out the

extent of the problem, i.e. is it a once off experiment or is it regular use. If there is cause for concern parents should try to discuss the matter with the child in a calm and reasonable way. It is important not to accuse if you have no definite proof.

Often listen and discuss – do not cut each other off. It's important to provide clear information for family members about drugs, the stages leading to the Drug Dependence Syndrome, tolerance, physical and psychological dependence.

This important for family members to be informed about drugs and to be vigilant, without being over-anxious. Family members need to be aware of influences on young people and to develop an understanding of adolescence. Parents can help children cope with demands of peer involvement, by encouraging the development of their individuality and personal strengths.

Family members must recognize the problem, admit it, and then find the tools to help end it.The first thing is to learn is that happiness is inside, not something outside. They must learn to accept their powerlessness over people and events.

Family members: what they must do and what they must not do in their relationships with the recovering addict.

Recommendations to family members:
- Remain in charge as parents
- Accept the reality of the situation
- Do not allow yourselves to be manipulated by abusers
- Have reasonable and consistent rules for behavior in the family home
- Be there to listen, support, advise and encourage
- Be understanding and compassionate towards the drug user
- Confront the problem and not the person
- Have fair discipline
- Have a stable family atmosphere.

Family members should not:
- Remain isolated
- Maintain a judgmental attitude
- Give money to the addict
- Pay off the addict's debts
- Move out from where they live presently
- Habitually compare the addict to others who are healthy or successful.

Because of the complexity of the problems typically experienced by codependent individuals, an integrative approach to treatment may be optimal.

7. Stages of recovery

Recovery is not easy. Letting go of the need to control people, places, events is not easy. Recovery means learning to take responsibility for their own actions, issues, feelings, behaviors, and their lives. The recovery process for a codependent person is simple to state, but takes time and efforts. They must learn to take care of oneself, and to let others take care of themselves. They must learn to love oneself, and to take responsibility for attending to one's own needs.

The recovery process may seem a little selfish at first. However, it is the only means by which codependents can truly enjoy their lives and be able to give a full measure of genuine caring and love to others. Recovering from codependency is a process of acknowledging and then letting go of pain, and finding ways to build a happy life.

The stages of recovery are:

- **Detachment:** Codependents can learn to separate themselves from unhealthy relationships with others. Detachment does not mean indifference, or avoiding responsibility. It simply means putting that energy to better use.
- **Removing the Victim Image:** Codependents acknowledge that they are not victims and have the power to create positive change.
- **Independence:** Codependent learns to trust themselves and realizes that can care for themselves without help from others.
- **Living Your Own Life:** Codependents begin to focus on themselves.
- **Accepting Reality:** The codependent acknowledges and accepts the problems in his life in order to begin solving them
- **Experiencing Feelings:** Recovery involves getting in touch with emotions and accepting them, both negative and positive.
- **Setting Goals:** Codependents realize that they can accomplish goals and create self-fulfillment.

8. Directions for future research

Future research should focus on other personality or situational factors that could be involved in the development of codependency, such as attachment style, temperament, personality traits, birth order, communication skills, and interpersonal relationships outside of the family.

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Module 1.9
Immunology of opioids

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Key messages

- Nowadays, human organism has been exposed to the constant influence of the steadily increasing radioactivity, various chemical and toxic substances;
- Humoral immunity – imunoglobulines, antigen-specific antibodies, B-lymphocytes which produce the antibodies and a lot of other serum factors;
- In the modern clinical medicine the multi-organ-humoral failure in occasional and multiple acute intoxication are of great interest;
- The complicated cerebro-psychological changes which appear in the organism when dependency is developed are caused by the action of two different processes: direct – cerebrotropic and indirect – organo-somatotropic.

Contents

1. Introduction

Nowadays, human organism has been exposed to the constant influence of the steadily increasing radioactivity, various chemicals and toxic substances in the working environment or outside. They have been used in large numbers for prophylaxis and treatment (vaccines, serums, chemotherapeutic agents, antibiotics, etc.)

This group of chemical factors has more or less influence on the macroorganisms, their immunological reactivity, potential for adaptation and functions of the immune system and the immunological homeostasis (the system for protection, rejection or elimination of all genetically extrinsic substances that come from the external environment).

The immunity is a basic phenomenon of the immune system and the possibility of the organism to recognize genetically extrinsic agents, so-called antigens, and to be protected from them.

The antigens can be microorganisms or their products, food, chemicals, medicaments, pollen, etc.
Due to immunity and its effects, the immune system can perform its main function: to take part in the maintenance of the homeostasis and the balance of the organism and to overcome the aggression of genetically extrinsic agents and the toxic effects of many potentially harmful factors.

2. Immunotoxic effects

As a result of the interaction of the immune system with medications or other chemical agents there can be seen at least two different types of pathological inclinations: immune suppression and immune activation. The increase in the sensibility towards infections and some forms of neoplasy result from the suppressed immune function. However, the excessive stimulation of certain parts of the immune system leads to reactions of oversensibility. In autoimmune diseases both elements of suppression and elements of stimulation of the immune system may take part. It is important to distinguish the consequences raised from immune toxic interactions from the others, congenital or acquired diseases and the possible interference between them.

2.1 Suppressed resistance to infections

As a rule, immune compromised patients have a decreased resistance to infections.
Several chemical factors of the environment may lead to suppression of the immune response: ionizing radiation, metals, different air pollution – sulphur and nitrogen oxides, carbon oxide, ozone, diesel components, chemotherapeutic and immunosuppressive medications.
Different aspects of the immune response can be considered:

- Immune deficit of T- cellular population: associated with the

development of frequent viral and opportunity infections due to the intracellular reproduction of micro-organisms and fungis (chicken pox, tuberculosis, lysteriosis, aspergilosis, etc.);
- Deficit of B-cellular functions - usually associated with severe bacterial infections (streptococcus, Kleibsiella pneumonia, Neisseria, etc.);
- Damaged phagocytosis and intracellular killing results in recurrent pus infections, chronic skin diseases;
- Deficit of the complementary system is associated with recurrent infections with streptococcus, Haemophilus influenzae, Neisseria meningitides.

2.2 More frequent carcinomas

Despite of the existing contradictions, there are a lot of clinical and experimental data proving that the immune suppression can lead to carcinogenesis and metastasis spreading. However, the facts about chemically induced carcinogenesis and the role of the immune suppression are still unclear.

Currently, it is considered that after continuous chemotherapy, cancerous patients often develop second malignant disease such as leukemia, macroglobulinemy, myeloma, etc. Undoubtedly, the damaged resistance to infections and the increased cancer development are major immune toxic consequences which are seen in the chemical and medication exposition.

2.3 Development of autoimmune diseases

The autoimmunity is a pathological immune response directed to one or more organism's own antigens with the production of antibodies and/or uncontrollable development of auto reactive T-cells. Wide range of diseases is associated with auto immune response – organ specific (like primary thyroidite, mixedem, diabetes type I) and multisystem (like systemic lupus with different organ presentation and a wide range of antibodies). In some these diseases was discovered genetic predisposition – genes connected or not to the HLA-system.

2.4 Reactions of over sensibility

Although the immune responses develop in order to protect the individual from infections and other genetically foreign agents, they are not always beneficial for it – they can be inappropriate or extraordinary strong, thus leading to damages on the tissues, which is the actual meaning of the concept "oversensibility". For example, IgE mediated reaction normally is manifested by urtikaria, conjunctivitis, rhino rhea, bronchial asthma or anaphylactic shock.

2.5 Changes in the hepatic metabolism

Suppression or stimulation of the hepatic enzymes by harmful chemical

substances or immuno-modullar therapeutic agents leads to disorders in the normal biotransformation in the liver, which may cause the accumulation of active metabolites, abnormal toxicity and pathological interleukin production. Phenobarbital and polycyclic hydrocarbons, which harm cytohrome P-450 monooxigenase functions, use similar mechanisms of action. Immuno-stimulation is also a factor that can modulate hepatic enzyme metabolism of medications. This fact should be taken into consideration by immuno-toxicologists.

3. Somatic problems and changes of the immune system in drug addicted patients

The complicated cerebro-psychological changes which appear in the organism when addiction is developed are caused by the action of two different processes: direct – cerebrotropic and indirect – organosomatotropic.

Direct cerebrotropic processes show up mainly in two dimensions independent of the agent's chemical nature - mediator and functional damages and metabolite disorder effects (2, 3).

Metabolite disorder is characterized with hypoxic intracellular indications and disorders in the biotransformation of proteins, lipids, monosaccharides and in the energy income. The mediator and the functional damages cause direct damage to the mediator structures which form the associative biological substrate of the higher neuropsychic action of the cerebrum in the organism.

In case of frequent contact with narcotic agent, the indirect somatotropic mechanisms of damage lead to the appearance of various symptoms and syndromes. Hepatic and kidney cells are most vulnerable, due to the obligatory and wide contact of these cells to the harming agent. The first ones are actively metabolizing molecules of the narcotic and the second ones assure the elimination of the toxic agent and its metabolites from the organism.

The regular use of narcotic substances increases the metabolic capacity of the hepatocytes. In order to achieve the desired effect the individual increases the dose periodically. This leads to the enlargement of the dose of the substance, which leads to acute and chronic toxic damages (4, 36).

In modern clinical medicine the multi-organ humoral failure in single and multiple acute intoxications are of interest. In fact this phenomenon is due to the fast structural-functional deficit which takes place in more than one organ or part of the body, appearing either at the same time or in a consequent way in the process of acute intoxication. We can distinguish primary or debut multi-organ failure and secondary or retarded multi-organ failure (2, 29).

According to some authors the multi-organ pathology in drug abusers is determined by the changes in the immune system (7, 19, 49, 53, 57). From the information we can find today it is clear that the narcotic analgesics

can influence both the humoral and the cellular immunity (9, 10).

Immunity is the major phenomenon of the immune system. It appears to be not only a reaction towards diseases with different etiology but also an expression of the major biological law for human survival and maintenance of the structural-functional uniformity (1, 30). As a rule immuno-compromised patients have decreased endurance to infections (5, 35). Narcotic abusers are not resistant to viral infections, including hepatitis B, C and HIV (17, 18, 48).

In subchronic experiment on mice treated with morphine it was found that there was statistically insignificant suppression of the activity of the spleen killers and the cytotoxic T-lymphocytes activity of the spleen and the peritoneum. However, in subacute experiment this suppression was statistically significant. These results provide an important explanation of the immune processes in heroin abusers with viral infections (10). Rats have been treated orally with different doses of morphine and methadone for 6 weeks.

When the doses of drugs were large, there was only a slight toxic effect found in liver and spleen. On the contrary – when low doses of morphine and methadone were used there was an increase in the relative weight of the mesenteric lymph nodes, hysto-pathological increase in the cellular density of the medullar cortex, indicating specific effect on the humoral immunity. The concentration of IgG in the serum was also increased (57).

Although the acute forms of hepatitis could be caused by different types of viruses, hepatitis C is the primary form of a chronic hepatitis, found in intravenous heroin abusers. In more than half of the cases with hepatitis C there are changes in the functional status of the liver – indications for persisting, potentially contagious infection with tendency for development of cirrhosis, liver failure and hepatocellular carcinoma (21, 22, 28, 53).

Hepatitis C is a global problem with an important medical, social and economical influence. It was found that there are about 170 million people world-wide infected with hepatitis C – almost 3% of the human population (59).

Hepatitis C spreads mainly by direct blood contact. In different countries there are various ways of transmission. In developed countries the most common way of transmission is the intravenous usage of narcotics or infection by blood, blood products or organs for transplantation which were not previously tested (44, 58).

In many developing countries the major ways of infection are blood transfusion and non-sterilized injections or surgical consumables. Additional sources of HCV infections are some rituals such as circumcision, blood releasing, tattoos or piercing.

Almost 20% of all HCV carriers are infected with HIV. There is co-infection in 52 to 92 % of the abusers using intravenous narcotics (16, 17, 18, 33, 43).

It is difficult to say exactly how hard HCV infection processes and there is a lot of influencing factors. Some patients are spontaneously healed. HCV is a disease with continuous character. Because of that a lot of patients die from other diseases even before the virus is detected. During the first 20 years of disease spreading, hard processing of the infection is found only in a small percentage of the infected. High percentages of the patients live 10 and more years, even after the progress of cirrhosis. Despite this with the progress of liver failure life expectancy reduces significantly (20, 25, 47, 48).

In 80% of the patients with acute hepatitis C it comes up to chronic disease. In chronic hepatitis C cirrhosis can be determined during the second or the third decade after the beginning of infection with compensated and moving to decompensated stage of the disease (8, 16, 23, 31).

The studies of Bakir AA, Dunea and etc. (6) establish that narcotic abuse complications cover the spectrum of glomerulus's interstitial and vascular damage and heroin-connected nephropathy typical for African and American intravenous narcotic abusers. However, this kind of nephropathy steps back from the HIV-connected nephropathy observed during the 90s.

The infection with methicilin-resistant Staphilococcus aureus bacterial super antigens in drug abusers may lead to acute glomerulonephritis. Chronic hepatitis B and C are known for their association with glomerulonephritis (GN).

After the infection with hepatitis B and C membrane-proliferating glomerulo-nephritis and cryoglobulinemy can be observed.

Dettmeyer R., Wessling B. and etc. (14) made a *post mortem* study of 179 venous drug abusers. All of them undergo kidney biopsy. In 61.7% of them was found monolymphocytar membrane-proliferating glomerulo-nephritis. In 37 out of 54 cases there were hepatic antibodies in the serum and 3 of these 54 cases were HIV-seropositive.

Cocaine causes rhabdomyolisis, extreme hypertonia, and sometimes – for lack of rhabdomyolisis – renal insufficiency and progressive increase in uremia in patients with hidden kidney failure (6). The amphetamine Ecstasy may lead to acute renal insufficiency, electrolytic misbalance and malign hypertonia (6).

Obviously, macrophages play a major role in the progress of glomerulo-sclerosis. Morphine increases the migration of monocytes, which may contribute to the progress of glomerulosclerosis in heroin abuse patients (50).

Narcotic abusers who inject the drug subcutaneously can develop amyloidosis. It was considered that chronic infections have a pathogenic role. Patients who inject cocaine and heroin subcutaneously ("skin popping") develop nephrotic syndrome with increase in serum creatinine and creatinine clearance (53).

There are cases of secondary amyloidosis with renal complications resulting from

parenteral (especially subcutaneous) usage of opioids, which progresses to terminal chronic renal insufficiency after continuous abuse with heroin. Nevertheless, it is possible to be completely cured after termination of the use of drug (6, 12, 41).

The effect of morphine was observed for the renomedullar interstitial cellular proliferation and matrix accumulation in rats. Increase in the proliferation of renomedullar cells was determined ($p<0.001$). This effect of morphine depends on the time and the dose. Morphine increases the accumulation of collagen type I and collagen type III by dose-depending type. This research prooved that morphine may play a role in the development of renal interstitial pathology in heroin dependent patients (51).

In contrast with the abusers in Africa and America, the ones in Europe do not develop focal segmental glomerulosclerosis but monolymphocytary membrane-proliferating glomerulonephritis (GN), partially due to heroin and other substances and obviously independent of hepatic infection (14).
There is description of the development of immune-complex glomerulonephritis in subacute endocarditis and staphylococcus pyogen abscesses of acute GN (6), induced by bacterial super antigens (6), and also description of membranous, mesangio-capillary, Ig A GN, and GN in cryoglobulinemy and node polyarthritis in chronic hepatitis B and C in intravenous abusers (6, 12).

HIV-associated nephropathy is described in the cases of venous usage of heroin and morphine by seropositive abusers (6, 12). Clinically, it is manifested with nephritic syndrome and quick progression of terminal chronic renal insufficiency. Histologically, it is manifested predominantly with collapse of the glomerulus, segment glomerulosclerosis and proliferation of the epithelial cells of the visceral lame of the capsule de Bauman. It is supposed that HIV has direct cytopathogenic effect on the renal tissue.

During the 70s of the previous century, the so-called heroin-associated nephropathy (HAN) was also described (6, 12, 41). Clinically, it is manifested with nephritic syndrome and quick progression to terminal chronic renal insufficiency; while morphologically it was characterized predominantly with segmental glomerulosclerosis and membrane-proliferating glomerulonephritis. The pathogenesis of this status is unclear but the antigenic role of heroin and its derivates, the formation of immune complexes in the glomerulus structures are assumptive. HAN shows also association with specific HLA haplotypes (41).

Studies with animals indicate that morphine and its derivates have direct effect on the glomerulus: stimulation of the production of TNF-alpha and NO by the mesangial cells (32), the proliferation of fibroblasts and suppression of collagen type IV degradation (12).

Furthermore, there was found the association of the intravenous usage of heroin with the development of hemolytic-uremic syndrome (HUS) (40), probably because of the role of heroin (morphine and its substances) as an antigen stimulus for the endothelial damage. The use of opioids is associated with the development of acute and chronic tubule-interstitial nephritis (41) with the toxic and toxoallergic genesis.

In heroin abused patients the auto antibodies (ANA, Rf, anti- DNA, anticardiolipin, antiplateletes anti-bodies, antibodies against the components of CNS- S 100, neuron specific enolase, myelin basic protein) were described. These antibodies are supposed to play a role in the development of systemic complications in abusers (11, 46, 52, 56).

Chronic exposition to morphine leads to suppression of cytotoxic T-lymphocytes activity in the spleen and the peritoneum through μ-opioid receptors. The metabolic activation of free radicals of morphine, cocaine and methadone may play a major role in the patho-physiological mechanisms of organic damages in abusers. The results from experimental trials with rats show that morphine, cocaine and methadone activate free radicals, which exert lipid membranes and stimulate release of histamine. This gives the idea that massive release of histamine by lipid cells can be an additional risk factor in cocaine and heroin overdose (15).

Opiate-induced asthma and other diseases induced by medicament abuse may contribute to the all other factors causing the death of drug abuse patients (37).

The inhalation of marijuana, cocaine, heroin leads to damages of the respiratory system, causes changes in the structures and functions of the pulmonary macrophages, triggering the development of pulmonary infections and malignant tumors (54).

The inhalation of heroin causes severe exacerbations of bronchial asthma. There are lethal cases after inhalation of overdose of heroin, in which the cause of the death is anaphylactic-like reaction. *Post mortem*, by immunocytochemical methods, the increased serum levels of the enzyme triptase, high concentration of eosinophil basic proteins, changes in the quantity and the allocation of the pulmonary mastocytes were found. Specific hystopathological changes, known in the literature as "narcotic lung", can be observed in the lungs (24).

In many countries, drug abusers use buprenorphine as cheaper substitute to heroin. For 60 days, adult male mice have been treated intraperitoneally with buprenorphine. The hematological markers were tested, and the leucopenia accompanied by decrease in the lymphocytes and monocytes, increase in neutrophils, decrease in hematocrit were found. However, the changes were reversible and the normal status was restored after 45 days after termination

of drugs use. Therefore, periodical monitoring of the blood tests in abusers is necessary (7).

By CT and hystomorphological analysis of the vertebral spongiose were found alterations in the bone metabolism in toxicomanies and abusers (45).

Mielke I. R., Deppe W. Ad etc. described 3 cases illustrating the damages on the peripheral nervous system (38).

The case of 25 years old man, after a large dose of alcohol combined with intranasal inhalation of heroin, was described with pain, oedema and eruption of the upper limbs and right sided paresis of the brachial plexus. The levels of creatininkinase, the total protein and IgE were increased. The pain was reduced by quanetidine blockage; the edema and the eruption disappeared after 7 days treatment with methyl-prednisolon (80 mg/day). The functions of the brachial plexus restored totally after 2.5 months (38).

The case of 27-year old man, who used heroin intravenously was described with fever - 39°C and proximal paralysis of the right arm. Leucocytosis, increased level of the creatininkinase and increased titer of antineutrophil cytoplasm antibodies was found. In the cerebrospinal liquid – the number of the cells and the protein was increased. After 2 days the patient developed acute renal insufficiency, which was overcame. The paresis persisted for 4 months (38).

21-year old woman with developed lesions of the upper brachial plexus after suicide attempt with flunitrazepam, combined with consumption of bottle of whisky and intravenous usage of heroin. The levels of C-reactive protein and IgM were increased. The paresis disappeared in 6 weeks without any specific treatment.
The authors discuss that the immune system might be involved in the pathogenesis of lesions of the brachial plexus and rhabdomyolisis (38).

There is a lot of clinical and experimental data according to which immuno-suppression may lead to carcinogenesis and metastasis. The data of chemically induced carcinogenesis and the role of immune depression are still uncertain.

Narcotic analgesics suppress the activity of NK-cells leading to stimulation of the tumor growth factor and its development.

After subcutaneous usage of heroin and cocaine, cervical intra-epithelial neoplasm and carcinoma of cervix uteri (11), non-healing ulcerations and skin necrosis of the lower limbs with 6 months duration (42) were observed. In patients using heroin intravenously, specialists found Pemphigus vegetans, type Noyman (19). In HIV-positive intravenous abusers, using their cervical veins to inject cocaine and heroin diffused thrombosis of the superficial veins of the whole body and periphlebitis with perivascular abscesses, oral candidosis, hepatitis C, broncho-pneumonitis,

endocarditis and failure of the tricuspid valve (34, 27) were observed.

Unusual ischemic cerebral lesions were also observed in drug abuse patients – heroin-associated vasculitis of the basal cerebral artery. After a corticoid therapy the neurological deficit could be eliminated (39).

In conclusion, the most frequently used psychoactive substances cause damages of different organs and tissues. A large part of these damages are mediated by immunological phenomena.

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Chapter 2

Drug consequence and treatment

Module 2.1

Integrated treatment of opioid dependence

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Key messages

- Treatment of addiction is as successful as the treatment of other chronic diseases;
- The treatment of addicted patients protect healthy people;
- Opioid addiction's treatment requires complex of detoxification, supportive treatment with opioid antagonists, rehabilitation and resocialisation;
- Rapid opioid detoxification could be used in general practice or even in outpatient settings according to cheap price, high effectiveness and safety of procedure.

Contents

Opioid addiction spreads like an infectious disease; so increased number of ex-users means decreased number of current drug users. That determines protection of numerous potential new users from involving into drug usage. Treatment usually begins when complete psychological and physical addiction occurs, though early stage remains invisible during a long time.

Chemical addiction is a chronic CNS disease, so hope of complete and fast recovery is naive. Without treatment this illness will spread more quickly, and outcomes will be more problematic. The treatment of addicted patients protects healthy people.

"Overall, treatment of addiction is as successful as treatment of other chronic diseases, such as diabetes, hypertension, and asthma. Drug treatment reduces drug use by 40% to 60%..."
Leshner A. I. JAMA, October 13, 1999

- ✓ Drug abuse: self administration of a drug that deviates from approved medical or social standards, and that has adverse consequences for individual
- ✓ Addiction: compulsive drug use associated with strong craving and preoccupation with obtaining and using the drug for its rewarding effects

Figure 1 Key concepts in dependence I

- ✓ Tolerance: decreased efficacy of a drug associated with long term administration
- ✓ Physical dependence: altered physiological state produced by long term administration in which target tissues adapt and require drug for normal functioning
- ✓ Discontinuation produces withdrawal or abstinence

Figure 2 Key concepts in dependence II

1. Key concepts in dependence - tolerance, withdrawal and neuroadaptation

Opiates are drugs derived from opium. The term **opioids** is used for the entire family of opiates including natural, synthetic and semi-synthetic. An opioid is any agent that binds to opioid receptors. There are four broad classes of opioids:

- Endogenous opioid, naturally produced in the body (endorphins);
- Opium alkaloids (morphine and codeine);
- Semi-synthetic opioids (heroin, oxycodone, and buprenorphine);
- Fully synthetic opioids (methadone).

Drug abuse: self - administration of a drug that deviates from approved medical or social standards, and that has adverse consequences for individuals.

Addiction: compulsive drug use associated with strong craving and preoccupation with obtaining and using the drug for its rewarding effects (Fig. 1).

Physical dependence: altered physiological state produced by long term administration in which target tissues adapt and require drug for normal functioning (Fig. 2).

Opioid dependence – patient's choices:

- No problem at all or something must be changed?
- Now or later?
- Treatment or harm reduction?
- By my own or by specialists?
- In-patient or out-patient settings?
- Which detoxification technique?
- Which way after detoxification?

Opioid dependence – specialist's choices:

- Integrated treatment or harm reduction?

The repeated administration of an opioid produces two important observable responses – tolerance and withdrawal. Tolerance is a phenomenon whereby repeated administration of the drug produces a diminished effect, as the body adapts to the presence of the drug. Tolerance to opioids can be dramatic; with repeated exposure to increasing doses of opioids, an individual can appear and function normally despite having taken doses which would be fatal in a non-tolerant individual.

Withdrawal is the phenomenon whereby after a period of prolonged exposure to opioid drugs, stopping the administration of the drug leads to physiological and psychological changes – an "abstinence syndrome". Tolerance and withdrawal are manifestations of the same process by which the body adapts to the presence of administered opioids. The term "neuroadaptation" is used to describe the changes inferred from observing tolerance and withdrawal. "Neuroadaptation" assumes adaptive changes occur in the CNS as a result of exposure to opioids; however, the mechanisms of neuroadaptation to opioids are not well understood. Neuroadaptation begins immediately following the administration of an opioid agonist. Four hours after the administration of a single dose of morphine to a nondependent subject, a mild withdrawal reaction can be precipitated by the administration of large doses of naloxone, indicating that a degree of neuroadaptation has already occurred. With repeated administration of an opioid, so long as the interval between doses is sufficiently short to ensure that there is time for neuroadaptation to completely reverse between doses, neuroadaptation and tolerance quickly become established. It is possible to progressively raise the

administered dose of an opioid within weeks, until tolerance is such that the patient can receive very large doses without evidence of toxicity.

The reversal of neuroadaptation begins quite rapidly when the level of opioid agonist drugs in the CNS begins to decline. Reversal of neuroadaptation is associated with the emergence of an abstinence syndrome – signs and symptoms of withdrawal. After about 3 weeks of regular opioid use, discontinuation is associated with the spontaneous emergence of symptoms and signs of withdrawal.

In general, the opiate withdrawal syndrome is characterised by:

- Dysphoria, irritability, dysphoria and delirium (delirium can last for up to 12 hours);
- Muscle tremor and twitches ("kicking the habit");
- Abdominal cramps and diarrhea;
- Tachicardia, arterial hypertension;
- Anorexia, nausea and vomiting;
- Hot and cold flushes, bone, joint and muscle pain;
- Insomnia and disturbed sleep;
- Intense craving for opioids;
- Restlessness, yawning, hyperventilation;
- Perspiration, rhinorrhoea;
- Dilated pupils;
- Piloerection ("cold turkey").

The severity of opioid withdrawal is determined by two major factors:

- The greater the dose of opioid being administered regularly, the more severe the withdrawal syndrome on discontinuing;
- The more rapid the rate at which the opioid is withdrawn, the more severe the withdrawal syndrome.

The more rapidly an opioid drug is cleared from the body, the more pronounced is the abstinence syndrome. Withdrawal from short-acting drugs tends to be more severe than withdrawal from long-acting drugs. Morphine has a half-life of about 2-3 hours, which means that morphine blood levels decline fairly rapidly, from a peak following intravenous administration. Abrupt cessation of regular morphine leads to quite a severe withdrawal syndrome. Long acting drugs such as methadone or buprenorphine have much more mild (but more prolonged) withdrawal symptoms on cessation. Even with these drugs, it is recommended that they be tapered over a period to allow more gradual and less symptomatically distressing reversal of neuroadaptation.

The most severe withdrawal reactions occur when an opioid antagonist is administered to a dependent patient who at the time has a high level of circulating opioid agonist. By competitively inhibiting the agonist, the administration of naloxone or naltrexone abruptly blocks agonist effects – instead of declining over many hours, drug effects are reversed in minutes. The result is a very severe withdrawal reaction, with profound physiological and psychological effects.

Based on this pattern of symptoms and signs, several scales for monitoring the severity of withdrawal have been

developed. However, scales which monitor only objective withdrawal signs often severely underestimate the severity of symptoms, and if symptomatic treatment is to be based on withdrawal severity, it is desirable to use a subjective withdrawal scale. One scale currently in use is the Subjective and Objective Withdrawal Scale (Handlesman, 1996). Because it was designed for repeated administration over short intervals, it is a useful scale for monitoring severity of withdrawal during detoxification.

After the acute phase of withdrawal, there appears to be a chronic withdrawal, in which low-grade symptoms of dysphoria and discomfort persist in many patients for 6 months or longer. No-one understands the mechanism of this protracted abstinence syndrome, but it is probably one factor contributing to the high rate of relapse in detoxified heroin users.

- Substance use monitoring
- Self-help and peer support groups
- Continuing care.

Components of comprehensive addiction treatment - associated services:

- Mental health services
- Medical services
- Educational services
- Financial services
- Housing services
- Family services
- Vocational services.

Financial sources for addiction treatment:

- Significantly lesser, than for prevention of drug offering and demand reduction;
- Major part of them goes to the harm reduction, treatment of addiction complications (infectious and mental diseases, etc.).

2. Components of comprehensive addiction treatment

Components of **comprehensive addiction treatment** - core elements:

- Intake processing and/or assessment
- Improvement of motivation;
- Treatment plan
- Pharmacotherapy
- Behavioral therapy and counseling

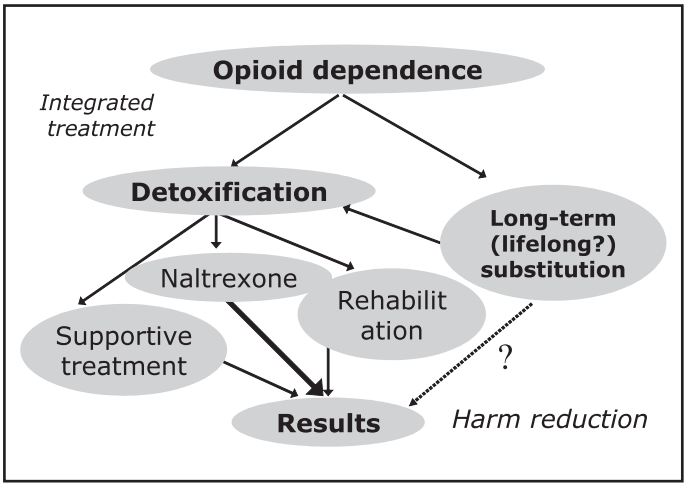


Figure 3 Opioid dependence – specialist's choices

Patients most likely to benefit from comprehensive addiction treatment are those who are strongly committed to abstinence, have good social support (employment, stable relationship, family support), and do not have serious psychological impairment.

3. Main trends of detoxification

As long as people have been using opiates, addicts and physicians have been searching for ways to achieve successful detoxification. Treatments in the past were not based on adequate theories on the nature of opiate addiction, therefore most of the opiate withdrawal methods were inadequate and sometimes even fatal. In the 1950s, methadone (a long-acting synthetic opiate) was introduced for opiate withdrawal treatment as a simpler, safer and less painful method. However, it proved to be associated with high relapse rates. During the 1970s, methods of rapid opiate detoxification precipitated and accelerated by administration of an opiate antagonist, such as naloxone or naltrexone were introduced. This method resulted in acute and severe withdrawal symptoms that could not be alleviated adequately in conscious patients, despite attempts to suppress withdrawal symptoms by using all kinds of adjuvant medication (e.g. anti-emetics, tranquillisers and analgesics). Other accelerated procedures which are also classified as rapid detoxification do exist (Fig. 3).

The goals of an episode of detoxification may be summarized as reversing (or at least reducing) neuroadaptation to opioids and promoting patients involvement in post-detoxification treatment. **Detoxification** is the process of providing symptomatic relief to assist patients to complete withdrawal and avoid adverse events associated with withdrawal. There has always been considerable consumer demand for detoxification. Patients are fearful of withdrawal, particularly after periods of heavy heroin use. Most commonly, patients present to detoxification services in times of crisis (Fig. 4).

Almost all people in this situation report wanting to become long-term abstinent. Withdrawal is often seen as the major barrier to discontinuing drug use. However, contrary to the hopes of patients, families, and health professionals, and assisting people, the to complete withdrawal is not usually followed by long-term abstinence from opioids. The great majority of subjects who undergo detoxification will return to heroin use within the next 12 months (usually, within the next month). However, many detoxified patients, having reduced their neuroadaptation, resume at much lower levels of heroin use. Often, several months after an episode of detoxification, subjects heroin use remains substantially lower than before entry to treatment.

Thus, while initially aiming for abstinence, a good outcome for some patients is that detoxification interrupts a heavy period of heroin use, allowing them to reduce their level of tolerance and regain, at least for a

time, a degree of control. Those patients who after an episode of detoxification continue with some other form of treatment – counselling, naltrexone, or maintenance with methadone – appear to do better than those who do not.

Opioid addiction is a tricky disease involving physiological, psychological, genetic, behavioral and environmental factors. This treatment requires complex of detoxification, supportive treatment with opioid antagonists, rehabilitation and resocialisation. When abstinence is the ultimate goal, the establishment of abstinence demand detoxification to manage the withdrawal symptoms. If eliminate the substitution with opioid agonists (the separate phenomenon without any hope on refusal from opioid abuse) there are four main trends of detoxification:

- Spontaneous opioid withdrawal;
- Permanent reduction of opioid dose till complete discontinuation;
- Traditional long-lasting methods;
- Rapid and ultra rapid detoxification.

Which technique is the best?

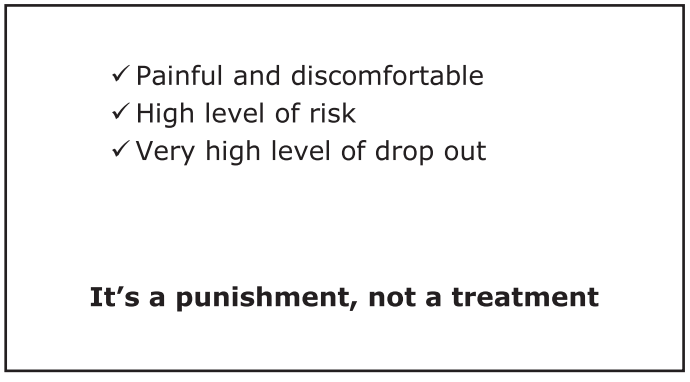
"In advanced family planning clinic, according to patient's confessional, ethical peculiarities and health conditions the great variety of birth control techniques can be suggested. All of them are available and suitable, if the results are achieved. Similar criterion of evaluation must be apply to the choise of detoxification techniques..."
Colin Brewer 2003

- ✓ No problem at all or something must be changed?
- ✓ Now or later?
- ✓ Treatment or harm reduction?
- ✓ By my own or by specialists?
- ✓ In-patient or out-patient settings?
- ✓ Which detoxification technique?
- ✓ Which way after detoxification?

Figure 4 Opioid dependence – patient's choices

- ✓ Without any medical support ("dry detox")
- ✓ Traditional
- ✓ Substitution with reducing doses of opioids
- ✓ Rapid opioid detoxification:
  - under general anesthesia (Ultra Rapid Opioid Detoxification)
  - under sedation (Rapid Opioid Detoxification)

Figure 5 Detoxification techniques



This is the main reason why many subjects fail to complete withdrawal. This method has high level of risk and drop out is painful and discomfortable.

Figure 6 "Dry detox"

3.1 Spontaneous opioid withdrawal - "Dry detox"

In people dependent on heroin, cessation of heroin use results in a withdrawal syndrome. The onset of symptoms of withdrawal is usually 8-24 hours after the last dose of heroin. Symptoms peak in 24-48 hours, then resolve after 5-7 days (Fig. 5 and Fig. 6).

Spontaneous withdrawal from opioids is not life-threatening. Occasionally, subjects with severe vomiting and diarrhoea may become dehydrated. Episodes of acute psychosis in patients with a history of schizophrenia have been reported. Some people harm themselves during withdrawal distress. However, serious adverse events are uncommon, and the majority of heroin dependent users have usually passed through multiple episodes of withdrawal, without any symptomatic treatment. Spontaneous withdrawal has been described as "objectively mild but subjectively severe". Patients are often severely distressed. Their intense craving for opioids is related to the knowledge that a dose of opioid will alleviate distress.

3.2 Substitution with tapering of opioids (Fig. 7)

- Advantages:
  - outpatients regime
  - safety
  - low costs
- Disadvantages:
  - large amount of relapses
  - impossibility to stop using.

Opioids for Substitution Therapy
- Methadone
- LAAM
- Morphine
- Heroin
- Drug of choice is buprenorphine – partial agonist at the μ receptors and κ antagonist:
  - doses should be titrated against severity of withdrawal
  - usual duration 7 -10 days.

3.3 Traditional detoxification

- Medicine:
  - no opioids
  - BZD, clonidine, carbamazepine q.s.
  - infusion therapy

- Disadvantages:
  - long duration (7 up to 28 days)
  - large amount of relapses
  - high costs and low effectiveness.

3.4 Rapid Opioid Detoxification

"Rapid detoxification" is the process of accelerating withdrawal from heroin (or other opioids) by administration of an opioid antagonist, while providing symptomatic relief to enable patients to tolerate the procedure (Fig. 8).

Consumer demand for rapid detoxification appears to be based on the belief that it offers quick, painless detoxification, which commits patients to abstinence. However, these perceptions are not well-founded.

- ✓ Drug of choise is buprenorphine – partial agonist at the μ (mu) receptors and κ (kappa) antagonist
- ✓ Doses should be titrated against severity of withdrawal
- ✓ Usual duration 7 -10 days

Figure 7 Substitution with reducing doses of opioids

- ✓ Opioid abstinence precipitated by administration of naltrexone and/or naloxone on in-patient settings
- ✓ Correction of symptoms of withdrawal
- ✓ Duration of detoxification 2-3 days
- ✓ Naltrexone doses of 0,2-10 mg prior to full dose (optional)
- ✓ Naltrexone full 50 mg dose 24-36 hours after heroin intake

Figure 8 Rapid Opioid Detoxification

Research consistently shows that rapid detoxification is neither quick nor painless. About 60% or more of the patients undergoing rapid detoxification will relapse to heroin addiction within 6 months.

Rapid detoxification appears to improve short-term induction onto naltrexone. The rationale for the technique of rapid detoxification is to improve induction onto naltrexone without compromising safety and without major increase in the severity of withdrawal. Antagonist precipitated withdrawal can be very severe. To minimize the risks of rapid detoxification, the major measures are:

- To delay the procedure until there are minimal drugs left in the CNS – at least 48 hours after the last use of heroin, or 7 days after the last use of methadone;
- To ensure patients are psychologically prepared and adequately supported;
- To exclude patients with intercurrent medical problems which would increase the risk of the procedure.

In view of the unpredictable severity of withdrawal reactions during rapid detoxification, it should only be performed in settings where there are:

- nursing staff adequate to deal with a severe reaction (1:1 nursing – for 4 hours in the event of a severe reaction);
- medical staff on-site for 4 hours from induction access to medications access to basic resuscitation equipment and staff trained in the use of this equipment;
- the capacity to retain a patient in in-patient care in the event of a significant reaction.

Rapid detoxification is appropriate for opioid-dependent patients who:

- Seeking for full abstinence, independent of duration, quantity, frequency and technique of opioids using;
- Show evidence of complete physical and psychological opioid dependence;
- Agree with this detox technique;
- Have no contraindications;
- Have been informed of the nature of the treatment and of treatment options.

Contraindications to rapid detoxification are:

- Disagreement for this detox technique;
- Severe somatic diseases: sepsis, cardiovascular insufficiency;
- Pregnancy;
- Acute psychosis;
- Consciousness impairment (GCS <15);
- Recent surgical intervention;
- A history of cardiac disease, or evidence of heart disease on clinical examination;
- Chronic renal impairment;
- Decompensated liver disease – jaundice and/or ascites, hepatic encephalopathy.

Relative contraindications to rapid detoxification are:

- Mental disorders, which can limit the collaboration;
- Planning treatment with opioid agonists;
- Current dependence on benzodiazepines, alcohol, or stimulants;
- History of treatment for depression;
- Unstable social circumstances.

Patient's evaluation – history:

- Motivations and goals for treatment;
- Opioid use – quantity and frequency;
- Other drugs use;
- High-risk drug behaviours, particulary overdoses, self-injury;
- Prior attempts for withdrawal, maintenance and other treatment;
- Social circumstances.

Patient's evaluation – examination:

- Mandatory:
  - Vital signs
  - Pregnancy or lactation
  - Evidence of intoxication or withdrawal from PAS
  - Evidence of complications of drug use
- Optional:
  - Urinary drug screens
  - Liver function test and viral serology.

The administration of opioid antagonists (such as naloxone or naltrexone) to opioid dependent people precipitates an immediate abstinence syndrome, often of considerable severity. This is the basis for the "naloxone challenge test" to diagnose opioid dependence. Antagonist precipitated withdrawal can be very severe. There have been reports of psychotic episodes during precipitated withdrawal. Without supportive treatment, patients may become dehydrated and develop electrolyte disturbances as a result of severe vomiting. Precipitated withdrawal is associated with significant physiological disturbances, including a marked increase in circulating catecholamines. The manifestations of precipitated withdrawal are atypical, and withdrawal scales do not provide an index of withdrawal severity.

- disagreement for this detox technique
- severe somatic diseases: sepsis, cardiovascular insufficiency
- pregnancy
- acute psychosis
- consciousness impairment (GCS <15)
- recently surgical intervention

Figure 9 Rapid Opioid Detoxification – absolute contraindications

✓ Standart medications for symptomatic treatment:
- infusion therapy up to 3000 ml crystaloids per day
- α_2 (alfa) agonist clonidine (0,6-1,2 mg per day)
- TIA - doxepin up to 50–100 mg per day
- BZD - diazepam up to 100 mg per day
- Neuroleptics - droperidol up to 5 mg per day
- octreotid (0,1-0,2 mg per day)

– $MgSO_4$, NSAID

Figure 10 Rapid Opioid Detoxification – standart medications for symptomatic treatment

The major factor associated with severity of precipitated withdrawal is recency of opioid use – the greater the interval between opioid use and administration of naltrexone, the less severe is the precipitated withdrawal. This is because the severity of withdrawal is proportional to the amount of drug still circulating. Heroin is a relatively short-acting drug. Heroin-dependent subjects who receive naltrexone within 12 hours after their last use of heroin, experience more severe withdrawal reactions than subjects in whom administration of naltrexone is delayed 24 - 48 hours. With longer half-life drugs such as methadone, much longer intervals are required. The severity of precipitated withdrawal is also influenced by the level of dependence - people with high opioid tolerance experience more severe precipitated withdrawal.

People maintained on methadone tend to have very severe precipitated withdrawal when given an antagonist. This reflects 2 factors:

- long-term exposure to a high dose of opioid, meaning high degree of neuroadaptation;
- the long half-life means that there is still circulating methadone up to 80 hours or longer after the last dose.

The major symptomatic medications used in rapid opioid detoxification are:

- Clonidine, a centrally acting alpha-2 agonist, to reduce sympathetic overactivity, agitation, and withdrawal distress up to 0,9 mg p/o;
- Octreotide, a synthetic somatostatin analog, the most effective agent for controlling gastrointestinal symptoms up to 0,1 μg;
- Benzopiazepine, usually Diazepam up to 100 mg per day or Lorazepam up to 20 mg per day;
- Infusion therapy up to 3 L crystaloids per day;
- MgSO4, NSAID, NMDA antagonists.

The standart medications for symptomatic treatment are shown on Figure 10.

Rapid detoxification requires a careful balance between the risks of too much medication and too little medication. Untreated, precipitated withdrawal can involve severe symptomatology and physiological disturbance. Inadequate sedation may be associated with severe distress. However, clonidine can produce significant hypotension and bradycardia. In the context of dehydration, this can contribute to acute renal failure. Benzodiazepines can contribute to worsening of delirium, and to depression of consciousness, respiration and gag reflex and risk of aspiration. The more drugs used to ameliorate symptoms, the greater the risks of drug interactions and potentiation of cardiovascular and respiratory toxicity are.

Advantages:

- short duration
- irreversibility of procedure
- real possibility to elevate withdrawal symptoms
- low costs.

Disadvantages:

- risk of psychosis, seizures, aspiration
- bradycardia, hypotension.

Postdetoxification period:

- Pharmacological correction:
  - sleep disturbances
  - depression
  - treatment of acquired collateral diseases
- Behavioral therapy:
  - group therapy
  - personal therapy
- Social rehabilitation
- Long-term naltrexone therapy.

Rapid opioid detoxification, could be used in general practice or even in out-patient settings according to cheap price, high effectiveness and safety of procedure. We choose this method in Vilnius Toxicology Clinic.

3.5 Ultra rapid opioid detoxification

- An acute abstinence induced by opiate antagonists under the general anaesthesia
- Performed only in ICU with skilled staff
- Duration of procedure 4-12 hours
- Induction of abstinence:
  - Naloxone/Naltrexone (full dose 1-4 hours after heroin intake)
- Correction of withdrawal symptoms:
  - alpha-2 agonists (clonidine)
  - octreotid
  - symptomatic treatment.

- Advantages:
  - early opioid antagonist induction
  - real possibility to elevate all withdrawal symptoms
- Disadvantages:
  - very high costs
  - 6 reported cases of death worldwide
  - complications of ALV and general anaesthesia.

"When detoxification is provided to patients, other approaches using clonidine, methadone, or buprenorphine are likely to be at least as effective as anesthesia-assisted detoxification and also are safer and far less costly."

Psychiatry News
October 7, 2005

4. Naltrexone treatment

- Marketed from 1984;
- Molecular structure is close to naloxone;
- Opioid lappa and delta receptor antagonist;
- Inhibits perception of opioid induced euphoria;
- Decrease craving;
- Most suitable antagonist for long-term therapy;
- Hepatotoxicity is possible only after huge doses;

Problem: early introduction of naltrexone (i.e. up to 5 days after heroin and 10 days after methadone intake) without special measures may produce severe withdrawal. Delirium, seizures, severe cardiovascular and gastrointestinal symptoms are possible

Figure 11 Naltrexone (administration)

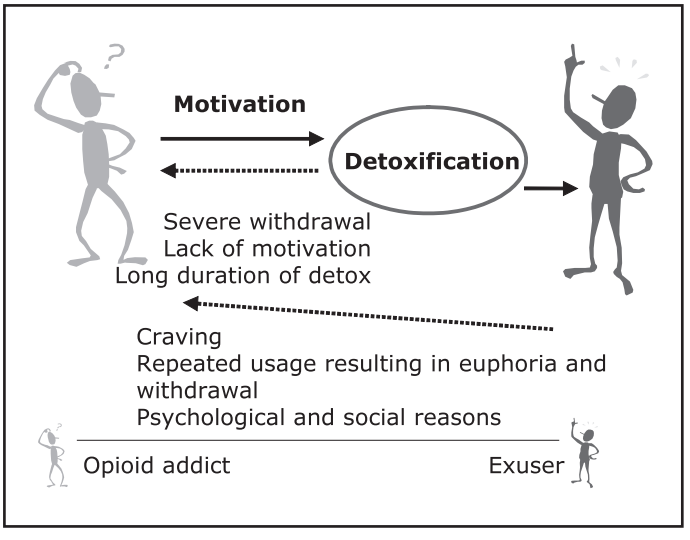


Figure 12 Reasons of relapse

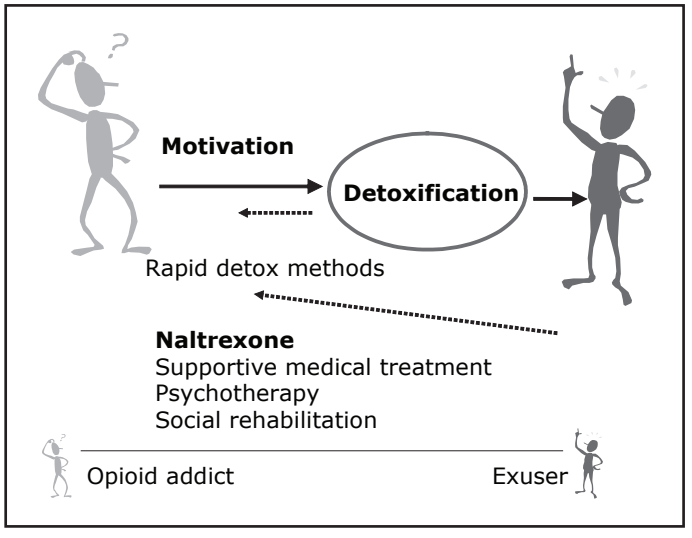


Figure 13 Prevention of relapse

- Injectable forms will be available within one year;

Naltrexone administration;

- Without rapid detox techniques:
  - 5-7 days after last heroin intake
  - 10-14 days after last methadone intake
- 1 time per day;
- Recommended duration of therapy 0,5-3 years;
- Side effects – dysphoria, abdominal pain, loss of concentration, co-ordination impairment – are rare (Fig. 11).

Detoxification followed by naltrexone use can be especially suitable for motivated, socially and emotionally stable opiate users, whose main obstacle in the pursuit of abstinence is apprehension of withdrawal symptoms. The detoxification is only the first step in the process of treating opiate addiction.

5. Conclusions

- Integrated complex treatment scheme with naltrexone could be a "golden standard" in treatment of opioid abuse;
- Effectiveness of opioid detoxification is directly related to correct evaluation and selection of patients;
- Rapid detoxification methods allows early introduction of naltrexone, thus decreasing incidence of early relapses (Fig. 12 and Fig. 13).

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Module 2.2
Cocaine cardiotoxicity

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Key messages

- Cocaine is the second most common illicit drug used and the most frequent cause of drug related deaths;
- Its use is associated with both acute and chronic complications that may involve any system, especially the cardiovascular system;
- Cocaine misuse has a major effect on young adult drug users in resulting loss of productivity and undue morbidity with cocaine related cardiac and cerebrovascular effects;
- Cocaine related cardiac complications: myocardial ischaemia, coronary artery spasm, acute myocardial infarction (MI), atherosclerosis, myocarditis, cardiomyopathy, arrhythmia, hypertension, and endocarditis;
- Many cocaine users have little or no idea of the risks associated with its use;
- The recognition of cocaine induced ischaemia or MI is crucial for optimal management. A previously healthy young person presenting with cardiac type chest pain or MI should be asked about cocaine use.

Contents

1. Introduction

The World Health Organization reports that 17 million deaths each year are attributable to cardiovascular disease (1). Cardiovascular disease is responsible for almost 49% deaths in Europe (2). The data of the Department of Statistics of the Republic of Lithuania show that cardiovascular disease prevailed in the Lithuania's mortality structure in 2001, accounting for 54.1% of all deaths. It is important to note that cardiovascular disease was the prime cause of mortality among both men and women (3).

Numerous epidemiologic studies undoubtedly demonstrated the association between main risk factors and cardiovascular disease, its progression and prognosis. In the 1990s investigators drew their attention to a specific group of cardiovascular disease of young (under 40 years), male patients who exercise frequently and intensively, have no risk factors or cardiovascular history. While specifying the disease history, some of them admitted using cocaine during the last 12 hours. A more thorough investigation was started, revealing the relationship between cocaine use and cardiovascular disease complications.

In 1999 approximately 25 million people in the USA had used cocaine at least once in their life, 3.7 million people had used cocaine in the past year and 1.5 million had been using cocaine constantly. At the same time cocaine use was responsible for 30% of drug related hospitalizations to an intensive care unit and became the main autopsy verified cause of drug induced deaths (4). The magnitude of the problem augmented in 2001, when the number of regular users increased to 5 million (5). The study performed in 2001 reported that 5% of the USA population aged 18–45 years were using cocaine regularly (6). Despite the fact that cocaine appeared in Lithuania lately, its rapid spread is a matter of great concern: study of alcohol and other drugs in European schools, conducted in Lithuania in 2003, revealed that 4% of 15–16 year old students had used cocaine (7). The increasing number of hospitalizations due to cocaine use, large amounts of this drug intercepted by the customs and police officers leave no hope of escaping cocaine invoked social, economic and healthcare problems in Lithuania (8).
For more information about the history of cocaine, its origin, use, effects and characteristics see Module 1.5.

2. Toxicokinetics, toxicodynamics of cocaine

Isolated from the leaves of the coca tree, cocaine (chemical name is benzoylmethylecgonine) is purified to white, sometimes bitterly, cocaine hydrochloride powder, which is the material for various forms of cocaine. It can be snorted, smoked, rubbed on the gums, used orally or injected intravenously. When injected intravenously or absorbed through nasopharynx, cocaine's activity starts after 1–3 minutes; when used orally – after 20–30 minutes, its concentration peaking after

60–90 minutes. If cocaine is snorted, 2 concentration peaks are observed – after 10 and 45 minutes. The first peak is due to fast resorption, meanwhile the second peak is probably caused by transient local vascular spasm which decreases resorption, and secondary resorption in the gastrointestinal tract (13). When cocaine is smoked or injected intravenously, the effect begins after several seconds, meanwhile if cocaine is snorted, vasoconstriction slows its resorption and the effect starts after 3 – 5 minutes (11). Cocaine is metabolized in the liver by hepatic esterases, plasma cholinesterase and nonenzymatic hydrolysis (9). The main metabolites are norcocaine, benzoylecgonine and ecgonine methyl esther. The concomitant use of cocaine and alcohol, which is common practice in young users, has a dangerous and multiplicative cardiovascular risk. They are metabolised in the liver to cocaethylene, which has been associated with 40-fold increase in risk for acute cardiac events and 25-fold increase in sudden death. Biological cocaine half-life is 0.5–1.5 hours. Approximately 80% of these metabolites are eliminated with urine over 24 hours; the excreted amount of nonmetabolized cocaine is relatively small. The cocaine metabolite benzoylecgonine, detected in the urine, is typically measured after 48 – 72 hours and even up to 22 days if cocaine was being used for a long time (9). Cocaine metabolites can be found in hair and nails for up to several months. The rate of metabolism depends on several factors: circulation, cholinesterase activity, duration of cocaine use (9).

Cocaine inhibits the reuptake of noradrenalin, adrenalin, serotonin and dopamine in the preganglic sympathetic nerve endings, increases the release of neuromediators to the synaptic gap, thus stimulating catecholamine accumulation in the postsynaptic nerve endings and causing central and peripheral adrenergic stimulation (9, 10, 14). Peripheral α-receptor activation causes vasoconstriction and hypertension. Their action is partially diminished by β-adrenergic receptor activation, also mediated by catecholamines. By inhibiting serotonin reuptake, cocaine acts similarly to selective serotonin reuptake inhibitors. The concomitant use of alcohol and cocaine results in the formation of cocaethylene - a metabolite, which is approximately 20 times more toxic than cocaine itself and its usual metabolites (10). If cocaine and nicotine are used together, the effect of the nicotine being in many aspects similar to that of cocaine's, the dual vasoconstrictive and hypertensive effect substantially increases the risk for myocardial infarction and other complications.

Cocaine administration, mechanism of action, short and long-term effects and complications in details are discussed in Module 1.5. This module deals with cocaine cardiotoxicity.

3. Cardiovascular effects of cocaine

For a long time it was considered that the only effect of cocaine is CNS stimulation. Nowadays it is evident that cocaine, being a universal vasoconstrictive agent,

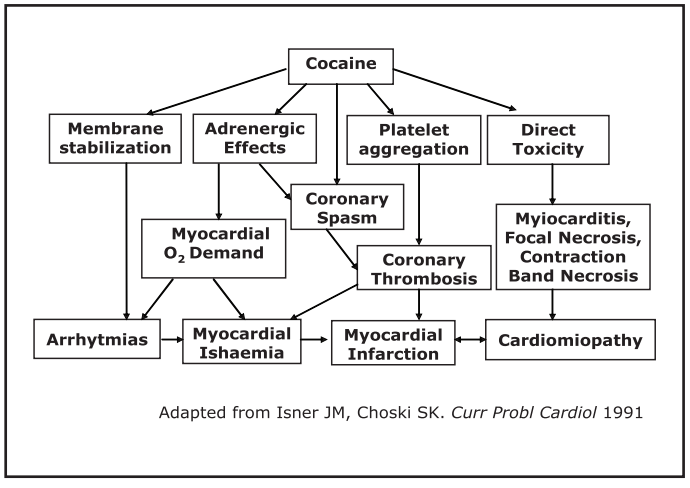

Figure 1 Possible mechanisms of cardiovascular complications of cocaine

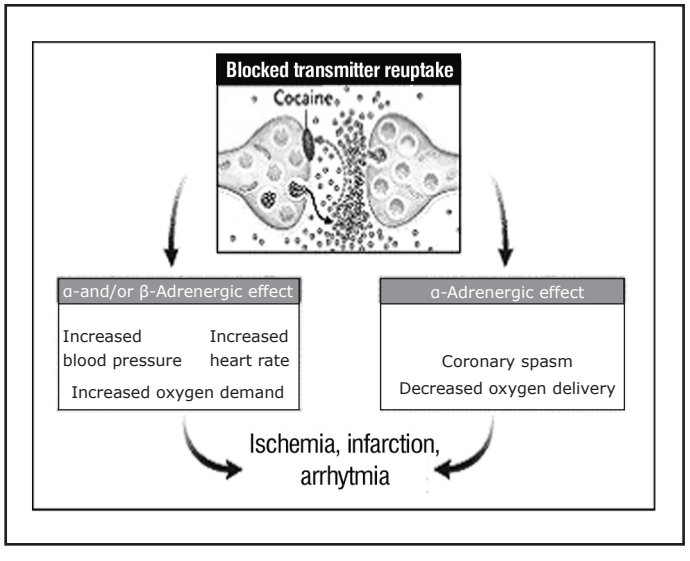

Figure 2 Acute cocaine effects

can affect every organ system, causing local ischaemia. Most commonly the cardiovascular system is damaged. Cocaine produces a dose-dependent increase in blood pressure and heart rate, which, in recreational doses, usually remains within the physiological range. The sympathomimetic actions of cocaine, at cellular level, are mediated by stimulation of the α- and ß-adrenergic receptors. Cocaine also interacts with the muscarinic receptors, and inhibits the reuptake of dopamine and seretonin by nerve endings. The most common symptom in cocaine users is chest pain, and the most common cardiac disorders are ischaemia and acute coronary syndrome, which can occur with all routes of cocaine intake.

Other cardiac problems include myocarditis, cardiomyopathy, and arrhythmias (Fig. 1 and Fig. 2).

4. Cocaine related chest pain and myocardial infarction

Cocaine users are usually hospitalized due to cardiovascular disease complications, prevailing acute myocardial infarction (MI) (15).

Retrospective CAMI (Cocaine Associated Myocardial Infarction) study analyzed data of 136 cocaine induced acute MIs, diagnosed in 29 hospitals in the USA during 1987 – 1993 (16). The majority of patients were young (mean age - 38 years), 88% had used cocaine during the previous 24 hours. Another study (Determinants of Myocardial Infarction

Onset Study), including 3946 patients, estimated that in the first hour cocaine use the risk for acute MI after was 23.7 times greater, in comparison to the control group. Moreover, cocaine use particularly increased the risk for acute MI in low cardiovascular risk individuals (17).

There exist several possible mechanisms of cocaine induced MI:

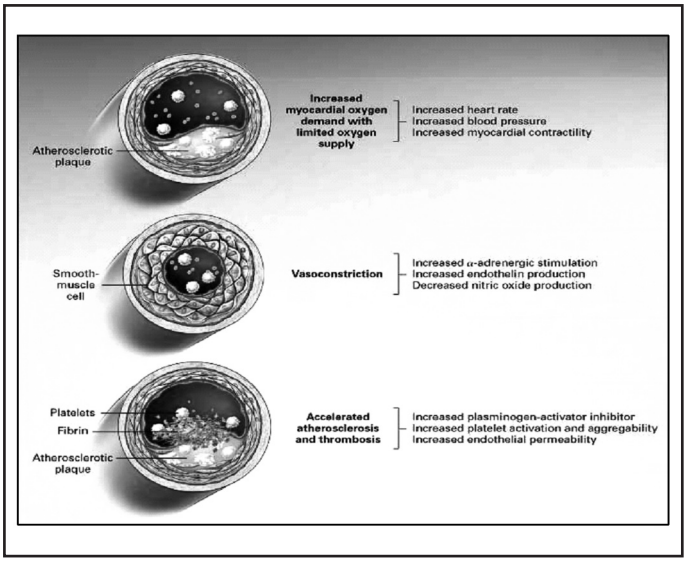

Figure 3 Cocaine effects on coronary arteries

- It is observed that in vitro cocaine causes platelet aggregation and increases thromboxane synthesis. This hypothesis is corroborated by autopsies, performed after cocaine induced fatal MI results: fresh, consisting plenty of platelets thrombi are being found in both healthy and atherosclerotic coronary arteries;
- The sympathomimetic cocaine effect elevates the heart rate and arterial blood pressure, thus increasing oxygen demand in the myocardium, followed by myocardial ischaemia and, subsequently MI, especially when concurrent coronary pathology is present;
- Cocaine induced coronary artery spasm can cause MI. The mechanism is not yet fully understood, but it is established, that in both single-time and regular cocaine users the concentration of powerful vasoconstrictor endothelin-1 markedly exceeds the rates of nonusers (18). The main cause of cocaine induced coronary artery spasm is α-receptor stimulation (it is demonstrated by positive α-receptor antagonist phentolamine effect, which eliminates cocaine induced coronary artery spasm);
- Some recent autopsy data reviews reported severe intimal hyperplasia and early atherosclerosis in young patients, who died of cocaine induced MI (19). Biopsies performed on cocaine users complaining of chest pain indicated significant thickening of small coronary arteries (20).

There is significant evidence that constant cocaine use accelerates development of atherosclerosis in coronary arteries (21). In addition, there is an evidence that cocaine activates platelets, increases platelets aggregability, and potentiates thromboxane production,

promoting thrombus formation. Thus, even when no coronary artery damage is present, the risk for coronary thrombosis increases considerably (21).

Long-term cocaine use wears out the dopamine reserve in the peripheral nerve endings. More than a third of ECGs of cocaine users with cocaine withdrawal syndrome show alterations in ST segment. It is important to note that most patients, including those who have had myocardial infarction, after quitting cocaine no longer experienced ischaemic chest pain (9, 11, 21) (Fig. 3).

Acute coronary events and MI can occur minutes after cocaine administration or as late as few days afterwards. The highest risk is in the first hour after cocaine use with no relation to the dose or route of administration. Cocaine induced MI often occurs in patients with normal coronary arteries and the typical patient is described as a man in his 30s with only smoking as a coronary risk factor. Half of these patients have experienced chest pain previously. Interestingly, the anterior wall is involved in most cases (77%) of cocaine induced MI. Chest pain and ECG changes are very common in cocaine users even in the absence of myocardial ischaemia and MI and only 6% of cocaine induced chest pain are attributable to MI. In one series, 1% of patients who have had an acute MI, have used cocaine within the previous year.

About 25% of this group, used cocaine within 60 minutes before the MI. Young patients presenting with chest pain and suspected acute coronary syndrome should be questioned about cocaine use.

Cocaine induced MI can be difficult to diagnose accurately, as the ECG is difficult to interpret in young patients, with high incidence of early repolarisation and left ventricular hypertrophy. On the other hand, MI can occur with normal ECG or with only non-specific findings.

Up to 84% of patients with cocaine induced chest pain may have an abnormal ECG and up to 43% of cocaine misusers without MI may have ST segment elevation in two or more ECG leads that may even meet the thrombolysis criteria. The reported ECG sensitivity for detecting cocaine induced MI is 36% with a 90 % specificity.

Serum creatine kinase is not a reliable indicator of myocardial injury and is increased in almost half of cocaine users without MI. This is considered to be attributable to rhabdomyolysis. In contrast, cardiac troponins are more sensitive and specific for myocardial injury and should be used for the diagnosis of MI.

Complications after cocaine induced MI, fortunately, have low incidence, probably because of the young age of most patients, and occur mostly within 12 hours of presentation. Ventricular arrhythmias occur in 4-17%, congestive heart failure in 5% to 7%, and death in less than 2%. However, continuous cocaine use and recurrent chest pain are common, with occasional recurrent non-fatal MI or death.

5. Cocaine related cardiac arrhythmias

It is established that cocaine use is responsible for various arrhythmias (22):

- Sinus tachycardia
- Sinus bradycardia
- Supraventricular tachycardia
- His bundle branch block
- Complete atrioventricular block
- Accelerated idioventricular rhythm
- Ventricular tachycardia
- Ventricular fibrillation
- Asystole.

Their mechanisms are not fully understood, but the most probable are:

- Direct toxic myocardial damage: multiple foci of myocarditis, micro-focal fibrosis, contractile fiber necrosis. These histological changes may be the anatomical substrate for rhythm disturbances;
- Central autoregulation mechanisms disorder due to increased levels of catecholamines and neuromediators. High levels of catecholamines in long-term cocaine users may cause poorly controlled arrhythmia. When cocaine blood level is high, asystole due to stabilization of membranes can be fatal (9, 10);
- As with chinidine, cocaine has a direct cardiotoxic action, accounting for reduced intraventricular conductivity and resulting in widened QRS complex and lengthened QT segment;
- Conductivity disorders due to vasospasm and ischaemia;
- Reentry mechanism (23).

At the cellular level cocaine, being an excellent local anesthetic, blocks sodium ion influx into the cell during depolarization (24). Rapid sodium channel blockade may result in negative inotropic response, bradycardia and hypotension. The electrocardiographic changes include wide QRS complexes and lengthened QT interval. The neuromediators released from sympathetic nervous system in the heart affects α- and β-adrenoreceptors. Their stimulation activates adenylate cyclase, which increases the level of cAMP, augmenting calcium influx into the cell, resulting in membrane depolarization, possible extrasystoles, torsade de pointes tachycardia, atrial fibrillation, supraventricular and ventricular tachycardia (25, 26). Long-term cocaine use is associated with enlargement of the left ventricle and hypertrophy of its walls. These changes later on increase the risk of arrhythmia (23, 27).

6. Cocaine related cardiomyopathy and myocarditis

Direct heart muscle damage is an uncommon cocaine induced pathology. This group of complications includes myocarditis and dilated cardiomyopathy. The risk for myocarditis is 5 times higher for cocaine users, compared to nonusers. The mechanism is not clear, however, myocarditis is considered to result from microvascular damage. Myocarditis is frequently diagnosed during autopsies of patients, who died of cocaine overdose. Transient toxic cardiomyopathy is caused by direct negative inotropic effect on the heart muscle (9-11, 21).

- Increased risk of bacterial endocarditis. The greater risk factor than the use of other drugs:
  - elevation of the heart rate and arterial pressure
  - immunosuppressive effects of cocaine
  - adulterans
- The endocarditis associated with cocaine abuse more often involves the left-sided cardiac valves

Figure 8 Endocarditis

After examining 1278 cases of dilated cardiomyopathy in John Hopkins hospital, investigators found that only 10 of them had a link to cocaine use. The authors assume that small number of cases was due to insufficient diagnostics and incomplete patient history (28).Myocarditis was reported in 20% to 30% of patients dying from cocaine misuse, as well as on myocardial biopsies of active users. The mechanism is thought to be either secondary to hypersensitivity reactions leading to vasculitis and myocarditis, or attributable to catecholamine induced cardiac toxicity. Fortunately, myocardial dysfunction is reversible with abstinence, also cocaine induced myocarditis in its early stages. Heart failure and cardiomegaly in a young person should raise the possibility of cocaine misuse.

7. Cocaine related stroke

The risk of stroke is considerably increased with cocaine use. Cerebral ischaemia and stroke result from multiple factors, similar to myocardial ischaemia. Cocaine causes vasospasm, because of high levels of monoamines (dopamine), and may cause thrombus formation leading to cerebral ischaemia, which results in hypoperfusion and neurological deficits. Long term cocaine use can also lead to cognitive deficits. Cocaine also can lead to rupture of pre-existing cerebral and mycotic aneurysms.

8. Cocaine related endocarditis

Cocaine use seems to be a greater independent risk factor for developing endocarditis than the use of other drugs. The endocarditis associated with cocaine misuse, in contrast with endocarditis associated with other drugs, often involves the left sided cardiac valves.
It is presumed that the increase in heart rate and blood pressure as result of cocaine use may lead to valvular and vascular injury that predisposes to bacterial invasion, as well as the immunosuppressive effects of cocaine that may increase the risk of infection (Fig. 8).

9. Cocaine related aortic dissection

When chest pain related to cocaine use is present, one must evaluate the possibility for dissection or rupture of the aorta. This complication can be caused

by severe increase in blood pressure. Literature describes rupture of mycotic and intracerebral aneurysms associated to cocaine use (30, 31, 32).

10. Differential diagnosis

A fair number of cocaine intoxications are not diagnosed even in the hospital, because the affected individuals are prone to conceal anamnesis, there is no possibility to detect the drug in biological media, while clinical presentation resembles most acute coronary syndromes. Having a young patient present with acute cardiovascular pathology and no history of disease, the physician must always consider possible cocaine effect. Acute cocaine intoxication is characterized by intense excitement, sometimes psychosis, aggravated breathing, epistaxis, abrupt convulsions, poorly controlled hypertension, and chest pain. Sometimes cocaine intoxication can be suspected if comorbidity related to cocaine use is present: thromboembolism, stroke, transient ischemic attack, pulmonary infarction, ischaemic skin changes, and nasal mucosal or even septal defect.

Cocaine induced cardiovascular disorders can also be differentiated from other pathology by typical clinical presentation of acute cocaine intoxication, characterized by three phases:

I phase – early stimulation:

- CNS – mydriasis, headache, bruxism, nausea, vomiting, vertigo, tremor (especially finger and facial muscles), tics, convulsive movements;
- Circulation – hypertension, tachycardia or bradycardia, pallor;
- Respiratory system – increased rate and volume;
- Thermoregulation – hyperthermia;
- Behaviour – euphoria, agitation, apprehension, excitation, restlessness, and emotional instability.

II phase – advanced stimulation:

- CNS – malignant encephalopathy, generalized seizures, decreased responsiveness to stimuli, greatly increased deep tendon reflexes;
- Circulation – hypertension; tachycardia; and possible ventricular arrhythmias, which then result in rapid and irregular pulse and hypotension, and peripheral cyanosis;
- Respiratory system – tachypnea, dyspnea, gasping, and irregular breathing;
- Thermoregulation – severe hyperthermia.

III phase – depression and agony:

- CNS – coma, areflexia, pupils fixed and dilated, paralysis;
- Circulation – cardiac arrest (ventricular fibrillation or asystole);
- Respiratory system – pulmonary edema, agonal respirations, and paralysis of respiration (9-14).

The accurate diagnosis of cocaine induced MI can be aggravated by at least two reasons:

- ECG alterations can be found in 56–84% of cocaine users complaining of

chest pain, even if MI is absent. In 43% of cocaine users changes in the ECG imitate acute myocardial infarction (ST segment elevation at least 1mm in more than two leads). The reported ECG sensitivity for detecting cocaine induced MI is 36% with 90% specificity. The high mistake incidence rate can be partially explained by relatively frequent early repolarization in young individuals (33, 34). During the first weeks of abstinence cocaine users usually experience silent myocardial ischaemia with ST segment elevation in the ECG;

- Serum creatine kinase is a nonspecific marker for myocardium damage, since its elevation is found in almost half of cocaine users without myocardial pathology (mostly because of rhabdomyolysis). These patients must have evaluated their serum troponin level.

In case of unclear diagnosis, a qualitative test and quantitative laboratory tests can be performed. Immunoenzyme assay is used for screening and reveals cocaine metabolite benzoylecgonine in the urine.

The test is highly specific, hence false positive results are virtually impossible. Quantitative tests include blood and urine tests performed by radioimmune assay, thin layer chromatography and gas chromatography (35).

11. Treatment options for cocaine induced cardiovascular disorders

All patients diagnosed with cocaine related cardiovascular complications should be treated and observed in an intensive care unit, their hemodynamics and respiratory measures being constantly monitored. Excitation due to hyperstimulation of the central nervous system complicates treatment. The major goal of treatment in the first phase of cocaine intoxication is immediate correction of hypertension, arrhythmias, seizures and hyperthermia. The treatment starts by stabilization and support of vital functions. Independently of their symptoms, all cocaine intoxicated patients should be first treated as follows:

- Oxygen supply;
- Benzodiazepines (diazepam) – first line drugs for anxiety, panic, psychosis, dysrhythmias, seizure control. They are to be administered only intravenously, starting from 5–10 mg, and repeating every 5 minutes until the effect is achieved;
- Hyperthermia is treated with external cooling devices;
- Correction of water and electrolytes, acid - base imbalance and hypoglycaemia;
- Gastric lavage and enterosorption with activated charcoal are only effective in case of severe peroral intoxication ("body packing" phenomenon).

The treatment of cocaine induced myocardial ischaemia or acute MI differ from the usual treatment algorithms for the pathology:

- Titrating nitrates is safe and appropriate, because it reduces cocaine induced vasoconstriction in healthy and atherosclerotic segments of the coronary arteries (11);
- Only low morphine doses can be administered for analgesia (2–8 mg intravenously);
- The second line treatment for reversing vasoconstriction is α-antagonist phentolamine (12);
- Nonselective β-blockers are strictly contraindicated. Although they effectively reduce cocaine induced tachycardia, however, even in the range of therapeutic dose uncontrolled hypertension and vasoconstriction of the coronary arteries due to substantial activation of α-adrenergic receptors and effect on peripheral blood vessels can emerge (36). For the management of uncontrolled tachycardia and hypertension a selective β1-blocker esmolol is recommended by some authors (37).

American Heart Association recommendations for the treatment of cocaine induced ischaemia or MI

First choice treatment:

- Oxygen
- Aspirin
- Nitroglycerine
- Benzodiazepines

Second choice treatment:

- Verapamil
- Phentolamine
- Thrombolysis or angioplasty (only after the occlusion is confirmed by angiography)

Avoidable:

- Propranolol.

Recognising that ischaemia or infarction is attributable to cocaine use is critical for optimal management.

The first line treatment in patients with chest pain and ECG changes after cocaine use, according the AHA/ACC guidelines, is benzodiazepines, aspirin, and nitrates. Benzodiazepines reduce blood pressure and heart rate and are recommended especially in patients with associated hypertension, tachycardia, or anxiety. Aspirin prevents thrombus formation and nitrates reverse cocaine induced coronary vasoconstriction. Oxygen also should be given and would help in limiting myocardial ischaemia.

Calcium channel blockers and blockers can be added as a second line treatment. Thrombolytic therapy should be used with caution and only if signs of infarction persist.

The use of ß-blockers can be deleterious and should be avoided in the acute stage, as their use may worsen vasospasm by permitting unopposed stimulation of receptors. Labetalol, which has a combined α1/ß-blocker effect, was shown to reduce the rise in blood pressure with no effect on cocaine induced coronary vasoconstriction.

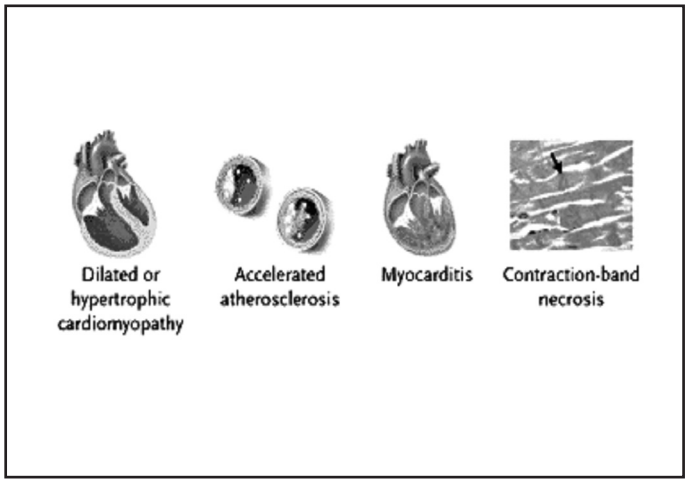

Figure 9 Chronic cocaine effects

The use of thrombolytic therapy in patients with cocaine related infarction remains controversial. It should be restricted to patients who have continued evidence of evolving MI despite the administration of first line medical treatment, and when immediate coronary angiography and angioplasty are not available, as experience with thrombolytic therapy in this clinical scenario is limited with reports of catastrophic complications associated with its use in cocaine users, in addition to the difficulty in identifying MI by standard ECG criteria.

Primary percutaneous coronary intervention may be a safer approach in those with definite MI, especially in the presence of cocaine use complications such as severe hypertension, seizures, intracerebral haemorrhage, or aortic dissection.

The proarrhythmic and proconvulsant effects of antiarrhythmic drugs may be additive to that of cocaine and their use should be cautious. The use of sodium bicarbonate for cocaine induced conduction abnormalities and rhythm disturbance is being evaluated.

The mechanism of MI and the high prevalence of chest pain without MI have important implications in management decisions. Not all patients who come to hospital with chest pain after cocaine use will need to be admitted.

A recent study suggested that a 12 hour observation period with serial ECG and cardiac enzymes would be safe and reasonable to rule out acute MI and select patients who need to be admitted.
This approach is expected to be highly cost effective. The incidence of late complications among patients, admitted with cocaine related chest pain, and in whom MI has been ruled out, seems to be low. In one study the one year survival was 98% and the incidence of late MI was around 1%. About two thirds of patients (60%) admitted with cocaine associated chest pain continue to use cocaine in the year after the symptomatic episode. The chronic cocaine effects are dilated or hypertrophic cardiomyopathy, acceletated atherosclerosis, myocarditis and contraction band necrosis (Fig. 4).

12. Conclusions

Cocaine can cause severe, sometimes lethal cardiovascular complications. The mechanism of its cardiotoxicity is not fully understood. There are hypotheses that the major causes for the pathology

are local or disseminated arterial spasm in healthy or atherosclerotic coronary arteries and thrombosis due to increased platelet aggregation. Increased myocardial oxygen demand and myocardial structure damage due to raised blood pressure and increased heart rate are influential in the development of the disease.

Long-term cocaine use is associated with multiple vasospasms, endothelial damage and atherosclerosis. Growing cocaine use is related to an increased number of complications, more frequent hospitalizations, and increased mortality. Regular cocaine use is linked to higher MI risk in young individuals, thus one should seriously consider the possibility of cocaine use complications in all young patients in low cardiac complications risk group, having MI, dilated cardiomyopathy, myocarditis and various arrhythmias. Pharmacological treatment of these patients remains problematic, since no well prepared prospective, randomized, controlled studies, comparing various cocaine induced ischaemia treatment schemes, exist. Benzodiazepines suppress toxic cocaine effects in the CNS and cardiovascular system by reducing excitement and blood pressure, slowing the heart rate, and therefore decreasing myocardial oxygen demand. Although there is no evidence from studies, antithrombotic aspirin therapy (if not contraindicated) is justifiable because of hypercoagulable cocaine effect. Nitrates can be used to reduce the extent of MI, relieve ischaemia related pain and eliminate coronary spasm.

Further clinical studies are highly limited by ethnicity and reluctance of the subjects to cooperate with the investigators.

Patients, health care professionals, and the public should be educated about the dangers and the considerable risks of cocaine use. People with cocaine misuse or dependence, particularly young men, should be encouraged to stop and should be referred for rehabilitation.

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Module 2.3
Acute poisoning with substances of abuse

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Contents

1. DSM-IV substance dependence and abuse criteria

1.1 Substance abuse

Substance abuse is defined as a maladaptive pattern of substance use leading to clinically significant impairment or distress as manifested by one (or more) of the following, occurring within a 12-month period:

- Recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home (such as repeated absences or poor work performance related to substance use; substance-related absences, suspensions, or expulsions from school; or neglect of children or household);
- Recurrent substance use in situations in which it is physically hazardous (such as driving an automobile or operating a machine when impaired by substance use);
- Recurrent substance-related legal problems (such as arrests for substance related disorderly conduct);
- Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance (for example, arguments with spouse about consequences of intoxication and physical fights).

1.2 Substance dependence

Addiction (termed substance dependence by the American Psychiatric Association) is defined as a maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring any time in the same 12-month period:

- Tolerance, as defined by either of the following:

(a) A need for markedly increased amounts of the substance to achieve intoxication or the desired effect

or

(b) Markedly diminished effect with continued use of the same amount of the substance;

- Withdrawal, as manifested by either of the following:

(a) The characteristic withdrawal syndrome for the substance

or

(b) The same (or closely related) substance is taken to relieve or avoid withdrawal symptoms;

- The substance is often taken in larger amounts or over a longer period than intended;
- There is a persistent desire or unsuccessful efforts to cut down or control substance use;
- A great deal of time is spent in activities necessary to obtain the substance, use the substance, or recover from its effects;
- Important social, occupational, or recreational activities are given up or reduced because of substance use;
- The substance use is continued despite the knowledge of having a persistent physical or psychological problem that is likely to have been caused or exacerbated by the substance

(for example, current cocaine use despite recognition of cocaine-induced depression or continued drinking, despite recognition that an ulcer was made worse by alcohol consumption).

2. ITC-10 criteria for mental and behavioural disorders due to psychoactive substance use

Identification of the psychoactive substance should be based on as many sources of information as possible. These include self-report data, analysis of blood and other body fluids, characteristic physical and psychological symptoms, clinical signs and behaviour.

2.1 Acute intoxication

A condition that follows the administration of a psychoactive substance resulting in disturbances in the level of consciousness, cognition, perception, affect or behaviour, or other psycho-physiological functions and responses.

The disturbances are directly related to the acute pharmacological effects of the substance and resolve with time, with complete recovery, except where tissue damage or other complications have arisen.

2.2 Harmful use

A pattern of psychoactive substance use that is causing damage to the health. The damage may be physical or mental.

2.3 Dependence syndrome

A cluster of behavioural, cognitive, and physiological phenomena that develop after repeated substance use and that typically include a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes physical withdrawal state.

2.4 Withdrawal state

A group of symptoms of variable clustering and severity occurring on absolute or relative withdrawal of a psychoactive substance after persistent use of that substance. The onset and course of the withdrawal state are time-limited and are related to the type of the psychoactive substance and the dose being used immediately before cessation or reduction of use. The withdrawal state may be complicated by convulsions.

2.5 Withdrawal state with delirium

A condition where the withdrawal state as defined in the common fourth character. Convulsions may also occur.

2.6 Psychotic disorder

A cluster of psychotic phenomena that occur during or following psychoactive substance use but that are not explained on the basis of acute intoxication alone and do not form part of a withdrawal state. The disorder is characterized by

hallucinations (typically auditory, but often in more than one sensory modality), perceptual distortions, delusions (often of a paranoid or persecutory nature), psychomotor disturbances (excitement or stupor), and an abnormal affect, which may range from intense fear to ecstasy. The sensorium is usually clear but some degree of clouding of consciousness, though not severe confusion, may be present.

2.7 Amnesic syndrome

A syndrome associated with chronic prominent impairment of recent and remote memory. Immediate recall is usually preserved and recent memory is characteristically more disturbed than remote memory. Other cognitive functions are usually relatively well preserved and amnesic defects are out of proportion to other disturbances.

2.8 Residual and late-onset psychotic disorder

A disorder in which psychoactive substance-induced changes of cognition, affect, personality, or behaviour persist beyond the period during which a direct psychoactive substance-related effect might reasonably be assumed to be operating.

3. Opioids

Common classifications divide the opioids into agonists - natural (Morphine, Codeine) semisynthetic (Heroin, Hydromorphone, Oxymorphone, Oxycodone) or synthetic (Methadone, Meperidine, Fentanyl, 3-methylfentanyl, Propoxyphene, Tramadol), partial agonists (Buprenorphine), antagonists (Naloxone, Nalmefene, Naltrexone).

3.1 Pathophysiology

Opioids bind to and enhance neurotransmission at opiate receptors:

- Mu (analgesia, euphoria, respiratory depression, and miosis);
- Kappa (analgesia, miosis, respiratory depression, and sedation);
- Sigma (dysphoria, hallucinations, and psychosis);
- Delta (euphoria, analgesia, and seizures).

The physiological effects of opioids are mediated principally through mu- and kappa-receptors. The opioid antagonists antagonize the effects at all type of receptors.

Generally, all opioid agonist drugs exert the same pharmacological effects in the CNS and periphery, but differ in pharmacokinetic properties, e.g. duration of action, potency, ability to cross blood-brain-barrier.

3.2 Overdose

Opiate toxicity should be suspected when the clinical triad of CNS depression, respiratory depression, and pupillary miosis are present. Needle tracks are observed occasionally, depending on the route of abuse.

CNS symptoms

- Both bradypnea and hypopnea are observed, rates as slow as 4-6 breaths

per minute and intensive central cyanosis often are observed;
- Sedation and drowsiness, unconsciousness up to coma;
- Miosis;
- Hypothermia;
- Suppression of cough;
- Suppression of pain;
- Nausea and vomiting;
- Euphoria or dysphoria, nightmares, anxiety, agitation, depression, paranoia, and hallucinations are encountered infrequently, mainly with high doses.

Periphery symptoms

- Mild peripheral vasodilation may occur and result in orthostatic hypotension;
- Urinary tract: urinary urgency and retention;
- Pruritus, flushed skin, and urticaria may arise because of histamine release;
- GI tract: constipation;
- Uterus: decreased contractions.

3.3 Treatment

- Cardiopulmonary resuscitation;
- Naloxone – bolus 2 mg I/V (0,4-2 mg) to 10 mg (If no I/V access - sublingual, endotracheal, i/m), continous infusion;
- In-patient monitoring at least 12 hours;
- Activated charcoal is the method of choice for patients with opiate intoxication following ingestion. Because of impairment of gastric emptying and GI motility produced by opiate intoxication, activated charcoal still may be effective when patients present late following ingestion;
- Heating, if necessary.

4. Cocaine

4.1 Neurochemical actions

The most noticeable systemic activity of cocaine is the stimulation of the CNS by blocking presynaptic reuptake and metabolism of norepinephrine, dopamine, serotonin, and acetylcholine.
- Blockade of reuptake of NE, DA and serotonin:
  - Low dose: preferential action on NE reuptake;
  - Moderate dose: NE and DA reuptake;
  - High doses: NE, DA and serotonin reuptake;
- Local anesthetic action:
  - Blockade of sodium channels

The local anesthetic effect of cocaine is due to a direct membrane effect. Cocaine blocks the initiation and conduction of electrical impulses within nerve cells by preventing the rapid increase in cell-membrane permeability to sodium ions during depolarization.

4.2 Cocaine overdose symptoms

- Neuropsychiatric complications occur in about 40% of all cocaine users and include depression, suicidal ideation, paranoia, kleptomania, violent antisocial behavior, catatonia, coma and auditory or visual hallucinations;
- Mydriasis;

- Hypertermia (>41°C);
- A moderate proportion of addicts develop panic attacks;
- Convulsions occur in about 3% of cocaine users. The majority of seizures are single, generalized, induced by intravenous or crack cocaine, and not associated with any lasting neurological deficits;
- Cerebrovascular disorders:
  - Ischemic manifestations of cocaine are postulated to be secondary to vasospasm or vasculitis or due to the procoagulant effect of the drug;
  - Ischemic stroke may be cardioembolic – a complication of endocarditis;
  - Cocaine-induced stroke in patients with underlying vascular malformations is thought to be due to the transient elevation of blood pressure;
  - Hemorrhage may occur within seconds or after up to 12 hours after cocaine use;
  - Subarachnoid hemorrhages primarily occur in patients with underlying vascular malformations.
- Movement and muscular disorders:
  - Opsoclonus and myoclonus are seen after cocaine inhalation;
  - During summer or in regions with warm climates, cocaine-intoxicated patients may show rhabdomyolysis;
  - Administration of neuroleptics in agitated long-term cocaine users can worsen the clinical picture and cause development of malignant hyperthermia.
- Cocaine may lead to myocardial infarction, cardiac arrhythmias, and respiratory arrest, lead to cerebral hypoperfusion or cerebral embolization;
- Pregnancy and newborns:
  - Women using cocaine have higher numbers of spontaneous abortions, premature births, and placenta previa than nonusers;
  - Congenital malformations are postulated to result from fetal ischemia during the first trimester;
  - Respiratory anomalies in newborns are more noticeable during sleep.

4.3 Cocaine overdose treatment

- No antidotes;
- Cardiopulmonary resuscitation;
- Agitation, psychosis, seizures, hypertension, tachycardia BZD (Diazepam 10-100 mg);
- Hyperthermia external cooling (<41°C);
- Severe hypertension - phentolamin, nitropruside;
- SVT - Ca antagonists;
- VT – lidocaine;
- No β-blockers;
- Dystonic reactions during the withdrawal phase subside quickly with administration of diphenhydramine;
- Administration of neuroleptics in agitated long-term cocaine users can cause development of malignant hyperthermia. These patients should be treated with a dopaminergic agonist (e.g., bromocriptine) and not with neuroleptics.

4.4 Heroin + Cocaine overdose symptoms

- Changing clinical signs:
  - Coma
  - Respiratory depression
  - Midriasis
  - Tachycardia.

4.5 Heroin + Cocaine overdose treatment

- Cardiopulmonary resuscitation;
- Naloxone: bolus 2 mg i/v + continous infusion;
- In-patient monitoring at least 12 hours;
- Symptomic treatment;
- Benzodiazepines.

5. Amphetamines

5.1 Neurochemical actions

Amphetamine compounds cause a general efflux of biogenic amines from neuronal synaptic terminals. They inhibit specific transporters responsible for reuptake of biogenic amines from the synaptic nerve ending and presynaptic vesicles. Amphetamines also inhibit monoamine oxidase, which degrades biogenic amine neurotransmitters intracellularly. Methamphetamine lacks much of the peripheral stimulant properties of amphetamine while still offering euphoric and hallucinogenic properties. These actions are similar to those of cocaine; however, while effects of cocaine last for 10-20 minutes, duration of amphetamine action is much longer, lasting as long as 10-12 hours.

5.2 Symptoms

- Central nervous system
  - Change of mental status, disorientation, and headache
  - Dyskinesias
  - Agitation
  - Formication
  - Symptoms of stroke
- Cardiovascular
  - Chest pain
  - Palpitations
  - Tachycardia and dysrhythmias
  - Hypertension or coronary vasospasm
  - Vasoconstriction
- Gastrointestinal
  - Dry mouth
  - Nausea and vomiting
  - Diarrhea
- Skin/cutaneous
  - Diaphoresis
  - Erythematous painful rashes, needle marks
  - Infected deep ulcerations (ecthyma)
- Ocular – Mydriasis
- Hyperthermia.

5.3 Treatment

- No antidotes;
- Cardiopulmonary resuscitation;
- GI decontamination is performed by the administration of activated charcoal;
- Agitation or persisting seizures require generous titration of benzodiazepines;

- Significant cardiac dysrhythmias may require cardioversion, defibrillation, and antidysrhythmics:
  - Use benzodiazepine sedation to initially manage hypertension;
  - Refractory cases can be managed with IV phentolamine, nitroglycerin;
  - Pulmonary edema can be managed with nitroglycerin and diuretics.
- Aggressive cooling. Patients with severe hyperthermia and psychomotor agitation may require immediate neuromuscular paralysis to rapidly decrease temperature;
- No β-blockers.

6. "Ecstasy" (MDMA)

6.1 Pathophysiology

MDMA causes catecholamine release from presynaptic vesicles. However, MDMA also is a selective serotonergic neurotoxin that causes massive release of serotonin and is postulated to inhibit its uptake. In animal models, it has been demonstrated to cause long-term destruction of 5-HT axons and axon terminals.

6.2 Symptoms

- Acute effects - anxiety, tachycardia, and elevated blood pressures;
- Associated symptoms - diaphoresis, bruxism, jaw clenching, paresthesias, dry mouth, increased psychomotor activity, and blurred vision;
- Within 1 hour - feelings of relaxation, euphoria, and increased communication;
- Cardiovascular effects:
  - Autonomic hyperactivity causes tachycardia, hypertension, and hyperthermia;
  - Fatal dysrhythmias have been reported following MDMA use.
- MDMA causes massive serotonin release, and numerous case reports link MDMA toxicity to the serotonin syndrome;
- Various cases of seizure and death secondary to hyponatremia have been reported:
  - Increased water intake;
  - Excessive sweating with physical exertion;
  - Release of vasopressin leading to the inappropriate antidiuretic hormone secretion.
- MDMA can lead to a subarachnoid hemorrhage, cerebral infarction, or intracranial bleeds.

6.3 Treatment

- Cardiopulmonary resuscitation;
- GI decontamination by administering activated charcoal. Whole bowel irrigation may be indicated if body packing of drugs is suspected;
- Hyperthermia require aggressive cooling measures and adequate fluid resuscitation. Antipyretics are not useful;
- Treat seizures with benzodiazepines;
- Treat the underlying cause and check electrolytes, especially hyponatremia.

7. Cannabinoids

7.1 Pathophysiology

Cannabis contains several pharmacologically active substances, of which, the most powerful is delta-9-tetrahydrocannabinol (THC). THC binding sites are known to be distributed widely throughout the brain. The density of these sites is highest in the basal ganglia and cerebellum. They are moderately dense in the hippocampus and cortex.

7.2 Symptoms

Onset of symptoms of marijuana intoxication occurs within a few minutes of smoking or within half an hour of oral ingestion. The duration of action is usually is 6-12 hours; the symptoms are most marked in the first 1-2 hours.
The following symptoms may be prominent in acute intoxication:

- Euphoria and relaxation, talkativeness;
- Subjective feelings of well-being or grandiosity;
- Perceptual changes (including visual distortions);
- A subjective sense of slowing of the passage of time;
- Increased appetite (the "munchies").

Although commonly misperceived as universally resulting in a relaxed and euphoric state, cannabis intoxication can produce a dysphoric reaction:

- Feelings of panic and anxiety;
- Disorientation and memory impairment (rare);
- Paranoia;
- Drowsiness and sluggishness;
- Headache;
- "Exploding chest";
- Sedation;
- Ataxia, tremor and diminished coordination;
- Dry mouth;
- Illusions or hallucinations, most often visual in type;
- Dysphoria;
- Recurrence of psychosis in patients with schizophrenia;
- Marijuana-induced seizures have been described;
- Acute intoxication may induce tachycardia and orthostatic hypotension;
- Marijuana has known antinausea properties;
- Injected conjunctivae may occur.

7.3 Treatment

- Benzodiazepines
- Symptomic treatment
- Psychoterapy.

8. Lysergic Acid Diethylamide (LSD)

8.1 Pathophysiology

Hallucinogens have a high affinity for serotonin 5-HT2 receptors, and LSD exhibits both agonist and antagonist properties. LSD may also stimulate both D1 and D2 dopamine receptors.

8.2 Symptoms

- Hallucinogen use rarely results in hospitalisation;

- Intensification or alterations of colors and sound (synesthesia);
- Sympathomimetic signs - mydriasis, hypertension, flushing, tachycardia, and, rarely, hyperthermia;
- Behavior can be agitated;
- An acute panic reaction, even in experienced users;
- Rarely, morbidity may be associated with the complications of hyperthermia:
  - Rhabdomyolysis
  - Myoglobinuric renal failure
  - Disseminated intravascular coagulopathy
- Generally, LSD-related deaths result from behavioral toxicity;
- The extreme agitation can lead to suicide or to accidental death.

8.3 Treatment

- Calm, stress-free environment;
- Benzodiazepines can safely be given to decrease agitation;
- Neuroleptic medications are not indicated in patients with LSD intoxication;
- Activated charcoal and gastric emptying are of little clinical value;
- Massive ingestions should be treated with supportive care and respiratory support;
- Hypertension, tachycardia, and hyperthermia should be treated symptomatically;
- Hypotension should be treated initially with fluids and subsequently with pressors if required.

9. Gamma-hydroxybutyric acid

9.1 Pathophysiology

GHB is found naturally in the CNS, with the highest concentrations in the basal ganglia. GHB binds to GABA-B receptors in the brain, inhibits noradrenaline release in the hypothalamus, and mediates the release of an opiate-like substance in the striatum.

It produces a biphasic dopamine response, increasing release at high doses and inhibiting release at lower doses. GHB has produced an increase in growth hormone in rats and in one small human study. GHB is also found in the peripheral blood and readily crosses the blood-brain and placental barriers.

9.2 Symptoms

- CNS depression is the hallmark of GHB use:
  - 10 mg/kg produces short-term amnesia and hypotonia;
  - 20-30 mg/kg produces drowsiness and sleep;
  - 50-70 mg/kg profound hypnosis and deep coma rapidly ensue.
- GHB does not produce analgesia or muscle relaxation;
- Extreme combativeness and agitation;
- GHB has been noted to cause bradycardia in approximately 30-35% of ingestions.

9.3 Teatment

- No specific antidotes;
- Cardiopulmonary resuscitation;
- Neuromuscular blockade should be used to avert the combativeness and agitation;
- Use atropine to treat symptomatic bradycardia that is unresponsive to stimulation.

10. Solvents

10.1 Symptoms

- Neurologic:
  - Decreased level of consciousness leading to coma
  - Dizziness and headaches
  - Decreased motor coordination
  - Confusion and hallucinations
  - Euphoria
  - Amnesia
  - Seizure activity
- Respiratory distress:
  - Bronchospasm, shortness of breath
  - Chest pain (with aspiration)
  - Tachypnea, hypoxia
- Gastrointestinal:
  - Nausea and vomiting
  - Abdominal pain
  - Hematemesis
- Glue sniffer's rash - perioral dermatitis secondary to contact of solvent vapors;
- Hypotension, tachycardia or bradycardia;
- Jaundice;
- Muscle weakness, muscle pain, paresthesias.

10.2 Treatment

- No antidotes;
- Administer supplemental oxygen;
- Cardiopulmonary resuscitation (if needed);
- Cardioversion of dysrhythmias may be necessary;
- Benzodiazepines.

11. Body packing and stuffing – is it the same?

- Packing – action, when a person transports illicit drugs in a body orifice. The risk of package rupture is more remote;
- Stuffing – action, when a person places drugs in a body orifice in a moment of imminent danger. In this case drugs are not well packaged for transportation, hence the high risk for leakage.

11.1 Investigations

- Ultrasonography;
- Contrast X-ray of the bowel;
- Computerized tomography;
- Drug detection in urine and blood.

11.2 First detected case in Lithuania

A 31 year old male was brought to the Department of Toxicology by customs officers after disembarking at the Vilnius International Airport suspecting of cocaine transport.

- There were no any complaints and examination of patient didn't show any pathology;

- All blood tests were normal;
- Patient refused endoscopy, but agree to contrast X-ray investigation;
- Foreign bodies were detected in the gastrointestinal tract by X-ray photography;
- Toxicological analysis for narcotics of urine and blood were done;
- Observation (blood pressure, heart frequency, temperature, neurological assessment every hour);
- Mild laxative in conjunction with sufficient beverages.

39 packets were excreted on the first day, 10 – on the second day, 3 – on the third day. X-ray 3 days later revealed foreign bodies in the gastrointestinal tract ("double condom'' sign). Because of customs officers demand, the patient was transferred to the Hospital of Prison, despite staff objection. 62 cocaine packets were excreted during the next 3 days.

Forensic analysis

- Condoms were filled with 3-8 g of cocaine each;
- 114 packages, weight 438,63 g, purity – 57%;
- 2 of cocaine packets were slightly injured;
- Blood sample – no answer, urine analysis – "possibility of cocaine metabolites".

Our mistakes

- Offer of gastroscopy;
- No express test (urine or blood).
- Removing from ICU settings to the Hospital of Prison without any emergency support, according to the patient's claim and officers' demand.

11.3 Management

- In no way endoscopic removal of the package should be attempted. The patient in whom only one packet fails to pass the pylorus may be the exception;
- Conservative management during spontaneous evacuation of the containers is the first choice approach to the body-packing;
- Surgery is indicated for patients with acute cocaine poisoning or gastrointestinal obstruction or perforation;
- Observation till the last package removes is obligatory;
- Clinical observation;
- Light solid diet;
- Free assumption of liquids.

12. Milestones in substance of abuse overdose treatment

- Naloxone
- Benzodiazepines
- Life support measures.

Module 2.4
Drugs in pregnancy

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Key messages

- For a pregnant woman, drug abuse is doubly dangerous;
- Use of drugs in pregnancy is not associated with birth defects;
- Withdrawal increases the risk of miscarriage in early pregnancy, premature labour, fetal distress and death in-utero;
- Virtually all illegal drugs, such as heroin and cocaine, pose dangers to a pregnant woman;
- Some drugs can be harmful when used at any time during pregnancy; others, however, are particularly damaging at specific stages.

Contents

1. Introduction

When a woman becomes pregnant, it is very important for her to lead a healthy life: to eat plenty of nourishing food, get plenty of rest, and exercise regularly. It is also vital that she avoid anything that might harm her or her baby-to-be. It is especially important to give up alcohol, cigarettes, and drugs.

For a pregnant woman, drug abuse is doubly dangerous. First, drugs may harm her own health, interfering with her ability to support the pregnancy. Second, some drugs can directly impair prenatal development.

Use of drugs in pregnancy is often associated with birth defects. The substances cross the placenta and can result in the fetus developing a tolerance to them. Infant withdrawal, Neonatal Abstinence Syndrome (NAS) may occur following delivery. Women in this situation are usually advised not to withdraw from drugs. Withdrawal increases the risk of miscarriage in early pregnancy, premature labour, fetal distress and death in-utero. To prevent withdrawal symptoms in pregnancy, women may feel the need to increase the use of drugs thus compounding the problems associated with illicit drug use.

2. Drugs and stages of pregnancy

Some drugs can be harmful when used at any time during pregnancy; others, however, are particularly damaging at specific stages.

2.1 The stage of organ formation

Most of the body organs and systems of the baby-to-be are formed within the first ten weeks or so of pregnancy (calculated from the date of the last menstrual period). During this stage, some drugs – and alcohol in particular – can cause malformations of such parts of the developing embryon as the heart, the limbs, and the facial features.

2.2 The stage of prenatal growth

After about the tenth week, the fetus should grow rapidly in weight and size. At this stage, certain drugs may damage organs that are still developing, such as the eyes, as well as the nervous system. Continuing drug use also increases the risk of miscarriage and premature delivery. But the greatest danger drugs pose at this stage is the potential to interfere with normal growth. Intrauterine growth retardation (IUGR) is likely to result in a low-birthweight baby – a baby born too early, too small, or both. Low-birthweight babies require special care and run a much higher risk of severe heath problems or even death.

2.3 The stage of birth

Some drugs can be especially harmful at the end of pregnancy. They may make delivery more difficult or dangerous, or they may create health problems for the newborn baby.

3. Which drugs are dangerous?

Virtually all illegal drugs, such as heroin and cocaine, pose dangers to a pregnant woman. Legal substances, such as alcohol and tobacco, are also dangerous, and even medical drugs, both prescription and over-the-counter, can be harmful. For her own health and the health of her baby-to-be, a woman should avoid all of them as much as possible; from the time she first plans to become pregnant or learns that she is pregnant.

3.1 Tobacco

Smoking during pregnancy appears to raise the risk of miscarriage or premature labour. But the primary danger is hindered fetal growth. Nicotine depresses the appetite at a time when a woman should be gaining weight, and smoking reduces the ability of the lungs to absorb oxygen. The fetus, deprived of sufficient nourishment and oxygen, may not grow as fast or as much as it should.

3.2 Alcohol

Alcohol crosses the placenta into the baby. It can cause problems such as miscarriage, premature birth and small babies due to slow growth in utero. There is a risk of birth defects resulting from heavy drinking during pregnancy (more than 6 standard drinks per day). This condition is known as Fetal Alcohol Syndrome. The risk of alcohol related birth defects correlates to the amount of alcohol consumed. Occasional binge drinking (> 5 standard drinks) may be harmful to the fetus.

Alcohol withdrawal during pregnancy is sometimes managed with diazepam. A dosage that appropriately controls withdrawal symptoms is given which is gradually reduced. Transient withdrawal symptoms such as tremors, lack of muscle tone and irritability have been observed among the newborn infants of women who drank heavily late in pregnancy.

The safety of some agents used in the treatment of alcohol dependence (e.g. acamprosate) has not yet been established during pregnancy. Use of these agents is not recommended.

3.3 Cannabis

Cannabis (marijuana) is not associated with causing birth defects. The effects of cannabis on fetal maturation are much the same as for cigarette smokers. There is an increased incidence of IUGR due to a lowered capacity for the blood to transport oxygen.

It is difficult to assess the effects of cannabis in the neonate but suspected effects include neonatal irritability, feeding difficulties and an unsettled baby.

Studies of cannabis use by pregnant women are inconclusive, because Marijuana is often used with other drugs, such as tobacco and alcohol. Like them it is associated with premature birth and low-birthweight babies.

3.4 Cocaine, Ecstasy, Amphetamine and Methamphetamine

There is no drug management option for stimulants such as cocaine, ecstasy, amphetamines and methamphetamines. Patient counseling and support can assist patients cease or reduce their drug use.

Management of stimulant withdrawal is symptomatic. Symptoms of withdrawal from stimulants can take up to a week to manifest. Often, it is the psychotic manifestations that prompt users to seek treatment. Severe agitation and psychosis requires psychiatric assessment, and short courses of antipsychotics, such as haloperidol may be required.

Speed (amphetamine) is commonly sold as cocaine or ecstasy (MDMA), or in combination. The duration of action is the most reliable way to ascertain the difference between these drugs. The effects of cocaine wear off after half an hour compared to amphetamines which last for about six hours.

Using amphetamines and cocaine during pregnancy causes decreased blood flow to the placenta due to vasoconstriction resulting in:

- Fetal malnutrition and distress, hypoxia and intra uterine growth retardation;
- Fetal hypoxia can stimulate the release of catecholamines which may cause cardic hypertrophy and hyperplasia;
- Substancial increase in arterial blood pressure and heart rate;
- Cocaine-induced vasoconstriction can result in hypertension, which has been associated with an increased risk of placental abruption.

Chronic cocaine use during pregnancy appears to be more problematic than amphetamine use. Some of the reported problems include:

- Spontaneous abortion in the first trimester;
- Premature labour;
- Fetal distress;
- Prematurity and IUGR;
- Fetal abnormalities – gastrointestinal and limb defects, cardiovascular malformations and perinatal cerebral infarction.

3.5 Heroin and other drugs

Heavy drugs use increases the danger of premature birth with such accompanying problems for the infant as low birthweight, breathing difficulties, hypoglycemia and intracranial hemorrhage.

The babies of drug-dependent mothers are often born dependent themselves and suffer withdrawal symptoms, such as irritability, vomiting and diarrhea, and joint stiffness.

Women who inject drugs may become infected with the HIV virus from dirty needles and may subsequently develop AIDS. HIV-infected women obviously run a high risk of passing the virus on to their babies.

3.6 Inhalants and volatile substances

At least one inhaled substance has been clearly connected with birth defects. The organic solvent toluene, widely used in paints and glues, appears to cause malformations like those produced by alcohol (which is itself an organic solvent). It is possible that all organic solvents may cause birth defects.

Volatile substances (petrol, glue, aerosol cans, butane gas) cross the placenta and can affect the developing fetus. The most likely effects will be an early labour, a premature baby with associated breathing problems and the risk of infection.

3.7 Benzodiazepines

Benzodiazepines are CNS depressants. Benzodiazepines cross the placenta and use during labour should be avoided. Chronic use of benzodiazepines during pregnancy may result in neonatal withdrawal. Benzodiazepines use during pregnancy is not associated with birth defects, but they can cause "floppy baby syndrome" which is a condition of reduced muscle tone, lethargy, sedation, decreased sucking and impaired temperature maintenance.

During pregnancy, the dose of benzodiazepines should be slowly reduced rather than abruptly ceased, as this may precipitate withdrawal symptoms which could have a detrimental effect on the fetus. To assist cessation of benzodiazepine use, an overall equivalent dosage of diazepam should be used and slowly decreased over a period of a few weeks. Diazepam is used as it has a relatively long half-life and is less psychoactive than some of the other benzodiazepines.

3.8 Phencyclidine (PCP)

Phencyclidine, or angel dust taken late in pregnancy can cause newborns to have withdrawal symptoms, such as lethargy alternating with tremors.

3.9 Medications

Many medications have side effects that are potentially harmful during pregnancy, but their benefits may outweigh their risks. A woman should consult her doctor or midwife before taking any drug, even one sold over the counter. Below are given a few examples of medical drugs that must be used with extreme caution or avoided altogether:

- Isotretinoin (Accutane) and entretinate (Tegison) are used to treat chronic acne and psoriasis. They may cause chronic malformations during the stage of organ development;
- Anticonvulsants, such as phenytoin (Dilantin) and carbamezapine (Tegretol), are used to prevent epileptic seizures. They are associated with defects of the heart and face, as well as mental retardation;
- Antimigraine drugs, such as ergotamine and methysergide, are used to head off migraine attacks but

raise the risk of premature labour;
- Aspirin, ibuprofen, and other non-steroidal anti-inflammatory drugs (NSAIDs) interfere with blood clotting and increase the risk of uncontrolled bleeding for both mother and baby. Toward the end of pregnancy, they hinder production of the hormones that stimulate labour, so that labour may be dangerously delayed or extended;
- Anticoagulant drugs based on coumarin are used in the treatment of heart disease and stroke, to slow blood clotting. Taken during early pregnancy, they are associated with facial malformations and mental retardation. Later on they raisethe risk of uncontrolled bleeding.

4. Methadone use in pregnancy

In pregnancy, methadone substitution for heroin, or other opiates, is the safest means of ensuring a healthy outcome for the mother and her baby. As methadone is a drug, it can be given as an opiate substitute to prevent drug withdrawal. It has duration of action of 24 hours and can therefore be given once a day. Pharmacotherapy management of addiction is based on the principles of harm minimization. Methadone treatment in pregnancy:
- Prevents withdrawal symptoms from opiates;
- Promotes psychosocial and lifestyle stability;
- Is associated with reduction in drug related crime;
- Decreases the risk of contracting blood borne viruses: Hepatitis B and C, and HIV;
- Creates a stable environment for fetal growth and survival;
- Results in less premature births;
- Encourages regular attendance for antenatal care and counseling.

Women should be advised to commence on methadone as soon as pregnancy is confirmed. Methadone stabilization in pregnancy is recommended as an inpatient procedure over 5 days. During this time, group sessions, drug and alcohol counseling and obstetric and midwifery care are given.

As with other drugs, as the pregnancy progresses, the methadone dose may need to be increased to prevent withdrawal. The reasons for this are:
- Increased volume of distribution;
- Increased liver metabolism;
- Increased glomerular filtration rate in increased metabolite excretion;
- Increased drug metabolism by placenta and fetus.

5. Buprenorphine in pregnancy

Buprenorphine is an alternative treatment to methadone, but is not currently recommended in pregnancy. Any patient seeking drug replacement treatment, who might become pregnant, should be counselled on the potential risks of buprenorphine during pregnancy. Women who conceive whilst on buprenorphine are advised to transfer to methadone maintenance. If, after a full explanation and consideration of the potential risks of

ongoing treatment with buprenorphine, the woman decides to continue with the treatment, she will be required to give consent.

6. Neonatal drug withdrawal

Infant drug withdrawal or Neonatal Abstinence Syndrome (NAS) can occur when an infant has been exposed to drugs (including heroine, methadone and buprenorphine) during pregnancy. It is not possible reliably to predict before birth which babies may develop NAS. The incidence or NAS is not directly related to the type or amount of drug used. NAS is readily diagnosed and treated.

Many babies show some signs of NAS, but not all of these babies will require drug treatment. Non-drug treatment involves the use of supportive therapy such as cuddling and pacifiers, in a quiet environment with reduced stimulation. Many babies benefit from receiving additional formula feeds during the first few days of establishing breastfeeding.

Babies who have been exposed to drugs in pregnancy are closely observed for signs of NAS. In Australia, a modified Finnegan scoring system is used to access the level of withdrawal in newborn babies. Babies are assessed several times a day according to symptoms relating to sleeping, feeding, skin colour, muscle tone and cry.

This assessment continues for up to 7 days following birth. If, after 7 days of assessment, the infant is not showing significant signs of NAS, and there are not other health issues, the baby will be discharged from hospital. The mother is referred to her local maternal and child health nurses (MCHN) and general practitioner (GP) for ongoing support and care.

If the infant does show significant symptoms of NAS during this 7 day period, he will be transferred to a nursery for further assessment of the need for drug treatment to manage NAS. If drug treatment is required, it will commence using a low dose of oral morphine. The dose is usually given every 6 hours with reduction in dose occurring every 3 days. During the treatment period, infants continue to be observed for signs of withdrawal. There may be variation in the treatment time according to the infant's progress. This gradual reduction of morphine takes approximately 4 weeks. Occasionally alternative drug therapy is used where withdrawal from drugs other than narcotics may occur.

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Module 2.5

Fetal alcohol syndrome and fetal alcohol spectrum disorders

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Key messages

- Fetal Alcohol Syndrome (FAS) is a term that describes a variety of physical and mental birth defects that are caused by women drinking alcohol during pregnancy;
- Fetal alcohol spectrum disorders (FASDs) is an umbrella term describing the range of effects that can occur in an individual whose mother drank alcohol during pregnancy;
- There is no cure or treatment for FAS and Fetal Alchohol Effect (FAE). However, FASDs are completely preventable if a woman does not drink alcohol while she is pregnant or could become pregnant.

Contents

1. What is FAS?

Fetal Alcohol Syndrome (FAS) is a term that describes a variety of physical and mental birth defects that are caused by women drinking alcohol during pregnancy. FAS is associated with defects such as mental retardation, behavioral maladjustments, central nervous system dysfunction, craniofacial abnormalities, and growth deficiencies. Fetal Alcohol Effect (FAE) describes a less severe case of the defects mentioned above.

FAS is directly linked to alcohol consumption during pregnancy. If a woman drink beer, liquor, or wine when she is pregnant, her baby could develop FAS or FAE. A baby with FAS can suffer from organ dysfunction, abnormal facial features, and other devastating disorders that will last a lifetime.

There is no cure or treatment for FAS and FAE, but these disorders are 100% preventable when a woman abstains from drinking alcohol during her pregnancy. FAS/FAE is the only cause of birth defects that can be completely prevented. The consumption of even the smallest amount of alcohol can result in FAS. About 1 out of 750 births are FAS sufferers; all races and socioeconomic groups are at equal risk.

The physical, mental, and emotional effects of FAS/FAE are irreversible. Many FAS/FAE sufferers are unable to understand cause and effect relationships and long-term consequences.

2. What is FASDs?

Fetal alcohol spectrum disorders (FASDs) is an umbrella term describing the range of effects that can occur in an individual whose mother drank alcohol during pregnancy. These effects include physical, mental, behavioral, and/or learning disabilities with possible lifelong implications. The term FASDs is not intended for use as a clinical diagnosis.

FASDs include FAS as well as other conditions in which individuals have some, but not all, of the clinical signs of FAS. Three terms often used are fetal alcohol effects (FAE), alcohol-related neurodevelopmental disorder (ARND), and alcohol-related birth defects (ARBD). The term FAE has been used to describe behavioral and cognitive problems in children, who were prenatally exposed to alcohol, but who do not have all of the typical diagnostic features of FAS. In 1996, the Institute of Medicine (IOM) replaced FAE with the terms ARND and ARBD. Children with ARND might have functional or mental problems linked to prenatal alcohol exposure. These include behavioral or cognitive abnormalities or a combination of both. Children with ARBD might have problems with the heart, kidneys, bones, and/or hearing. All FASDs are 100% preventable – if a woman does not drink alcohol while she is pregnant.

3. How common are FAS and FASDs?

The reported rates of FAS vary widely. These different rates depend on the population studied and the surveillance methods used. CDC studies show FAS rates ranging from 0.2 to 1.5 per 1,000 live births in different areas of the United States. Other FASDs are believed to occur approximately three times as often as FAS.

4. What are the characteristics of children with FAS and other FASDs?

FAS is the severe end of a spectrum of effects that can occur when a woman drinks during pregnancy. Fetal death is the most extreme outcome. FAS is a disorder characterized by abnormal facial features and growth and central nervous system (CNS) problems.

If a pregnant woman drinks alcohol but her child does not have all of the symptoms of FAS, it is possible that her child has another FASD, such as alcohol-related neurodevelopmental disorder (ARND). Children with ARND do not have full FAS but might demonstrate learning and behavioral problems caused by prenatal exposure to alcohol. Examples of these problems are difficulties with mathematical skills, difficulties with memory or attention, poor school performance, and poor impulse control and/or judgment.

Children with FASDs might have the following characteristics or exhibit the following behaviors (Fig. 1):

- Small size for gestational age or small stature in relation to peers;
- Facial abnormalities such as small eye openings;
- Poor coordination;
- Hyperactive behavior;
- Learning disabilities;
- Developmental disabilities (e.g. speech and language delays);
- Mental retardation or low IQ;
- Problems with daily living;
- Poor reasoning and judgment skills;
- Sleep and sucking disturbances in infancy.

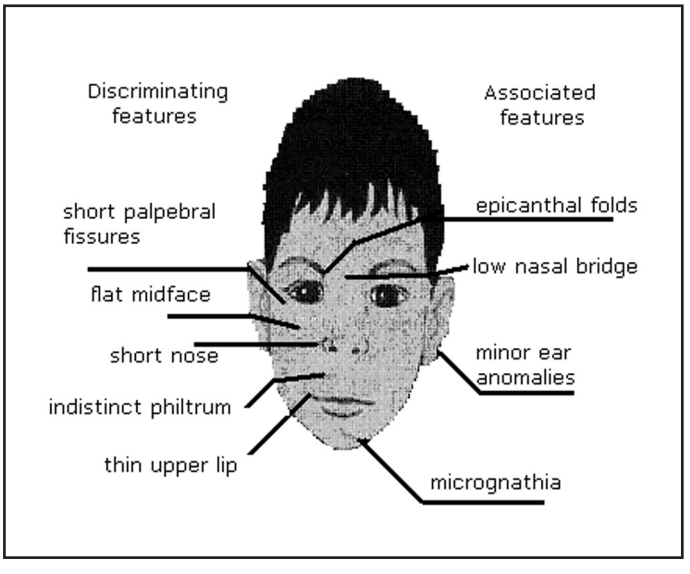

Figure 1 Characteristics of children with FAS and other FASDs

Children with FASDs are at risk for psychiatric problems, criminal behavior, unemployment, and incomplete education. These are secondary conditions that an individual is not born with but might acquire as a result of FAS or a related disorder. These conditions can be very serious, but there are protective factors that have been found to help individuals with FASDs. For example, a child who is diagnosed early in life can be placed in appropriate educational classes and given access to social services that can help the child and his or her family. Children with FASDs, who receive special education are more likely to achieve their developmental and educational potential. In addition, children with FASDs need a loving, nurturing, and stable home life to avoid disruptions, transient lifestyles, or harmful relationships. Children with FASDs, who live in abusive or unstable homes or who become involved in youth violence are much more likely than those who do not have such negative experiences to develop secondary conditions.

5. How does alcohol cause these problems?

When a pregnant woman drinks beer, wine, hard liquor, or other alcoholic drinks, alcohol gets into her blood. This alcohol moves to the fetal circulation through the **umbilical cord**. Once the alcohol is in the fetus, it can cause defects.

Drinking alcohol in the early stages of pregnancy can cause the facial and other physical defects of FAS. Drinking alcohol at any time during pregnancy can slow down the fetal growth and harm the brain. There is no safe time during pregnancy to drink any amount of alcohol.

6. How can we prevent FASDs?

FASDs are completely preventable – if a woman does not drink alcohol while she is pregnant or could become pregnant. If a woman is drinking during pregnancy, it is never too late for her to stop. The sooner a woman stops drinking, the better it will be for both her baby and herself. If a woman is not able to stop drinking, she should contact her doctor, local Alcoholics Anonymous, or local alcohol treatment center. The Substance Abuse and Mental Health Services Administration has a "Substance Abuse Treatment Facility locator". This locator helps people find drug and alcohol treatment programs in their area. If a woman is sexually active and is not using an effective form of birth control, she should not drink alcohol. She could become pregnant and not know it for several weeks or more.

Mothers are not the only ones who can prevent FASDs. The father's role is also important in helping the mother abstain from drinking alcohol during pregnancy. He can encourage her not drinking alcohol by avoiding social situations that involve drinking and by not drinking alcohol himself. Other, family members, schools, health and social service organizations, and communities can also help prevent FASDs through education and intervention.

In February 2005, the U.S. Surgeon General issued an Advisory on Alcohol Use in Pregnancy to raise public awareness about this important health concern. To reduce prenatal alcohol exposure, prevention efforts should target not only pregnant women who are currently drinking, but also women who could become pregnant, are drinking at high-risk levels, and are having unprotected sex.

7. Can FAS be cured?

FAS is permanent. There is no cure or treatment for it. But children with FAS can be helped. Regular medical care, hearing aids and eyeglasses can help these children live more normal lives. Children with FAS need special help at school. As children with FAS get older, they often need special services and support to help them live on their own.

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Module 2.6
Treatment of alcohol withdrawal

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Key messages

- Alcohol withdrawal (AW) is a syndrome which starts within 24-48 hours after cessation (or reduction) in alcohol use that has been heavy and prolonged;
- The most typical alcohol withdrawal symptoms are tremor, sweating, tachycardia, hypertension, anxiety, insomnia;
- The most critical are life-threatening findings such as seizures, hallucinations, arrhythmias and delirium tremens;
- Delirium tremens generally begins 2-3 days after cessation;
- Benzodiazepines are recommended as first choice medicine for alcohol withdrawal;
- 60% patients with AW respond to non-pharmacological interventions such as reassurance, reality orientation, and general nursing care.

Contents

1. Diagnosis and complications

Alcohol withdrawal (AW) is a syndrome which starts within 24-48 hours after cessation (or reduction) in alcohol use that has been heavy and prolonged. AW is characterized by a spectrum of symptoms ranging in severity. The most typical are tremor, sweating, tachycardia, hypertension, anxiety, and insomnia. The most critical are life-threatening findings such as seizures, hallucinations, arrhythmias and delirium tremens.

95% of patients have an uncomplicated withdrawal: self limited over few days, with associated insomnia and irritability. Most of them with mild symptoms of AW do not seek treatment. Patients with mild-to-moderate symptoms can be safely treated as outpatients. In cases of moderate-to-severe withdrawal or coexisting problems inpatient treatment should be offered.

1.1 Symptoms of uncomplicated alcohol withdrawal

- Tremor;
- Anorexia;
- Nausea, vomiting;
- Diaphoresis;
- Craving for alcohol;
- Insomnia;
- Anxiety;
- Agitation;
- Sensory (tactile, visual, auditory) disturbances;
- Tachycardia, hypertension.

Withdrawal seizures usually occur 24-48 hours after cessation. Late seizures can develop up to 5 day after cessation. Seizures can precipitate delirium (after 1/3 of all cases). Seizures are typically generalized tonic — clonic without focality, one or two in number. Status epilepticus and focality are connected with underlying brain pathology.

Delirium tremens generally begins 2-3 days after cessation. Complicated medical conditions often predispose delirium tremens. Withdrawal delirium may develop on medical or surgical service. It should be differentiated from somatic delirium, especially in elderly patients. Delirium tremens is critical condition, requiring intensive care unit.

1.2 Risk factors for complicated alcohol withdrawal

- Long duration of alcohol intake;
- Large amount of alcohol intake;
- Prior seizures;
- Prior delirium tremens;
- Prior detoxification ;
- Coexisting acute illness;
- Severe withdrawal symptoms at presentation.

2. Supportive care

60% patients with AW respond to non-pharmacological interventions such as reassurance, reality orientation, and general nursing care. Environmental influence can be reduced by using a quite private room, a comfortable bed, controlled lighting. Fluids should be

offered every 30 minutes. Regular diet should be available on patient request. Patient can be permitted to smoke up to four cigarettes per hour. Patient's physical comfort can be ensured by assisting to the patient in changing of positions in the bed, allowing the patient to walk, assisting to the bathroom.

3. The treatment of alcohol withdrawal

3.1 Benzodiazepines

Benzodiazepines (BZDs) are recommended as first choice medicine for alcohol withdrawal. All BZDs are equally efficacious in reducing signs and symptoms of AW. Long acting BZDs may be more effective in preventing withdrawal seizures. Withdrawal treated with long acting BZDs usually goes smoother and has fewer rebound symptoms. Short acting BZDs are associated with a lower risk of oversedation. Short — acting glucuronidated BZDs should be used in cases of hepatic dysfunction and in elderly patients. Some BZD have a higher liability for abuse. Phenobarbital is an acceptable alternative for the treatment of AW, although the margin of safety for this agent may be lower than for BZDs. The doses of medication needed to control symptoms can vary significantly. AW cannot be treated by providing only a fixed standardized dose for all patients. For some patients large amounts of medication should be administered rapidly if needed.

Structured assessment scales can be used for initial assessment and monitoring. Severity of AW can been rated with CIWA Ar (Clinical institute withdrawal assessment) scales. It gives a possibility to titrate a dose according to individual needs. In general this tactic of symptom-triggered treatment ("if needed") reduces administration of unnecessary medication. In patients with acute concomitant illness or concurrent withdrawal from others drugs such scales should be used with caution because some symptoms can be influenced by the other condition.

The use of structured scales and symptom-triggered therapy requires inpatient treatment and training of staff. An alternative is the use of fixed-schedule therapy with the provision of additional medicine when symptoms are not controlled with scheduled doses.

Table 1 Equivalent, potential initial doses of benzodiazepines

Drug	Administration	
	Oral (mg)	Intravenous (mg)
Chlordiazepoxide	100	-
Oxazepam	120	-
Lorazepam	4	1-2
Diazepam	20	5-10

3.2 ASAM guidelines recommend to administer a medication according the clinical considerations:

- For patients with mild symptoms (CIWA-Ar scores under 8-10), a reasonable clinical tactic is supportive nonpharmacological therapy and continued monitoring.
- Patients with moderate symptoms (CIWA-Ar scores between 8-15) should be treated with medication which also reduces the risk of complications.
- Patients with severe symptoms (CIWA – Ar scores 15 and above) have a significant risk of major complications (seizures or delirium tremens) if untreated.Such patients should receive BZD to control symptoms.
- Monitoring the severity of AW should be continued until symptoms are controlled.

3.3 Other medication

β-blockers, clonidine and carbamazepine are not recommended as monotherapy. They can be effective to control some symptoms of AW, but not prevent seizures nor delirium. They can be used in conjunction with BZD.

Carbamazepine can be used in case when AW goes together with BZD withdrawal. Carbamazepine does not potentiate CNS depression caused by alcohol and has no abuse potential.

Neuroleptics are not recommended as monotherapy as they do not reduce delirium and increase seizures. They can be considered for use in conjunction with BZDs for marked agitation or hallucinations.

Ethyl alcohol is not recommended. Thiamine should be administered to all patients with alcohol dependence from very beginning of the treatment. It not reduces delirium or seizures, but prevents Wernicke's disease and Wernicke-Korsakoff's (amnestic) syndrome.

Magnesium and potassium can be beneficial in patients with cardiac arrhythmias associated with hypomagnesaemia and hypokalaemia.

Seizures should be treated with intravenous diazepam or lorazepam. Long term anticonvulsant therapy of AWs seizures is not indicated.

Table 2 Examples of specific treatment regimens (ASAM guidelines)

Monitor the patient every 4-8 hours by means of CIWA-Ar until the score has been below 8-10 for 24 hours. Use additional assessments as needed.
Symptom-triggered regimens: Administer one of the following medications every hour when the CIWA-Ar is ≥8-10: chlordiazepoxide 50-100 mg, diazepam 10-20 mg, lorazepam 2-4 mg. Repeat CIWA-Ar one hour after every dose to assess need for further medication.
Fixed-schedule regimens: Chlordiazepoxide 50 mg every 6 hours for 4 doses, then 25 mg every 6 hours for 8 doses. Diazepam 10 mg every 6 hours for 4 doses, then 5 mg every 6 hours for 8 doses. Lorazepam 2 mg every 6 hours for 4 doses, then 1 mg every 6 hours for 8 doses. Provide additional medication as needed when symptoms not controlled (i.e CIWA-Ar ≥8-10) with above. Other benzodiazepines may be used at equivalent doses.

Table 3 Addiction Research Foundation Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar)

Patient	**Date**	**Time**
Pulse or heart rate, taken for one minute		**Blood pressure**
NAUSEA AND VOMITING "Do you feel sick to your stomach? Have you vomited?" Observation 0 no nausea and no vomiting 1 mild nausea with no vomiting 2 3 4 intermittent nausea with dry heaves 5 6 7 constant nausea, frequent dry heaves and vomiting		**TACTILE DISTURBANCES** "Have you any itching, pins and needles sensations, any burning, any numbness, or do you feel bugs crawling on or under your skin?" Observation 0 none 1 very mild itching, pins and needles, burning or numbness 2 mild itching, pins and needles, burning or numbness 3 moderate itching, pins and needles, burning or numbness 4 moderately severe hallucinations 5 severe hallucinations 6 extremely severe hallucinations 7 continuous hallucinations

TREMOR Arms extended and fingers spread apart. Observation 0 no tremor 1 not visible, but can be felt fingertip to fingertip 2 3 4 moderate, with patient's arms extended 5 6 7 severe, even with arms not extended	**AUDITORY DISTURBANCES** "Are you more aware of sounds around you? Are they harsh? Do they frighten you? Are you hearing anything that is disturbing to you? Are you hearing things you know are not there?" Observation 0 not present 1 very mild harshness or ability to frighten 2 mild harshness or ability to frighten 3 moderate harshness or ability to frighten 4 moderately severe hallucinations 5 severe hallucinations 6 extremely severe hallucinations 7 continuous hallucinations
PAROXYSMAL SWEATS Observation 0 no sweat visible 1 barely perceptible sweating, palms moist 2 3 4 beads of sweat obvious on forehead 5 6 7 drenching sweats	**VISUAL DISTURBANCES** "Does the light appear to be too bright? Is its colour different? Does it hurt your eyes? Are you seeing anything that is disturbing to you? Are you seeing things you know are not there?" Observation 0 not present 1 very mild sensitivity 2 mild sensitivity 3 moderate sensitivity 4 moderately severe hallucinations 5 severe hallucinations 6 extremely severe hallucinations 7 continuous hallucinations
ANXIETY "Do you feel nervous?" Observation 0 no anxiety, at ease 1 mild anxious 2 3 4 moderately anxious, or guarded, so anxiety is inferred 5 6 7 equivalent to acute panic states as seen in severe delirium or acute schizophrenic reactions	**HEADACHE, FULLNESS IN HEAD** "Does your head feel different? Does it feel like there is a band around your head?" Do not rate for dizziness or lightheadedness. Otherwise, rate severity 0 not present 1 very mild 2 mild 3 moderate 4 moderately severe 5 severe 6 very severe 7 extremely severe

AGITATION Observation 0 normal activity 1 somewhat more than normal activity 2 3 4 moderately fidgety and restless 5 6 7 paces back and forth during most of the interview, or constantly thrashes about	**ORIENTATION AND CLOUDING OF SENSORIUM** "What day is this? Where are you? Who am I?" 0 oriented and can do serial additions 1 cannot do serial additions or is uncertain about date 2 disoriented for date by no more than 2 calendar days 3 disoriented for date by more than 2 calendar days 4 disoriented for place/or person
Total **CIWA-Ar** Score	
Rater's Initials	
Maximum Possible Score	67
The **CIWA-Ar** is not copyrighted and may be reproduced freely. This assessment for monitoring withdrawal symptoms requires approximately 5 minutes to administer. The maximum score is 67 (see instrument). Patients scoring less than 10 do not usually need additional medication for withdrawal.	

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DRUG ABUSE TREATMENT AND PREVENTION

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