

# **Substance addiction.**

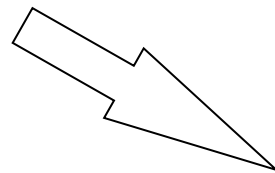
## **Types of addiction, therapy of substance abuse.**

Notes for Pharmacology II

This study material is exclusively for students of general medicine in Pharmacology II course. It contains basic notes of discussed topics, which should be completed with more details from recommended study sources.

# Demography of pharmacotherapy

- about 3 – 5 % of population suffers from dependency on medicaments
- analogy with dependence on alcohol or marijuana
- the most favourites medicaments: analgesics, sedatives/anxiolytics, stimulants
  
- patients visit more physicians
- no mutual awareness about medicaments used or prescribed by other doctors



polypragmasy


# Substance dependence (according to WHO)

- **psychological** or **physical** condition resulting from action of a medicament or psychotropic substance on organism
- changes in behaviour and other reactive conditions
- pathological adhesion to continual or repeated administration of a psychotropic substance


# SUBSTANCE DEPENDENCE

**non-uniform terminology:** substance dependence, addiction, toxicomania, narcomania, abusos of drugs (wider meaning), drug dependence

result of adaptation (habituation) of organism on repeated drug administration

- **psychological dependence**
  - compulsive longing (craving) for repetition of pleasant feelings associated with psychotropic effects of a drug
- **physical (somatic) dependence**
  - changed physiological condition (neuroadaptation), which requires repeated administration of a drug in order to avoid withdrawal syndrom 

# Syndrom of dependence

- **strong longing** or urge to use a substance - **CRAVING**
- **deteriorated ability to control** behaviour associated with drug use
- physiological **symptoms of withdrawal syndrome**, if substance use is limited or stopped
- **evidence of tolerance** to drug effect
- **gradual neglecting of other pleasant events or hobbies** in favour of the used psychoactive drug
- **continuing use of drug** despite clear evidence of harmful consequences 

# SUBSTANCE DEPENDENCE

**withdrawal syndrome** - produced by sudden lack of psychotropic substance (after previous repeated administration)

- symptoms are usually opposite of pharmacodynamic effects of the abused substance, or more precisely „rebound“ effects on the level of target structures, which were originally affected by the substance

# Substance dependence may be accompanied by:

## ➤ tolerance

- It is necessary to increase the dose of the substance in order to achieve the same pharmacodynamic effect

## ➤ sensitisation

- smaller dose of the substance is sufficient to produce the same pharmacodynamic effect

# Sensitisation

“reverse tolerance“

increased response after repeated drug administration (locomotion, stereotypic movements)

opioids, psychostimulants  
(cocaine, amphetamine,...), ethanol,  
nicotine,...

conditioned by intermittent administration of the drug

# Tolerance

decreased response to drug, which must be administered in gradually increasing doses to achieve the same effect

substance is administered in shorter intervals or continuously

**Important in dependence on psychotropic substances !!**

8 **risk of relaps in ex-addicts !!!**



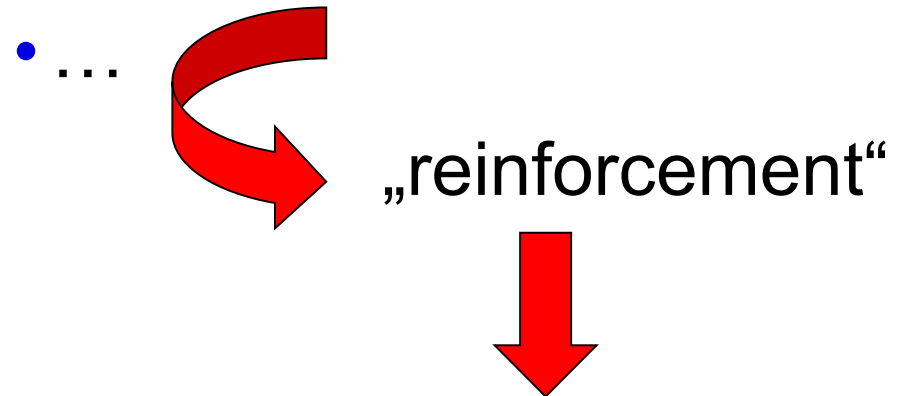
# Sensitisation is the most frequent to the following behavioural effects

## Lab. animals:

- simple stimulation of locomotion
- stereotypies

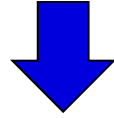
## Humans:

- stimulation of locomotion
- stereotypies
- „reward“ properties of the drug



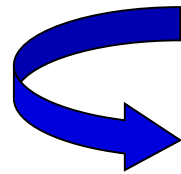
**risk of relapses in ex-addicts  
after re-exposition to the drug**

# Tolerance

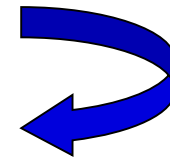


it leads to gradual increase in dose

# Tolerance



tolerance to effect



tolerance to toxicity



e.g. → supression of resp. center

**CAVE! In barbiturates NO tolerance to toxicity!**

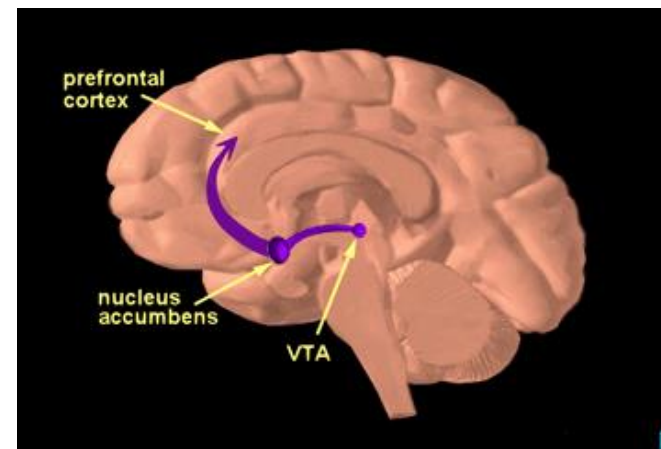
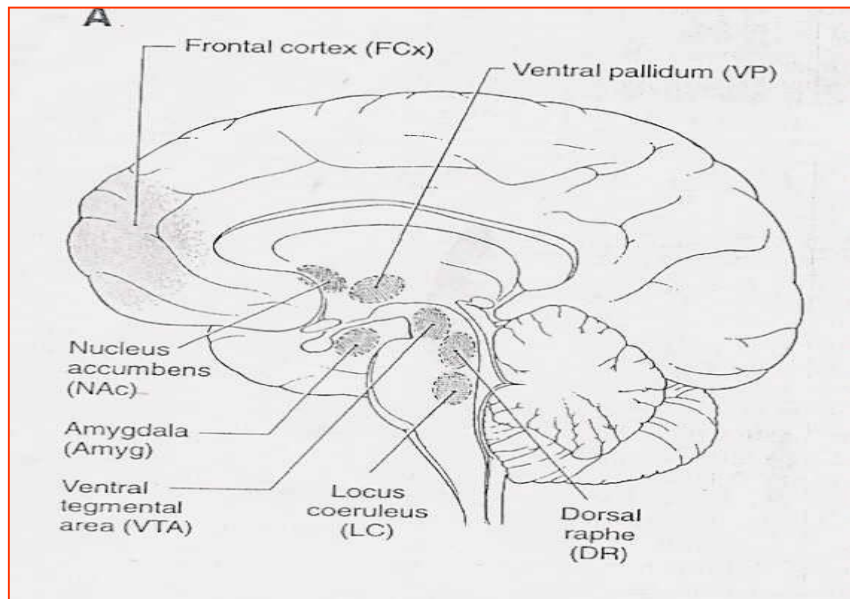
# Tolerance

## Principle of tolerance development:


- **pharmacokinetic** (autoinduction of biotransformation enzymes, e.g. barbiturates)
- **pharmacodynamic** (tissue type)
  - changes in receptor density (most of abused substances are agonists)
  - changes in receptor sensitivity (desensitization, adaptation on the level of postreceptor processes)

# Mechanism of dependence development – neuroanatomical and neurochemical backgrounds – DOPAMINERGIC SYSTEM („DA REWARD PATHWAY“)

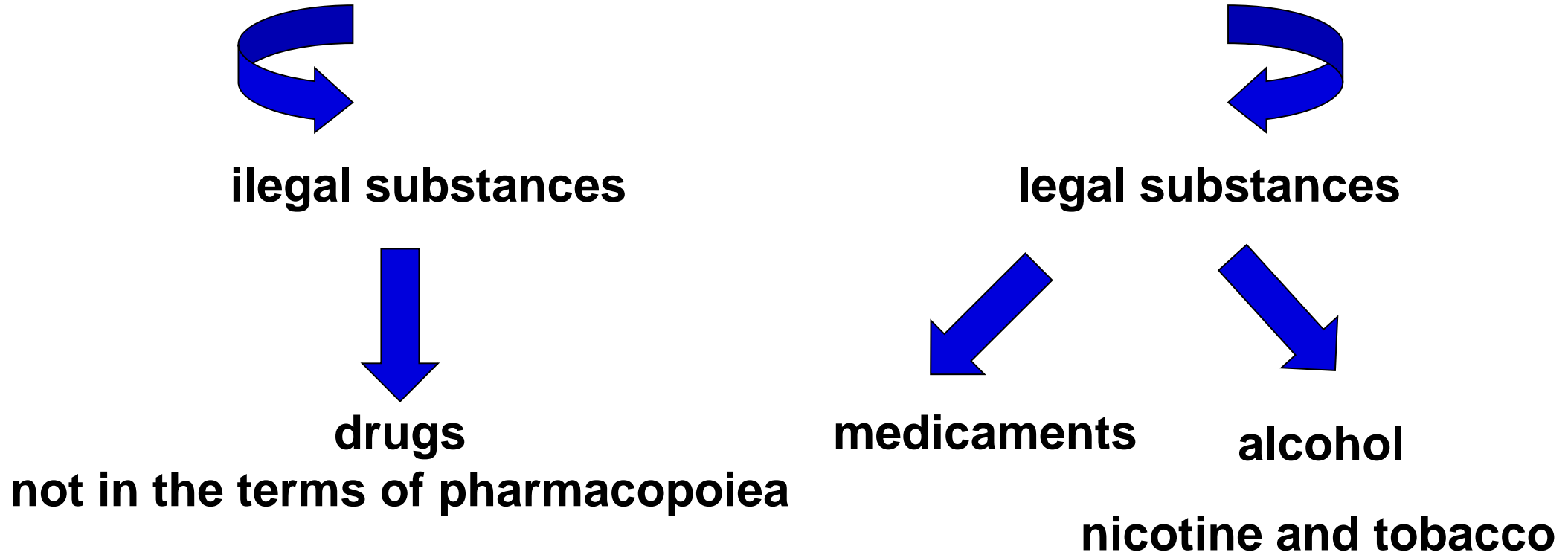
effects on dopaminergic reward system (food, water, sex, substances of abuse) in CNS



# Mechanism of dependence development - neuroanatomical and neurochemical backgrounds

- Dopaminergic system !!! 
- serotonergic system
- adrenergic system
- opioid system
- endocannabinoid system
- other

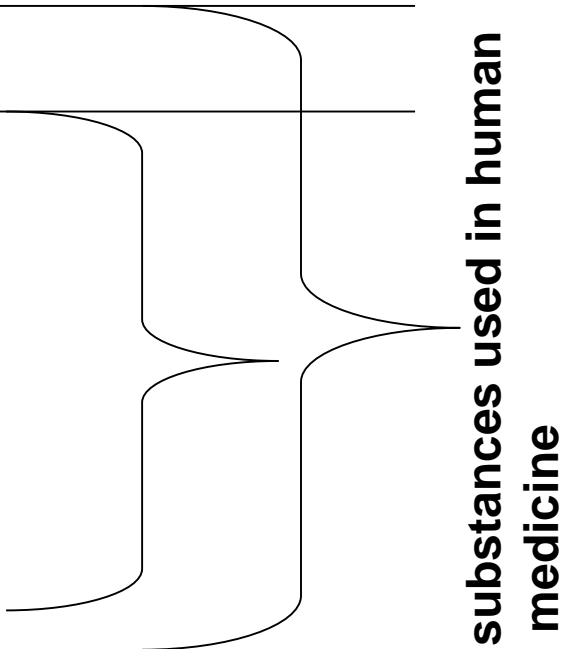
# Classification of abused substances



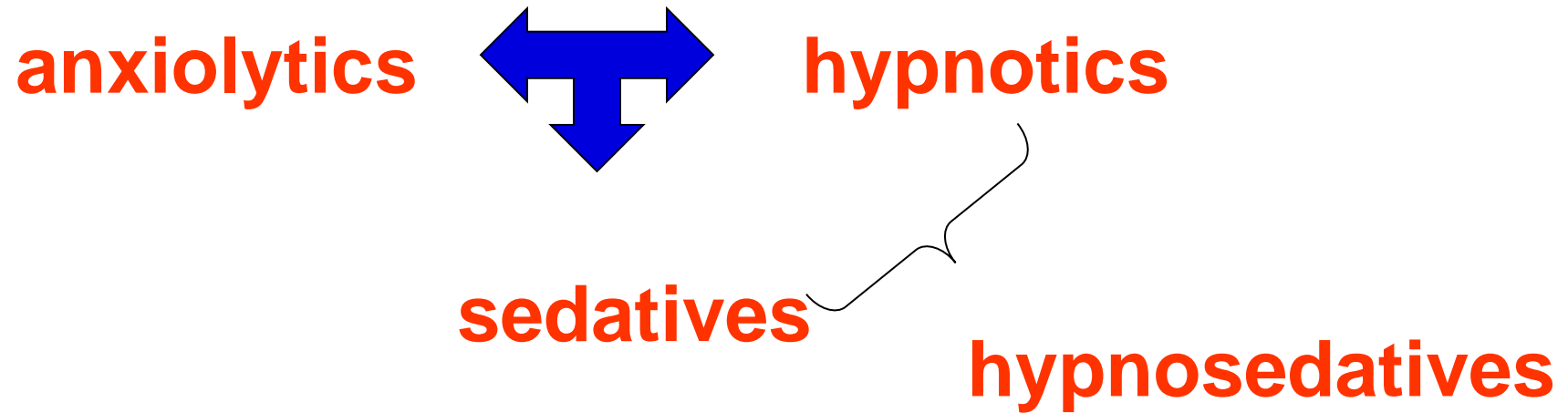
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misuse of substance not producing „classical dependence“  
(rhinological drugs, laxatives, diuretics...)

# Classification of abused substances producing dependence

- nicotine (tobacco)
  - ethanol
  - psychotomimetics (halucinogens, „party drugs“, delirogens,..)
  - solvents and volatile substances
  - cannabinoids (Cannabis)
  - psychostimulants
  - opioids
  - other substances suppressing CNS (anxiolytics, sedatives/hypnotics)
  - other
- 
- substances used in human medicine

# Substances suppressing CNS (with addictive potential)





# Substances suppressing CNS (with addictive potential)

- anxiolytics, sedatives and hypnotics are most frequently prescribed psychoactive drugs
- sleep disorders and anxiety
- **benzodiazepines** – most significant world-wide
- **they are not perceived** by patients, physicians and pharmacists as a

**risk !!!**

# Most frequent dependence on medicaments

- alprazolam
- diazepam
- oxazepam
- zolpidem, zopiclone
- bromazepam
- tramadol
- morphine
- buprenorphine

# Acute intoxication

- drunkenness – euphoria
- disinhibition
- emotional lability
- aggressive behaviour
- damping and apathy
- impairment of attention and psychomotoric functions

# Harmful use

- substance can paradoxically provoke disorders that should be using the drug treated – sleep disorders, restlessness, anxiety, depression
- impairment of cognitive functions
- significant deterioration by alcohol!!!

# Syndrome of dependence

- during inadequate use of sedatives or hypnotics
- therapeutical use max 4 – 6 weeks

# Withdrawal syndrome

- can be dramatic, particularly following **sudden withdrawal of high doses**
- tremor, tachycardia, nausea, vomitus, psychomotoric unrest, headache, transient optical or tactile hallucinations

# Epidemiology

- part of dependent individuals is not treated; they continue in substance abuse
- there are no reliable data
- medical professionals are also involved

# Course and prognosis

- very persistent and **hardly curable**
- **simultaneous solution of primary disorder**

# Treatment

- **Treatment of acute intoxication**

Frequently requires intensive care including non-stop monitoring of vital functions

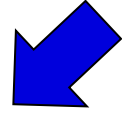
- **Treatment of withdrawal condition**

Frequently long-term process

- **Treatment of dependence**

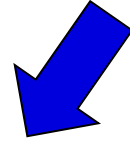


# Benzodiazepines – features of dependence

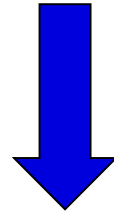


- it develops during several months (**sometimes even weeks**) of regular administration!!!
- **typical somatic withdrawal condition**  
tremor, tachycardia, nausea, vomitus, psychomotoric unrest,  
headache, transient optical or tactile hallucinations  
sometimes cramps of „grand mal“ type

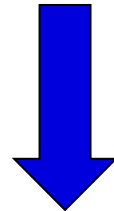
# Benzodiazepines – features of dependence



frequently coincidence with other dependences



**BZD + opioids (frequently illegal – heroin)**



**REASON: Possibility to achieve the same effect with lower dose or to decrease withdrawal syndrome  
!! In the past misuse of flunitrazepam (Rohypnol)**

# Benzodiazepines – withdrawal

- schemes and tables for **slow** withdrawal of benzodiazepines
- withdrawal of **shortly** acting BZD by substitution for **long** acting BZD
- withdrawal of **long** acting BZD
- alprazolam 6 mg/day ~ diazepam 120mg/day

# HYPNOTICS

- **Z-substances (zolpidem, zopiclone)** selective agonists of  $\Omega_1$  benzodiazepine receptors ( $\Omega_1$  rec.= today: BZD<sub>1</sub> rec.)
- selective hypnotic effect without muscle relaxant, anxiolytic and anticonvulsant influence
- non-benzodiazepine structure
- they do not produce morning sleepiness, **but they also produce dependence!!!**

# Anxiolytics/sedatives/hypnotics – summary and features of dependence

## Barbiturates, benzodiazepines, hypnotics of III. generation:

- **Mechanism of action:** GABA receptors coupled with chloride channels – increased response to inhibitory effects of GABA
- **Tolerance** (one of complication of pharmacotherapy)
- **Psychological and physical dependence** (more significant in barbiturates !!!) No sudden withdrawal following chronic treatment!
- **Risk of acute intoxication** and respiratory depression is much higher in barbiturates!
- **Newer hypnotics (e.g. zolpidem)** – decreased (but still existing) risk!!!

# Opioid analgesics and abused opioids

strong physical dependence



strong psychological dependence

## ACUTE EFFECTS:

- feeling of numbness
- sleepy condition
- euphoria
- miosis

Psychotropic effects are associated with the way of administration

**i.v.** - *“rush“ and „flush“ effect*

**oral** – *euphoria and hapiness*

**other routes of administration:** nasal, inhalation (smoking - opium), other parenteral ways (s.c.)

# Opioid analgesics and abused opioids

## After chronic abuse:

fatigue, paranoia, cachexia, personality disorder, deprivation

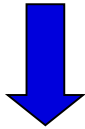
## Tolerance:

to majority of effects (very fast to dysphoria, nausea; gradually also to euphoria and toxicity – respiratory depression; chronic abusers tolerate doses lethal for a „normal“ subject)

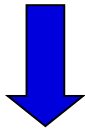
exceptions: miosis and constipation

# Opioid analgesics and abused opioids

**DEPENDENCE**



**PHYSICAL**



**after opioid withdrawal – typical withdrawal syndrome:**

**early symptoms:**

profuse nasal and eye secretion, sweat, „cold turkey“ (flu-like symptoms)

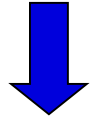
**late symptoms:**

mydriasis, tremor, hyperalgesia, insomnia, nausea, diarrhea, abdominal  
cramps

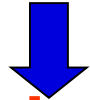


# Opioid analgesics and abused opioids

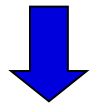
**DEPENDENCE**



**PSYCHOLOGICAL**



**after opioid withdrawal:**



**intensive longing for a dose – „**CRAVING**“  
unrest, anxiety, depression, suicidal thoughts**

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# Opioid analgesics and abused opioids

## Withdrawal symptoms

- **develop after 3 – 4 weeks of opioid administration and their sudden withdrawal**
- craving („drogenhunger“)

# Opioid analgesics and abused opioids

- **Withdrawal syndrome** in healthy individuals is not fatal (it is possible to withdraw even without pharmacological support)
- **Substances moderating withdrawal symptoms:**
  - BZD
  - beta-blockers
  - spasmolytics

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bupropion (anticraving effect???)

# Opioid analgesics and abused opioids

## SUBSTITUTION

**methadone** – similar to morphine; also agonist of opioid receptors, **significantly longer half-time ( $t_{0.5} >24$  h)**

- withdrawal syndrome occurs later and it is milder
- change in administration route – to p.o. administration
- gradual, slow decrease in dose
- mainly in heroin and morphine dependences
- complex care – in specialized facilities

## **buprenorphine**

- partial agonist of  $\mu$  receptors
- lower AE, lower dependence potential
- strong motivation of patient is necessary
- sublingual administration

**combination buprenorphine + naloxone**

# Other pharmacs - psychostimulants

- substances with **weak effect**: caffeine, theophylline (methylxanthines)
- substances with **moderate effect**: ephedrine, pseudoephedrine
- substances with **strong effect**: amphetamine, cocaine, methamphetamine

**amphetamine psychostimulants,**

**substances related to amphetamines and other stimulants**

- administration of stimulants is due to the risk of dependence development limited to small number of indications - narcolepsy, hyperkinetic syndrome with attention deficiency – ADHD

# Psychostimulants

## **acute effects**

euphoria, feeling of increased energy, psychomotoric unrest,...

## **more severe intoxication**

stereotypic behaviour, sometimes hallucinations, paranoid toxic psychosis

## **somatic symptoms**

arrhythmia, tachycardia, hypertension, dilatation of pupils, sweat, chest pain

# Psychostimulants

## **syndrome of dependence**

develops during several weeks to months

## **withdrawal syndrome**

fatigue, damping or on the contrary unrest, sleep disorders, increased appetite, dysphoria

## **chronic use**

risk of severe depression disorder, suicidal risk, paranoid conditions with anxiety and unrest

# Other medicaments with potential of dependence

## Laxatives

### abused to:

- treatment of chronic constipation
- decrease in weight

### abused laxatives:

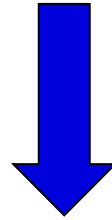
- contact/stimulatory: they decrease absorption by mucous membrane irritation, senna leaves, picosulphate

### treatment:

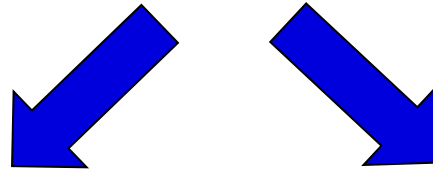
- no sudden withdrawal:
  - deterioration of constipation, flatulence, abdominal pain
  - sudden weigh gain due to salt and fluid retention with swelling
- gradual decrease in dose
- change to osmotic laxatives



# Abuse of laxatives

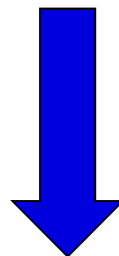


**WHO ARE ABUSERS OF LAXATIVES????**

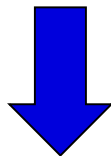


**people with eating disorders (or unsatisfied with body weight) – told by 10% of patients, estimated number – in 50% of patients**

**frequently in older patients (particularly women) with decreased mobility**

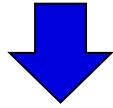


**slowed intestinal peristalsy → chronic constipation**

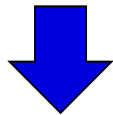


**frequently also combined misuse of diuretics, anoretics, etc.**

# Misuse/overuse of laxatives



in pharmacologically caused constipation



- **anticholinergics and sympatomimetics**
- **opioids**
- **Ca<sup>2+</sup> channel blockers (verapamil)**
- **diuretics**
- **antacides**
- **antihistamines (particularly H1-antihistamines)**
- **NSAIDs**
- **salts of ferrum**

# Laxatives misuse

## Adverse effects:

- particularly following long term administration or with too large doses
- painful spasms in GIT
- diarrhea → risk of dehydration and electrolyte dysbalance
- atrophy of smooth muscles → megacolon
- development of pharmacoresistant constipation
- meteorism, flatulence
- deficiency of minerals and H<sub>2</sub>O

# Cannabinoids (marijuana, hashish)

**MAIN ACTIVE SUBSTANCE:  $\delta$ -9-THC** 

**ENDOGENOUS SUBSTANCE: ANANDAMIDE**

## Therapeutical use:

- Pain
- Asthma
- Glaucoma
- Vomitus
- Oncology
- Parkinson's disease

## **After acute use:**

Euphoria, pleasure, anxiety, hallucinations

## **After chronic misuse:**

apathy, aggressivity  
impairment of memory, loss of interest, amotivational syndrome

# Psychodysleptics (psychotomimetics, hallucinogens, psychedelics)

## Hallucinogens

- some ergot alkaloids
- LSD
- psilocybin, psilocine (source in mushrooms *Psilocybe*)
- dependence potential – relatively low

# Nicotine and tobacco

- increases vigilance, concentration ability, improves memory, suppresses irritation and aggressivity (after acute administration)
- decreases appetite, prevents increase in body weight
- accelerates elimination of simultaneously given drugs (enzymatic induction)

# Nicotinism

## Consequences:

Impairment of developing fetus in pregnancy

↑ risk of ischemic heart disease, myocardial infarction, stroke

↑ risk of bronchogenic carcinoma

↑ risk of COPD

↑ risk of cancer

↑ risk of infertility, impotence, ...

# Nicotinism

- 1/3 of population in CR
- 20 000 of people die each year in CR due to smoking
- in age 13-15 years - 50% smokers

**Treatment:** substitution therapy with nicotine (chewing gums, plasters, nasal sprays) 

- varenicline – partial agonist of nicotinic receptors 
- bupropion – antidepressant NDRI 



# Ethanol

- produces strong physical and psychical dependence 🗨️
- physical dependence affects about 5% of adult population
- 95% is metabolized (mainly in liver), the rest is excreted unchanged by breath, urine and sweat

# Ethanol

- Psychical changes: delirium tremens, psychotic conditions, alcoholic dementia,...
- Physical changes: impairment of liver and pancreas, GIT, kidneys, CVS, neurological complications (alcoholic polyneuropathy)
- Pregnancy: risk of fetal alcohol syndrome)

# Ethanol

## Pharmacological possibilities of treatment:

- Detoxification
- Treatment of alcohol withdrawal syndrome
- Sensibilizing therapy
- Anticraving therapy

# Ethanol

## Pharmacological possibilities of treatment:

- Treatment of withdrawal syndrome → **BZD, clomethiazol, antipsychotics**
- Sensibilizing therapy → **disulfiram** = irreversible inhibitor of liver aldehyde dehydrogenase (in combination with alcohol intermediate product acetaldehyde is cumulated in organism – unpleasant somatic condition develops – development of psychological barrier to consumption of alcohol)

# Ethanol

## Pharmacological possibilities of treatment:

- **Anticraving therapy**

**acamprosate** → agonist of GABA receptors, inhibits activity of glutamate → decreases craving

## **Opioid antagonists**

**naltrexone** → mu antagonist, blocks effects of endogenous and exogenous opioids, decreases craving

**nalmefene** → mu + delta antagonist, partial agonist of kappa receptors, decreases consumption of alcohol, apparently by modulation of cortico-mesolimbic functions

## Additional therapy:

antidepressants, anxiolytics, antipsychotics, hypnotics, psychotherapy

# Solvents

- Various lipophilic organic solvents act as non-specific narcotics (e.g. **toluene**, **acetone**)
- **Routes of administration:** inhalation (plastic bags)
  - Lower doses – disinhibition → euphoria, hallucinations, pleasant dreams
  - High doses – inhibitory effect on CNS, coma and respiratory depression
  - Highly danger and relatively probable risk of overdosing with possible fatal consequences
- **Chronic misuse** – neurodegeneration + behavioural and mental disorders, organ toxicity - hepatotoxicity

# Other misused substances

**Arecoline** – from nut of palm *Areca catechu*

- cholinomimetic effects – stimulation of M and N receptors, effect is very similar to nicotine
- chewing, particularly in Asia
- mild psychostimulatory effects

# Other misused substances

**ketamin** – intravenous general anesthetic drug

- interferes with membrane effects of glutamate on NMDA receptors
- produces dissociative anesthesia
- hallucinogenic effects similar to phencyclidine (angel dust)
- hallucinations are associated with feeling of depersonalisation and derealisation
- it has, unlike other hallucinogens, high potential for development of psychological dependence

**esketamin** – in combination with SSRI or SNRI in resistant depression



# Other misused substances

**Antidepressants** – in general, potential for their misuse and to produce dependence is very low

- however mild withdrawal syndrome may occur after the end of therapy; gradual decrease of doses is recommended (or change to other antidepressant drug)
- **tianeptine** – RUE (re-uptake enhancer) – increases reuptake of monoamines, particularly of 5-HT, from the synaptic cleft
- there are some data on abuse of high doses in patients with comorbidity (dependence on other psychotropic drugs, e.g. alcohol)