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General principles of poisoning management. Specific antidotes in poisoning therapy.

General principles of drug addiction

Department of Pharmacology FM MU

Pharmacology vs. Toxicology

Interconnection of both disciplines

They study the effects of chemicals on biological systems

Pharmacology - therapeutically useful effects, drugs

Toxicology - adverse, harmful (toxic) effects, poisons and toxins

Paracelsus (1493-1548):
“All substances are poisonous; there is none which is not a poison. The right dose differentiates a poison and a remedy”

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Causes of poisoning

1. drugs - 52%
2. industrial products - 30% (chemicals for cleaning, organic solvents, cosmetics...)
3. plants - 8%
4. pure bulk chemicals -5%
5. funghi - 2%
6. animal poisons (snakebite) -1%
7. others -1%

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General principles of acute poisoning treatment

Treatment has to be provided as quickly as possible but always with judgment so that therapeutical procedures do not cause worsening of the patient´s state or even death !!!

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General principles of poisoning treatment:

eliminate the substance from organism as quickly as possible
(= decontamination)

antidote (rapid counteraction for poison by means of specific actions);

„a drug, chelating substance, or a chemical that counteracts (neutralizes) the effects of another drug or a poison“

vital functions + symptomatic treatment

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1. Elimination of unabsorbed toxic substances from organism

Gastric lavage and administration of emetic, preferably within 1 hour of intoxication (the first treatments should be done prior to transportation to the hospital)

An average patient arrives only after 3 hours

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1. Elimination of unabsorbed toxic substances from organism

Induced vomiting

in p.o. poisoning within 4 hours
within 8 hours after anticholinergic agents
within 12 hours of pylorospasm inducing agents (eg, salicylates)

the patient is conscious, without spasms

Syrup of ipeca (emetin)- non-reg., apomorphine *(s.c.)*

mechanic stimulation of pharynx

Can not evacuate whole stomach content (max 30-50%) !

DO NOT INDUCE VOMITING IF ACIDS OR ALKALI WERE INGESTED

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OTHER CONTRAINDICATIONS OF INDUCED VOMITING:

Somnolence and loss of consciousness

Intoxication with foaming agents

Intoxication with hydrocarbons

Attacks of spasms

Alimentary intoxications in small infants

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1. Elimination of unabsorbed toxic substances from organism

Adsorbents

With poisons ingested p.o.

Charcoal (adsorbing carbon = Carbo adsorbens) / diosmectit → large active surface

50 – 100 g in 5 – 10% suspension, possibly with stomach tube, then repeatedly 50 g per 4 hours

up to 2.5 g/kg

\+: paracetamol, salicylic acid, diazepam, amphetamine

— methyl/ethylalcohol, Li, strong acids and alkali

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Toxic substances that are poorly adsorbable by charcoal

acids
alkali
chlorates
chlorids
cyanides
nitrates
ethanol
ethylenglycol
isopropanol
methanol

fluorides
iron
ferrous sulphate
potassium
sodium
detergents

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1. Elimination of unabsorbed toxic substances from organism

Gastric lavage

In p.o. intoxications within 4 hours

The patient is conscious, without spasms
when unconscious, ONLY in lying position and intubated

warm water (37°C), saline (preparation: 2 teaspoons of salt per 1 litre water), 300 ml

Sample for toxicological analysis

In the end (the last lavage) add adsorbent (30 g of activated carbon) or a laxative (Na_2SO_4)

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1. Elimination of unabsorbed toxic substances from organism - PEG - laxative , GIT dialysis

- PEG - polyethylene glycol in ionic solutions

- 4 liters / 2 hours until the evacuated rectal content is clear

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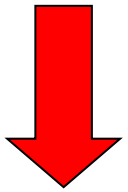
1. Elimination of unabsorbed toxic substances from organism

Increasing the intestinal passage

The patient is conscious, with no spasms
Administration of big doses of strong and quick-acting laxatives
Sodium sulphate (20 – 30 g with a large volume of water)
Mannitol (ca 50g per 1 litre water; 0.5 – 1 litre is administered p.o.)
Castor oil (20 – 30 ml)



CI in poisons soluble in fats!!! (castor oil ↑bile secretion and resorption of fats)

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1. Elimination of unabsorbed toxic substances from organism

Total intestinal lavage

Large-volume solution (25 ml/kg)
Through stomach tube, until clean solution flows off

Without resorption, does not cause diarrhoea

It only rinses the intestine
polyethylenglycol + $NaSO_4$, NaCl

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1. Elimination of absorbed toxic substances from organism

Forced osmotic diuresis

Infusion of saccharide solutions (20% mannitol; possible combination with furosemide), physiological solution

Up to several litres / day

CI: brain and lung oedema, heart failure, anuria

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1. Elimination of absorbed toxic substances from organism

Forced alkali diuresis

Speeds up elimination of slightly acidic poisons

Alkalinisation of urine and blood (pH 7.5 – 9.0)
$NaHCO_3$ solutions

I: salicylates, barbiturates, sulphonamides, antipsychotic drugs,...

CI: pulmonary oedema, shock, serious impairment of kidneys

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1. Elimination of absorbed toxic substances from organism

Forced acidic diuresis

Speeds up elimination of slightly alkalinic poisons

Acidification of blood and urine

5% Glc solutions with ammonium chloride in i.v. infusion

I: amphetamines, quinine, quinidine, nicotine, morphine,...

CI: serious impairment of kidneys

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1. Elimination of absorbed toxic substances from organism

Peritoneal dialysis

Haemodialysis

Haemoperfusion

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2. Neutralization of poison through administration of antidote

Antidote – a substance that neutralises the effect of poison

specific (using antagonistic effects of pharmaceuticals – antidotes that can counteract the effects of poison either partly or completely)

non-specific (adsorption – activated – medicinal carbon = carbo adsorbens – carbo activatus – carbo medicinalis)

RATIO OF CARBON : TOXIC SUBSTANCE = 10 : 1
(usually 50g / 3 – 4h; most often intoxications with medicines, chemicals)

It is necessary to administer antidote as quickly as possible

Dosage according to plasmatic level of toxin

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Specific Antidotes

https://www.annemergmed.com/article/S0196-0644(17)30657-1/fulltext

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3. Symptomatic treatment

Check vital signs

Intubation

Entry into bloodstream

Support of CVS (inotropics, vasopressors)

Therapy of spasms

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Toxicological Information Centre

Website of the Toxikologické informační střediskoTIS).

Acute poisoning - what to do?

Dial +420 **224 91 92 93** or **224 91 54 02**

To receive advice on first aid and what to do next.

Prepare:

- precise information on the accident
- **full name**
- **birth identification number**
- **health insurance company**
- healthcare professional also their IČP (organization identification number)

In order to facilitate the consultation, the doctors are asked to calculate (provided it can be ascertained) the quantity of medication (active substance) that intoxicated the patient. Also please try to estimate or find out the body weight of the patient.

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Toxicological Information Centre

A 24/7 nationwide telephone medical information service to consult cases of **acute human and animal intoxications**

For both laypersons and doctors

The goal of the TIS is **to decrease the number and severity of intoxications** and to favourably effect **the course of accidents. The Centre provides information on the chemical composition of commercial products and on the therapy of acute intoxications with these products**

It does not deal with:

the influence of chemical compounds on foetus
cancerogeneity
adverse effects of medicinal drugs
impact of chemical compounds on the environment

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Intoxication with medicines

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Intoxication with medicines

Most often: *sedatives, hypnotics, analgesics*

Causes of death:

Injury to CNS – *psychotropics*
Injury to CVS – cardio*glycosides antiasthmatic drugs*
Liver injury – *paracetamol, nimesulide, protease inhibitors,*

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General principles of drug addiction

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Addiction = compulsive drug use despite harmful consequences

is characterized by an inability to stop using a drug (failure to meet work, social, or family obligations; tolerance and withdrawal).

accompanied by unnatural cravings that prompt the compulsive behaviors.

It is a primary, **chronic, neurobiologic disease** with genetic, psychosocial and environmental factors that influence its development and manifestations.

It is characterized by behaviours that include one or more of the following:

loss of control over drug use

continued use despite harm

compulsive use and craving

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International Statistical Classification of Diseases and Related Health Problems 10th Revision:

Mental and behavioural disorders due to psychoactive substance use (F10-F19)

F10: Mental and behavioural disorders due to use of alcohol

F11: Mental and behavioural disorders due to use of opioids

F12: Mental and behavioural disorders due to use of cannabinoids

F13: Mental and behavioural disorders due to use of sedatives or hypnotics

F14: Mental and behavioural disorders due to use of cocaine

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International Statistical Classification of Diseases and Related Health Problems 10th Revision:

F15: Mental and behavioural disorders due to use of other stimulants, including caffeine

F16: Mental and behavioural disorders due to use of hallucinogens

F17: Mental and behavioural disorders due to use of tobacco

F18: Mental and behavioural disorders due to use of volatile solvents

F19: Mental and behavioural disorders due to multiple drug use and use of other psychoactive substances

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Historic context of drug use

Opium known already in neolithic age (8 000 – 5 000 years B.C.)

Coca and resin from hemp – known thousands years

Drugs were first used for their therapeutic purposes, secondary for they narcotic purposes

Isolation of morphine (1805),

caffeine (1820),

nicotine (1828),

cocaine (1859),

ephedrine (1887)

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Summary of frequently abused substances

alcohol

nicotine

cannabinoids (hemp drugs)

opioids

benzodiazepines

„classical“ psychostimulant drugs

MDMA (exctasy)

„new“ synthetic substances

hallucinogens

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19th century: beginning of commercial narcotics production

(e.g. morphine since 1828, cocaine 1862, heroine 1898)

Legal consumption of drugs was ended by opium conventions:

1909 Shanghai,

1912 Haag

1925 Geneva

Illegal way: French Connection (France), Cosa Nostra (USA)

After WWII:

Single Convention on Narcotic Drugs of 1961 - an international treaty to prohibit production and supply of specific (nominally narcotic) drugs and of drugs with similar effects

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Council of the Government for Drug Policy Coordination - Annual registr (2012):

CZ – the most frequently abused drugs:

Psychostimulant drugs (particularly methamphetamine, syn. pervitin)

Hemp drugs (particularly tetrahydrocannabinol – THC).

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Tolerance x Dependence x Sensitization

Tolerance: a decrease in the effect of a drug as a consequence of repeated exposure (the effectiveness can decrease with continued use).

Mechanisms of Tolerance:

Pharmacokinetic Tolerance (enzyme induction effect)

It occurs because of a decreased quantity of the substance reaching the site it affects.

This may be caused by an increase in induction of the enzymes required for degradation of the drug e.g. CYP450 enzymes.

This is most commonly seen with substances such as ethanol.

This type of tolerance is most evident with oral ingestion, because other routes of drug administration bypass first-pass metabolism.

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Tolerance x Dependence x Sensitization

Pharmacodynamic Tolerance (NT depletion, receptor plasticity)

It occurs when the cellular response to a substance is reduced with repeated use.
This may be caused by a reduced receptor response to receptor agonists (receptor desensitization), a reduction in receptor density (usually associated with receptor agonists), or other mechanisms leading to changes in action potential firing rate.

Dependence: a maladaptive pattern of substance use, leading to clinically significant tolerance, impairment, or distress; an adaptive state associated with a withdrawal syndrome upon cessation of repeated exposure to a stimulus (e.g., drug intake).

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Tolerance x Dependence x Sensitization

Dependence develops when the neurons adapt to the repeated drug exposure and only function normally in the presence of the drug.

When the drug is withdrawn, several physiologic reactions occur. These can be mild (caffeine) or even life threatening (alcohol).

This is known as the **withdrawal syndrome**.

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Tolerance x Dependence x Sensitization

Physical dependence x psychological dependence

Physical dependence (physiologic dependence) referrers to the adverse physical symptoms and signs that result from the withdrawal of the drug.

It results from many of the same mechanisms that produce tolerance.

As with tolerance, homeostatic set-points are altered to compensate for the presence of the drug.
If drug use is discontinued, the altered set-points produce **effects opposite** to those manifested in the presence of the drug.

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Tolerance x Dependence x Sensitization

Physical dependence x psychological dependence

Psychological dependence

Psychological dependence is a change in emotional state that occurs after using a substance or engaging in a behaviour over a period of time.

i.e. dependency on specific psychological phenomena provoked by the drug (e.g. euphoria)

This change in emotional state is a result of changes in brain chemicals.

It can cause **craving**, motivation to seek out the substance or behavior, irritability, anxiety, or general dissatisfaction when withdrawing from the substance or activity.

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Dependence producing substances

Inverse tolerance (sensitization): the drug becomes more effective with repeated doses.

Tolerance

Decreased response to substance effects. A higher dose is required to achieve the same effect.

Substance is usually given in shorter intervals or continuously

Senzitization

(Robinson & Berridge, 1993)

Increased response following repeated drug administration

Intermitent drug administration

Inverse tolerance (sensitization):

There are two hypothesis to explain mechanism of sensitization to psychostimulants:

1) Intermittent exposure to a drug will cause intermittent dopamine release. This will lead to decreased sensitivity or density of pre-synaptic dopamine autoreceptors.

These receptors are responsible for negative feed back → increased dopamine release → increase stimulatory effects of dopamine.

Important rather for development of sensitization than expression.

2) Long-term intermittent exposure to a drug provokes intermittent release of high amounts of dopamine → gradual depletion of dopamine in cytoplasm.

This results in increased sensitivity of D_1 postsynaptic receptor (because they are not stimulated by their natural ligand).

Thus, after challenge dose administration (that acts through activation of the same post receptors), an augmented behavioural response can be expected.

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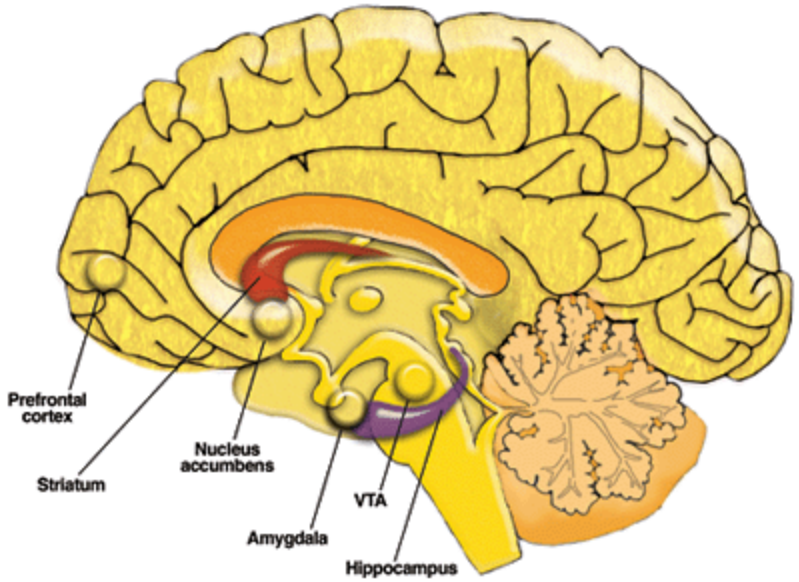
Exposure to alcohol and other drugs (AODs):

Plastic changes associated with AOD use - release of the neurotransmitter dopamine from cells in ventral tegmental area (VTA) induced by addictive drugs.

The VTA is one of the components of the mesolimbic dopamine system – **REWARD PATHWAY**.

Neurons whose cell bodies are located in the VTA, extend long axons most prominently to the nucleus accumbens (NAc) and the prefrontal cortex

Dopamine release in the mesolimbic system is critical for the drive to ingest AODs.



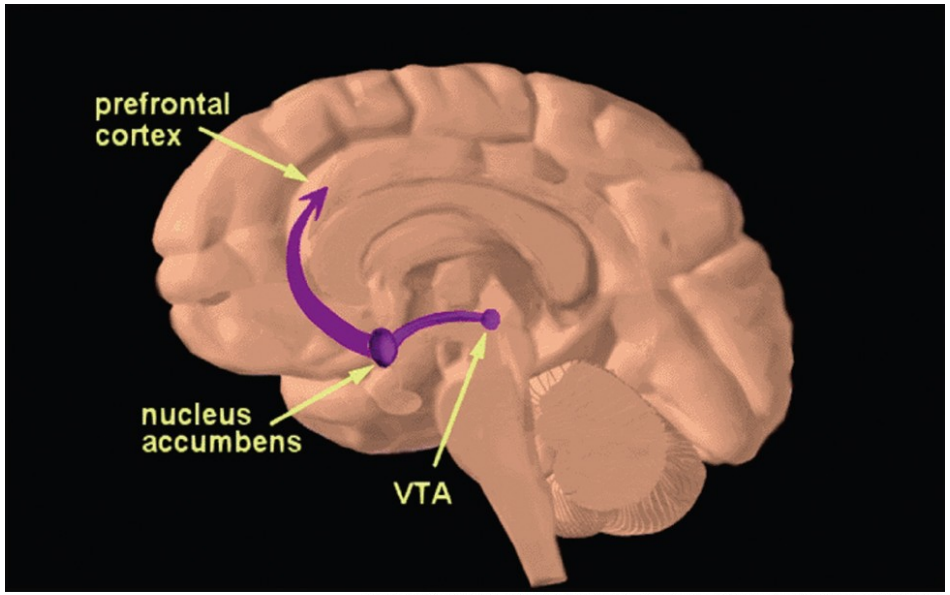


Image retrieved from http://www.nida.nih.gov/pubs/teaching/teaching3/largegifs/slide-4.gif (Accessed 3 Nov 2010).

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The mesocorticolimbic dopamine system as an initial target of addictive drugs.

The VTA, at the origin of the mesocorticolimbic system, is composed of dopamine projection neurons that are under inhibitory control of GABA interneurons

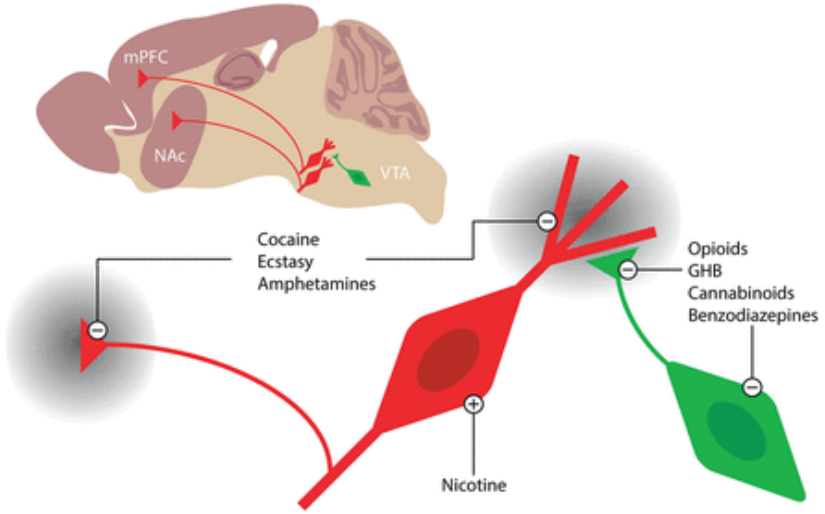
The main targets are the NAc and the mPFC.

Addictive drugs cause an increase in mesocorticolimbic dopamine through:

1) direct activation of dopamine neurons (e.g., nicotine);

2) indirect disinhibition of dopamine neurons (opioids, cannabinoids, benzodiazepines);

3) interference with dopamine reuptake (cocaine, ecstasy, and amphetamines).



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