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General principles of poisoning treatment, specific antidotes of medicines, and the mechanisms of their effects

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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”

Causes of poisoning

1. drugs - 52%
2. Industrial Products - 30% (chemicals for cleaning, organic solvents, cosmetics etc.)
3. plants - 8%
4. Pure bulk chemicals -5%
5. funghi - 2%
6. Animal poisons (snakebite) -1%
7. others -1%

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 !!!

General principles of acute 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

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

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
- (red-eyed treefrog secretion)

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

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

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

1. Elimination of unabsorbed toxic substances from organism

- $KMnO_4$ – oxidation of strychnine and cyanides (light pink solution)
- Lime water - Ca(OH)2 - binds F^- and oxalic acid into insoluble salts
- Flour/starches –binds iodine into insoluble iodides
- Paraffin oil binds phenols and organic solvents (benzene, toluene)
- Liquid paraffin (Paraffinum subliquidum – 100 – 300 ml) → it is a non-resorbable fatty substance → decreases resorption of poisons soluble in fats (simple and halogenated hydrocarbons)

1. Elimination of unabsorbed toxic substances from organism

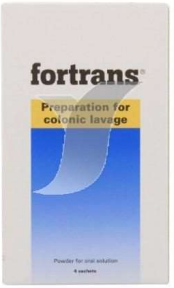
Gastric lavage

- 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)

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

Indications (toxic and lethal doses):



- rugs bound poorly by charcoal: iron, lithium
- retarded tablets: theophylline, calcium blockers -verapamil, diltiaz

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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)

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

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

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

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

1. Elimination of absorbed toxic substances from organism

Peritoneal dialysis

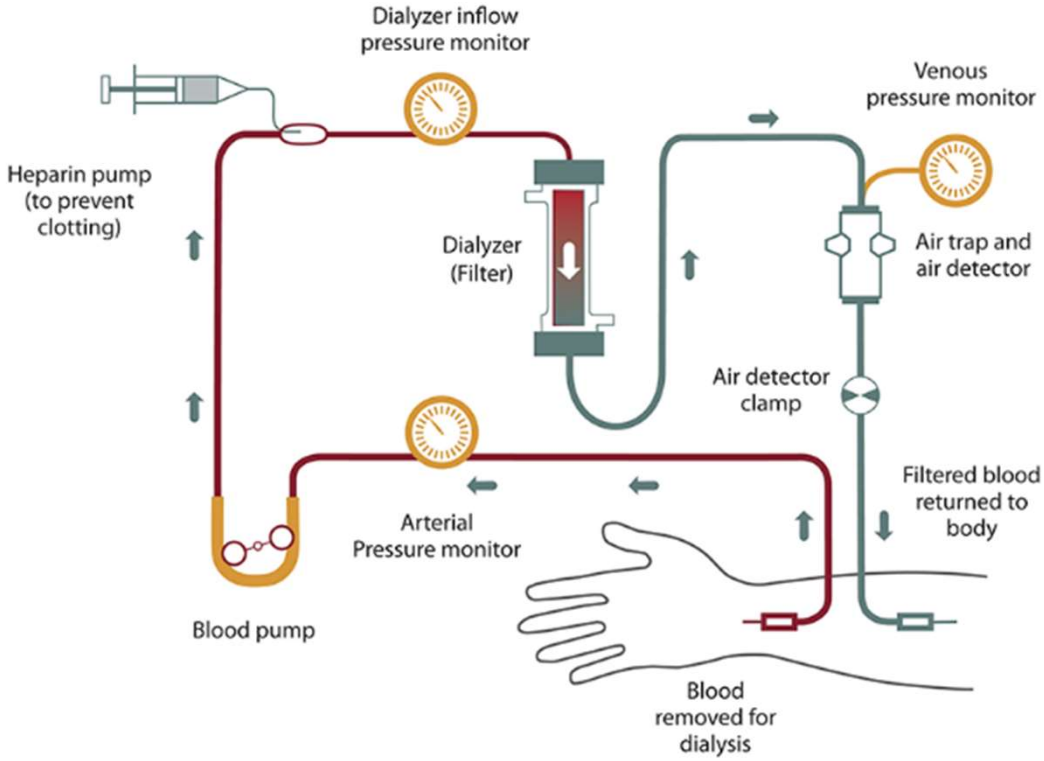
- dialysis solution via catheter into abdominal cavity
- Intestinal mucosa and peritoneum serve as a membrane
- Replacement after 2 hours
- I: unavailability of haemodialysis in case forced diuresis cannot be applied
- For poisoning with some analgesics, hypnotics, barbiturates,...

- -: low efficiency, risk of infection

1. Elimination of absorbed toxic substances from organism

Haemodialysis/CRRT

- I: salicylates, barbiturates, alcohols, ethylenglycol, toluene, mushrooms



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INDICATION OF HAEMODIALYSIS

- **Acute renal failure** – e.g. rapidly progressing glomerulonephritis
- **hypercalemia** > 6 mmol/l that cannot be managed by conservative therapies
- **hypercalcaemia** > 3.5 mmol/l
- **hyperuricemia** > 1000 µmol/l
- uncorrectable **metabolic acidosis**, pH < 7.1
- **hyperhydrating** with heart failure
- **oligouria** lasting more than 3 days

INDICATION OF HAEMODIALYSIS – cont.

Indication for dialysis (sooner in diabetics):

- urea > 30 mmol/l
- creatinine 600–800 μmol/l
- Creatinine clearance < 0.25 ml/s

Patient on dialysis

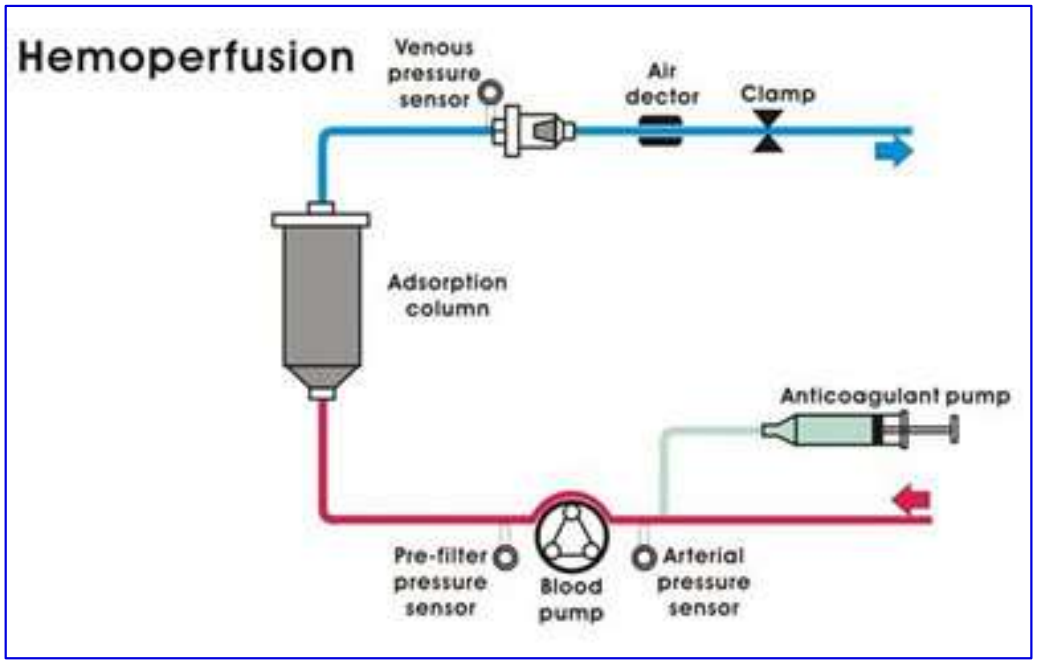
Diseases that lead to dialysis are as follows:

- diabetic nephropathy
- hypertension nephropathy
- chronic glomerulonephritis
- rapidly progressing glomerulonephritis (RPGN) – when irreversible fibrotic changes occur
- Autosomal dominant polycystic disease of kidneys

1. Elimination of absorbed toxic substances from organism

Haemoperfusion

- perfusion of blood through a capsule containing sorbents
- I: barbiturates, theophylline, phenothiazines, paracetamol, salicylates, phenobarbital, carbamazepine
- +: highly efficient



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Haemodialysis, haemoperfusion
Indication (on fulfilment of at least 3 criteria):

- Clinical picture of severe intoxication (deep unconsciousness, hypotension, hypothermia, hypoventilation in intoxications with depressant substances)
- Clinical state can only be influenced by a complex resuscitation care
- Clinical state becomes worse despite complex resuscitation care
- Protracted unconsciousness with pulmonary complications (pneumonia, diffuse alveolar damage, COPD)
- Proven high plasmatic level of toxic substance that can be eliminated applying available methods

Haemodialysis, haemoperfusion
Contraindication of extracorporeal elimination methods:

- Effective antidote is available
- The toxic substance is quickly metabolised and its metabolites are not toxic
- Toxicity appears quickly and irreversibly
- Intoxication is caused by a substance with low toxicity
- The toxic substance has a large distribution volume
- Shock
- Severe haemocoagulation disorders

Lipidic (micro)emulsions

- Novel (Commercial RMP) – decreases the free fraction of lipophilic drugs in serious intox. (Intralipid®)
- for the treatment of severe arrhythmias (e.g. ventricular tachycardia, atrial fibrillation, cardiac conduction systém block, asystole)
- in lipid soluble drugs
- if conventional therapy fails
- free drug fraction - binding by lipid emulsion a
- reducing the pharmacological effect
- commonly used to treat a topical toxicity of local anaesthetics, cardiotoxicity of local anesthetics, some beta-blockers, TCA

Lipidic (micro)emulsions

- however, the blood in the blood abolishes the possibility of hemodialysis or ECMO - hence this therapy is preferated over lipids when other options fail

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

2. Neutralization of poison through administration of antidote

- Decrease bioavailability of the toxic substance
- Increase rate of elimination of (especially non-transformed) toxic substance
- Slow down biotransformation of the toxic substance leading to activation of the tox. substance
- Incr. rate of biotransformation to inactive metabolite
- Influence the distribution of the toxic substance within the organism

Specific Antidotes

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

Specific Antidotes

(http://www.farmakologie.net/lecbaotrav.php)

Lékové informační centrum 3. LF UK

(Information Centre for Pharmaceutical Drugs at the Third Faculty of Medicine, Charles University)

3. Symptomatic treatment

- Check vital signs
- Intubation
- Entry into bloodstream
- Support of CVS (inotropics, vasopressors)
- Therapy of spasms

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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Toxicological Information Centre

120 00 Praha 2, Na Bojišti 1

http://www.tis-cz.cz/

E-mail: tis@vfn.cz

Phone: +420 **224 91 92 93** or +420 **224 91 54 02**

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Snakebite poisoning

Anaesthesiology and Resuscitation Clinic

1st FM CU in Prague and VFN in Prague

Praha 2

Phone: 224 962 243

Lékové informační centrum (Information Centre for Pharmaceutical Drugs)

Lékárna FN U sv. Anny

Brno

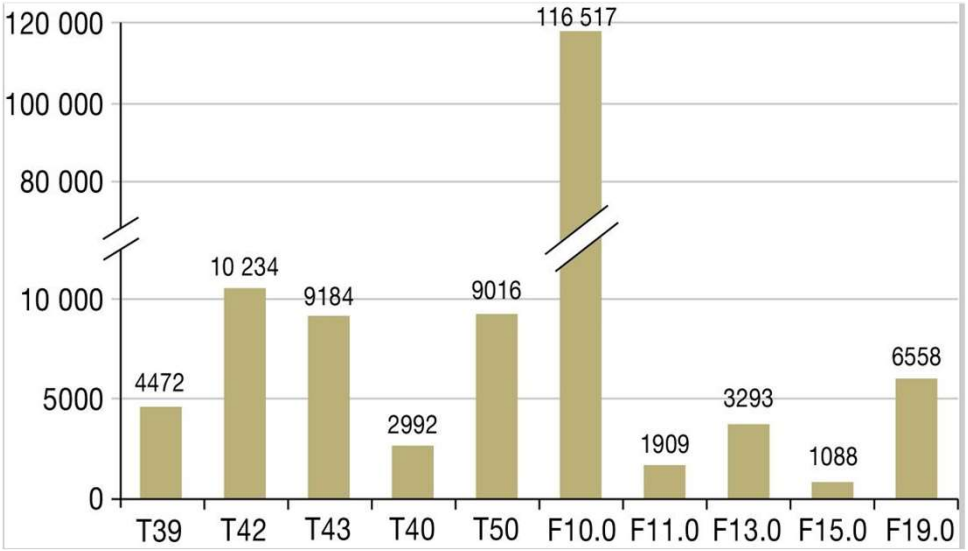
Phone: 543 182 175-7

- **Poisoning causes 10% of deaths !!!**
  - Coincidence
  - Suicide
  - Criminal act
  - Abuse of habit-forming substances
  - Occupational injury
  - ...

- **2/3 of all intoxications are related with children!**
- Most frequent entry: p.o. or inhalation

Intoxication with drugs

2011 German hospitals



T42 = hypnotics (ca. 50% benzodiazepines) **and antiepileptic drugs**

T43 = antidepressants, neuroleptic drugs, psychotropic substances (not further classified)

T40 = narcotics, methadone, hallucinogens (especially morphine and codeine)

T50 = other medications, not further specified

Mental and behavioral disturbances due to acute intoxication with:

F10.0 = alcohol (ethanol)

F11.0 = opioids

F13.0 = hypnotics, sedatives

F15.0 = stimulants

F19.0 = multiple substance use

T39 = **analgesics** (ca. 40% 4-aminophenol derivatives)

38 Dtsch Arztebl Int. 2013 Oct; 110(41): 690–700.

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General overview of neurologic symptomatology at unknown poison intoxication

- **Convulsion** – spasmso skeletal muscles: substances with excitatory effects (strychnine, HCN, organophosphates, psychotomimetics, psychostimulants [caffeine included!])
- **Excited state** – states similar to ebriety (often during intoxication with solvents, benzine, alcohol, atropine, scopolamine, PS-lytics, cocaine, hashish, fly agaric [amanita muscaria])

..General overview of neurologic symptomatology at unknown poison intoxication

- **Hallucination, delirious sta**tes – analeptics, atropine*(Atropa belladonna*), scopolamine, panther mushroom (also causes states of confusion), organophosphates, ergot alkaloids, yohimbine

- **Manifestations of depression** – sedation, somnolence, sopor to comatose states with depression of breath and blood circulation – hypnotics, „narcotics“, sedatives, antipyretics, analgesics, codeine antitussives, alcohol, CO, poisoning...

..General overview of neurologic symptomatology at unknown poison intoxication

- **Vision disorders** – atropine (transitory disorder – mydriasis, focusing disorder), H2S, As, myorelaxants (focusing disorder), alcohol (vision hallucinations), amphetamines (tactile hallucinations: bedbugs creeping below one´s skin → excoriation),

- **Hearing disorders** – streptomycine (and other AMG - at ↑doses), quinine and salicylates (transitory worsening of hearing, tinnitus)

Intoxication with medicines

Intoxication with medicines

Most often: sedatives, hypnotics, analgesics

Causes of death:

- Injury to CNS – psychotropics
- Injury to CVS – cardioglycosides antiasthmatic drugs
- Liver injury – paracetamol, nimesulide, pretease inhibitors

TOXICITY of MEDICATIONS

1. **ANALGESICS:**

a) **paracetamol** 10 - 15 tb. (15 – 20 tb. of Panadol 500mg → serious to lethal intoxication)

- hepatotoxicity; it changes into N-acetyl-p-benzochinone imine(minor metabolite) =hepatotoxic
- GIT problems (vomiting, renal failure)
- Th.: activated carbon + N-acetylcysteine

b) **salicylates**: breath stimulation, hyperventilation

- alkalosis = brain and lung oedema
- Th.: alkalizing of urine + activated carbon + haemodialysis

c) **opioids** – see Psychopharmaceuticals

TOXICITY of MEDICATIONS

2. PSYCHOTROPICS

a) antipsychotic (neuroleptic) drugs, TCA antidepressants

- depressed consciousness, sedation, somnolence, sopor (it is difficult to wake up the patient), coma + increased muscle tone, convulsions, cardiotoxicity
- Th.: act. carbon, laxatives, symptomatic treatment antidote = physostigmine – mitigates anticholinergic symptoms, haemoperfusion

b) psychostimulants (amphetamines, cocaine)

- ↑endogenous catecholamine secretion, stimulation of sympathetic nervous system
- euphoria, hallucination, unconsciousness, hypertension, arrythmia

TOXICITY of MEDICATIONS

2. PSYCHOTROPICS

c) opioids

- euphoria, breath depression, miosis, BP decrease, heart rate decrease, apnoe, coma
- Th.: naloxone

d) hypnotics, sedatives

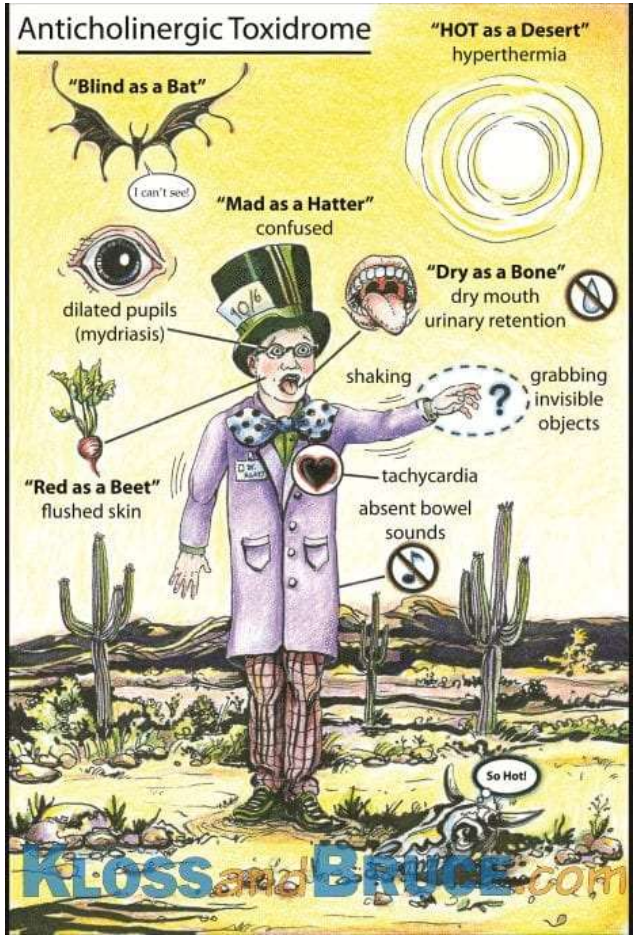
- BZD:
  - ➢ CNS depression
  - ➢ Th.: flumazenil
- BARBITURATES:
  - ➢ CNS depression
  - ➢ Th.: charcoal, alkali forced diuresis, haemoperfusion

Intoxication with anticholinergic drugs

- Anticholigics (atropin, TCA, antihistaminics, antipsychotics)

- HOT as a hare (hypertermia)
- RED as a beet (flush)
- DRY as a bone (dry skin, mucosas)
- BLIND as a bat (mydriasis)
- MAD as a hatter (delirium)

- tachycardia, urinary retention
- urine, absence of peristalsis



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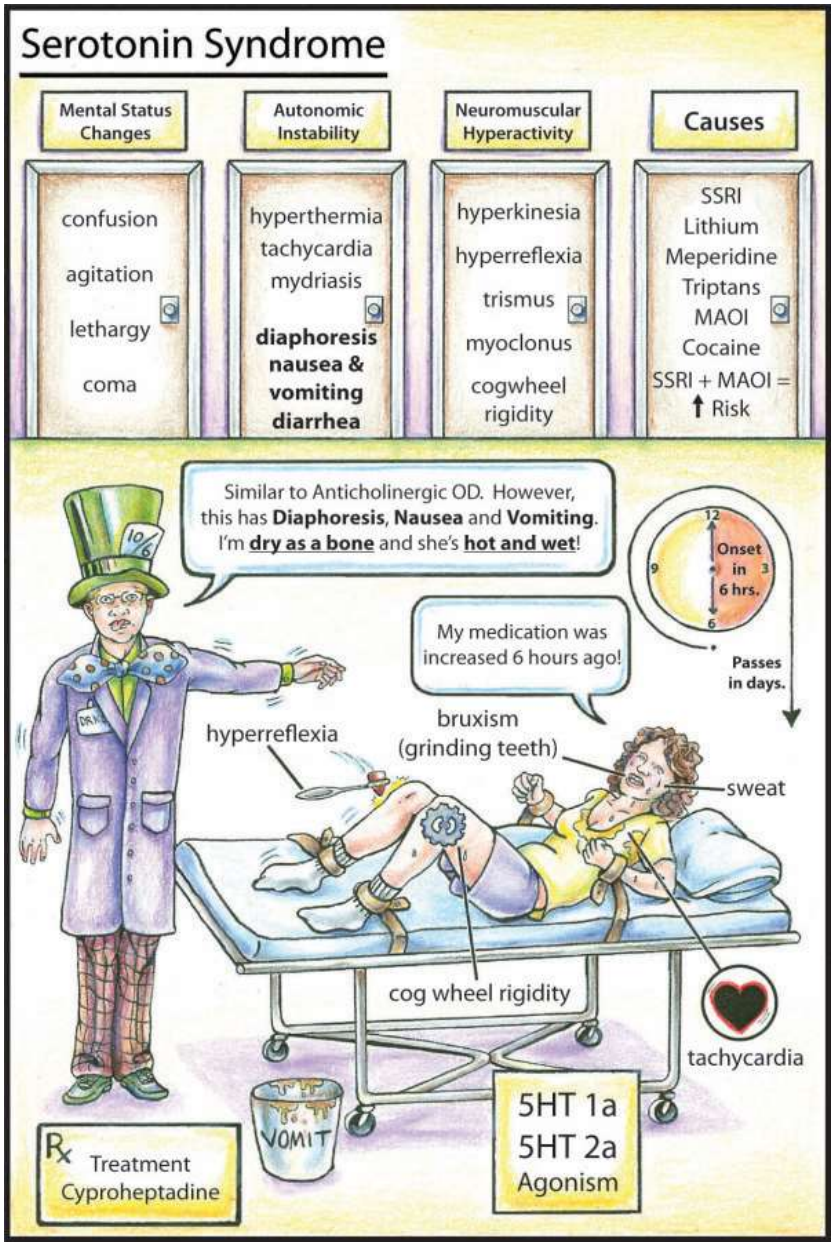
Intoxication with serotonergic drugs – serotonergic toxidrome

- Serotonin increrase within CNS (antidepressants MAOIs, SSRIs, triptans, TCAs, ecstasy, dextromethorphan, opioids, prokinetics)
- mydriasis, agitation / coma, confusion, hallucinations,
- tachycardia, hypertension, hyperthermia, tremor, hyperreflexia,
- convulsions, tachypnea, diaphoresis

Th.: discontinue 5-HT agonists

Symptomatic treatment: lorazepam, propranolol, cyproheptadine


Serotonin Syndrome
Mental Status Changes
confusion
agitation
lethargy
coma
Autonomic Instability
hyperthermia
tachycardia
mydriasis
diaphoresis
nausea & vomiting
diarrhea
Neuromuscular Hyperactivity
hyperkinesia
hyperreflexia
trismus
myoclonus
cogwheel rigidity
Causes
SSRI
Lithium
Meperidine
Triptans
MAOI
Cocaine
SSRI + MAOI = ↑ Risk
Similar to Anticholinergic OD. However, this has Diaphoresis, Nausea and Vomiting. I'm dry as a bone and she's hot and wet!
My medication was increased 6 hours ago!
Onset in 6 hrs.
Passes in days.
hyperreflexia
bruxism (grinding teeth)
sweat
cog wheel rigidity
tachycardia
VOMIT
Rx Treatment
Cyproheptadine
5HT 1a
5HT 2a
Agonism

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Mushroom poisoning

- Quite frequent in this country
- Less frequent after ingestion of edible mushrooms that developed toxic products due to metabolic processes
- Death cap mushroom – *Amanita Phalloides* =phaloidine, amanitine alpha, beta, gamma, ...
- Most frequently confused with champignons

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POISONING with Amanita phalloides

POISONING with Amanita phalloides "destroying angel"- „death cap"

A quarter to half of mushroom of average 30 - 35 g mass causes a serious poisoning in an adult person !

Lethal intoxication – caused by ingestion of only 1 mushroom (children are more sensitive!!!)

Prognosis: very serious especially in children, death rate 60 - 80% !!!

POISONING with Amanita phalloides

POISONING with Amanita phalloides "destroying angel"- „death cap"

Th.:

- gastric lavage
- forced diuresis
- PNC G (displaces amanitine from its binding to serum albumine)

- silymarine → hepatoprotective – 20 mg/kg/day in 4 infusions, other hepatoprotectives,
- CRRT- haemoperfusion
- charcoal

Symptoms of muscarine intoxication

Typical for excessive stimulation of PS (?):

(identification of muskarine in plasma, but in a very low concentr.)

- salivation, lacrimation, sweating
- bradycardia, hypotension
- Decr. breathing (bronchoconstriction, hypersecretion of bronchial glands)
- Diarrhoea (hypermotility and hypersecretion in the GIT)
- Muscular tremor

Poisoning with amanita results from joint action of muscarine, ibotenic acid with muscimole and also mykoatropine (but atropine poisoning symptoms may be also present (PL effects).

Plants

- nearly all plants that are used in traditional medicine can be toxic in higher doses (primarily in children)
- **„red berries“** – common rue, perfoliate honeysuckle (or fly, Japanese h.), bittersweet – solanum, common yew, lily-of-the-valley
- **„blue berries“** – privet (*Ligustrum*), common juniper, deadly nightshade (*Atropa Belladonna*)

- datura, daffodil, raw and green haricot beans = toxic dose 3-10 beans

Poisoning with organophosphates (insecticides)

Cholinergic crisis (organophosphates, carbamates, pilocarpine)

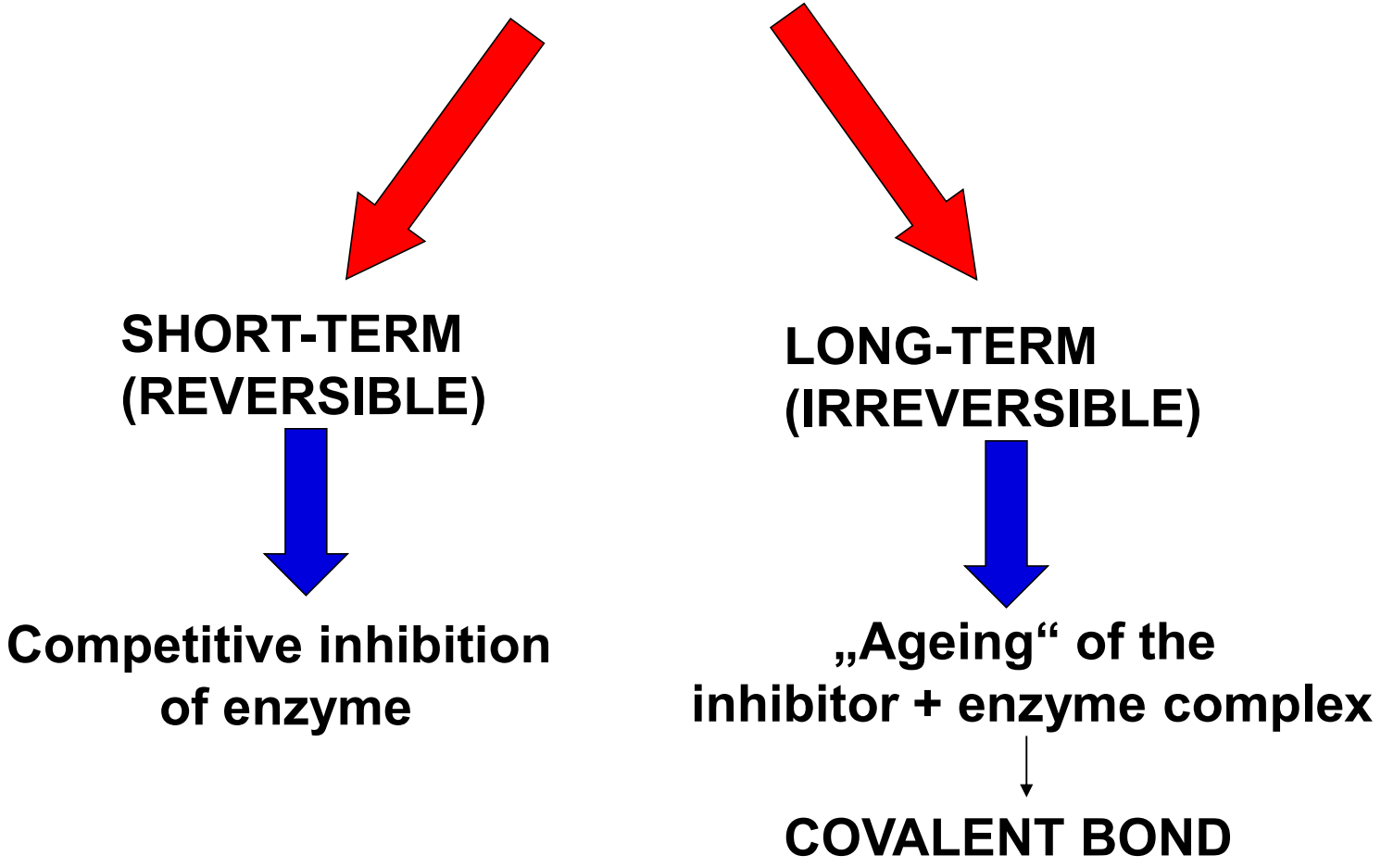
i **AChE –** SLUDGE-M:

salivation, **l**acrimation, **u**rination, **d**iarrhea/**d**iaphoresis,

emesis, **m**iosys.

Bradycardia, bronchosecretion

AchE INHIBITORS



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Poisoning with organophosphates (insecticides)

- Irreversible inhibition of Ach-esterase – cumulation of Ach
- Late neurotoxic effects – 1-2 weeks (paresis of extremities)

Th.:

- atropine – antagonist on Ach receptors
- reactivators of Ach-esterase (trimedoxin, pralidoxim)
- reversible inhibitors of AchE
- symptomatol. treatment (e.g. treatment of spasms – BZD)

Intoxication with organic solvents and alcohols

ethylalcohol (alcohol, ethanol)

alcohol → (alcohol dehydrogenase) → acetaldehyde + acetic acid + CO2 + H2O

Th.: artificial respiratory support, glc infusion, BZD (to dampen restlessness+ convulsions), fomepizol (competitive inhibiton of ADH)

methylalcohol (methanol)

methanol → ADH → formaldehyde + CO_2 + H_2O + formic acid

- Metabolic acidosis
- Damaged eye

Th.: gastric lavage, laxatives, paraffine, ethylalcohol, fomepizol, haemodialysis

organic solvents: petrol, trichlorethylene, toluen, xylen, benzene, hexane...

Th.: paraffine oil – not absorbed