

# Withdrawal states / complications in substance use/addictive disorders



Lucie Kališová, M.D., PhD.

# Dependence on psychoactive substance

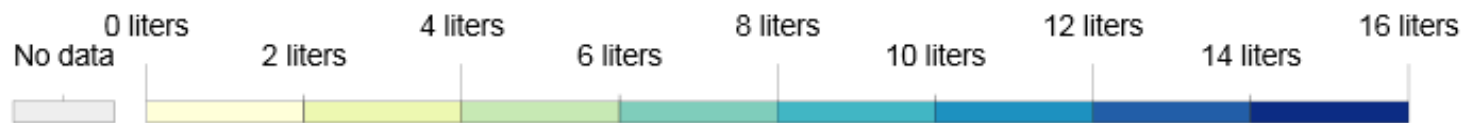
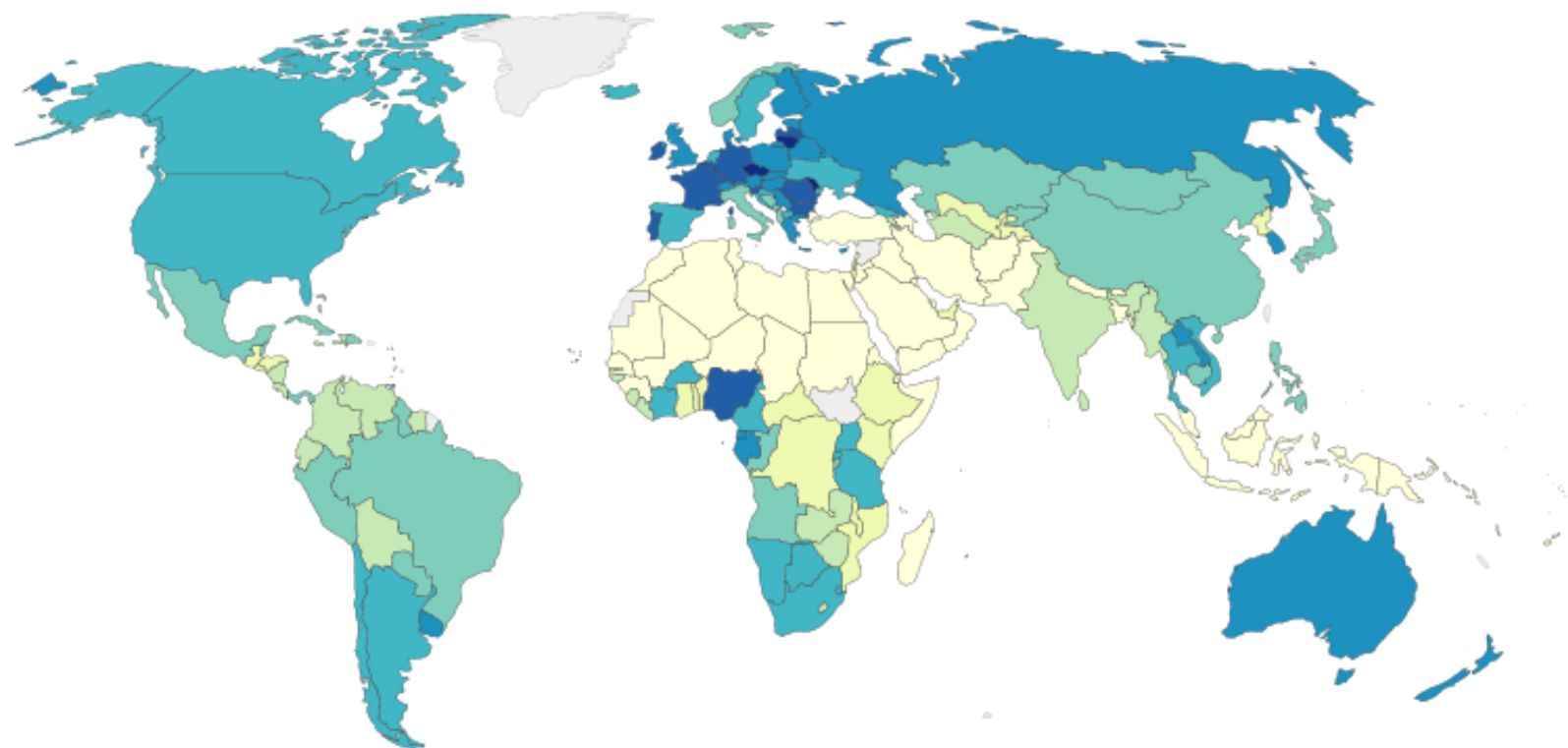
- F1x.2 – according to ICD – 10
- **A strong desire or sense of compulsion to take the substance;**
- **Difficulties in controlling substance-taking behavior;**
- **Evidence of tolerance, such that increased doses of the psychoactive substance are required in order to achieve effects originally produced by lower doses;**
- **Progressive neglect of alternative pleasures or interests because of psychoactive substance use;**
- **Persisting with substance use despite clear evidence of overtly harmful consequences;**
- **A physiological withdrawal state when substance use has ceased or have been reduced**

# 1. ALCOHOL

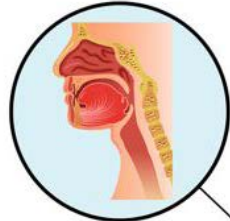


# Alcohol consumption per person, 2016

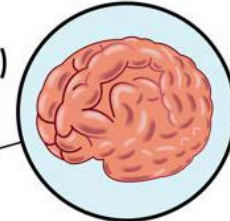
Consumption of alcohol is measured in liters of pure alcohol per person aged 15 or older.



# Alcoholism (damaging effects on man)



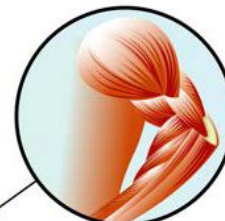
Cancer  
Bleeding esophageal varices



Impaired memory  
Lesser ability to focus  
Vision changes  
Wernicke-Korsakoff syndrome



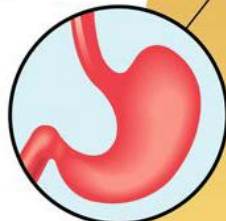
Alcoholic cardiomyopathy  
Anemia



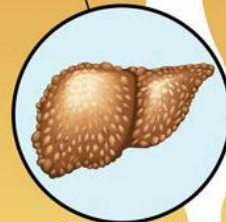
Chronic fatigue



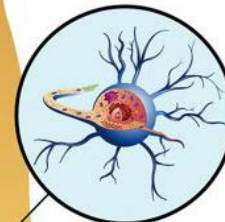
Pancreatitis



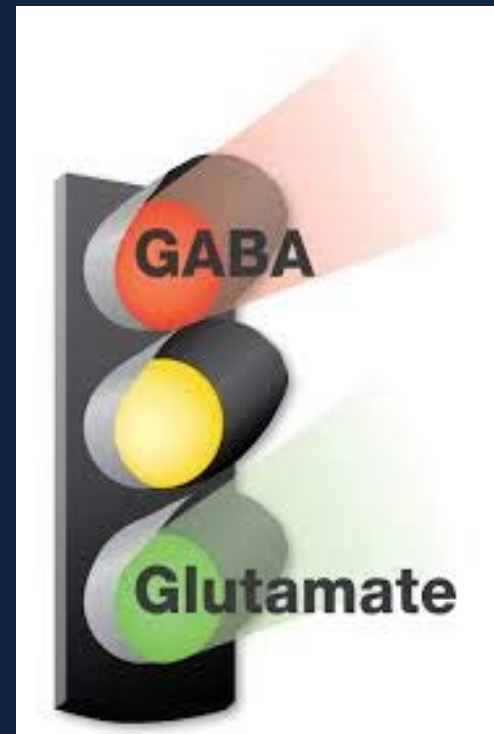
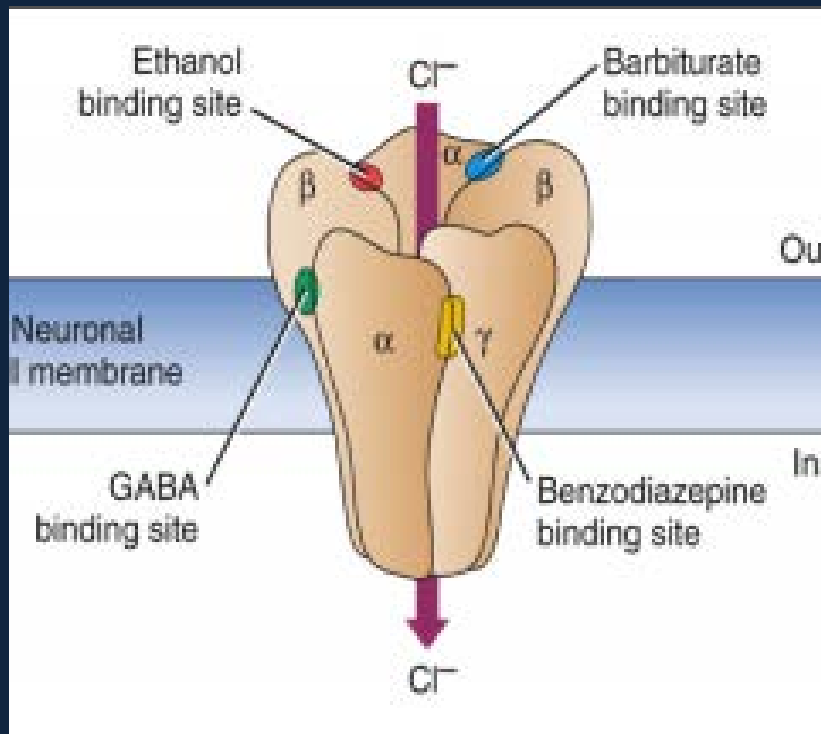
Chronic gastritis



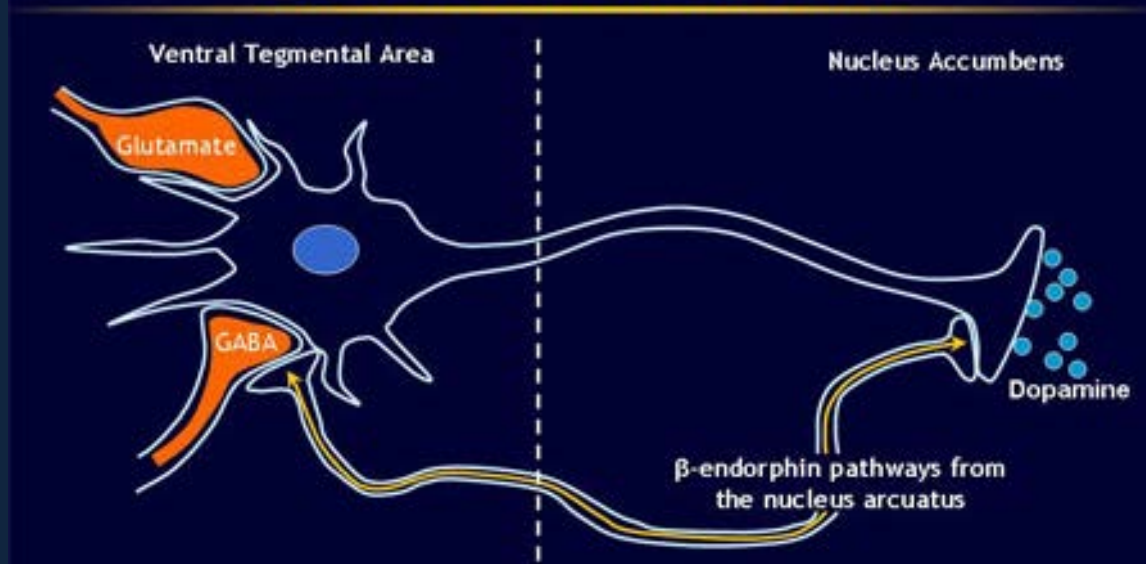
Cirrhosis  
Hepatitis  
Liver damage  
Liver disease



Ataxia  
(degeneration of the  
nervous system)  
Alcoholic neuropathy



## Neurotransmitter Systems



# Effects of alcohol

- **ETHANOL (C<sub>2</sub>H<sub>5</sub>OH)** - binds to **GABA<sub>A</sub>** receptor (main receptors for inhibitory neurotransmission)
- **Glutamate** – NMDA receptors – influx of calcium, excitotoxic effect. **Ethanol inhibits this excitation.**
- Other metabolic effects – inhibition of gluconeogenesis (hypoglycemia)
- Peripheral vasodilatation – frost damages..
- Ethanol transformates in liver via oxidation through alcoholdehydrogenasis to acetaldehyd, acetaldehyd via dehydrogensis to acetic acid, CO<sub>2</sub> and water.
- Speed of elimination **0,15 per mil/hour**

# **Withdrawal state in alcohol dependence**

- **After 4 hours – several days, maximum 2<sup>nd</sup> day of abstinence**
- **Severe desire (craving) for alcohol**
- **tremulousness (tongue, eye-lids, hands)**
- **sweating, higher temperature, facial reddening**
- **Nausea/vomiting, loss of appetite**
- **tachycardia, hypertension**
- **psychomotor agitation, irritability**
- **insomnia, headache, weariness, weakness**
- **transient hallucinations**
- **Grand mal seizures**



# Clinical/ laboratory features

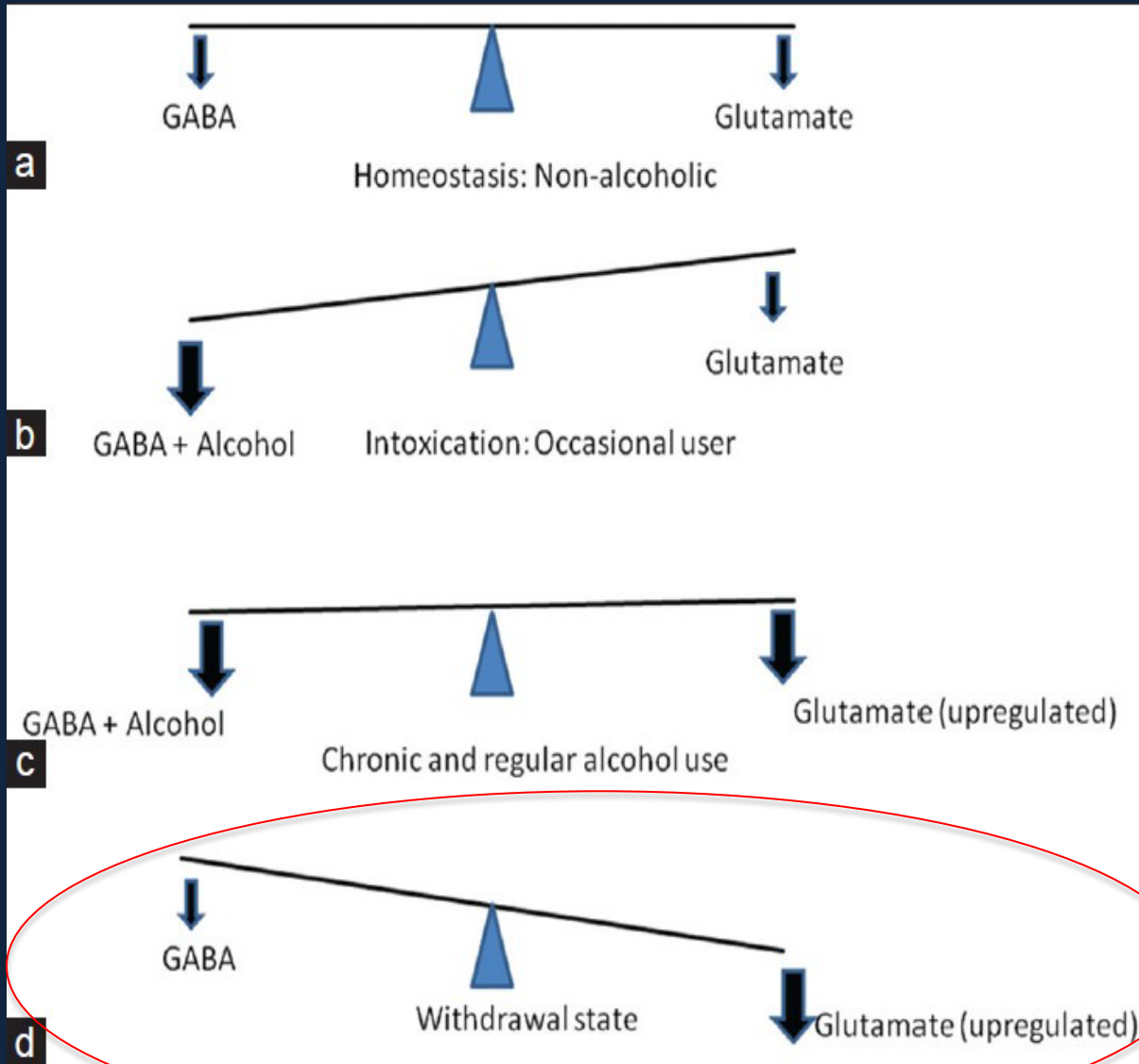
- Somatic manifestations – see before
- Hypopotassemia
- Hyperosmolarity /dehydration/
- Higher AST, ALT and GGT
- Blood count – increased the mean corpuscular volume of erythrocytes
- Hypertension
- Tachycardia
- Hypertermia

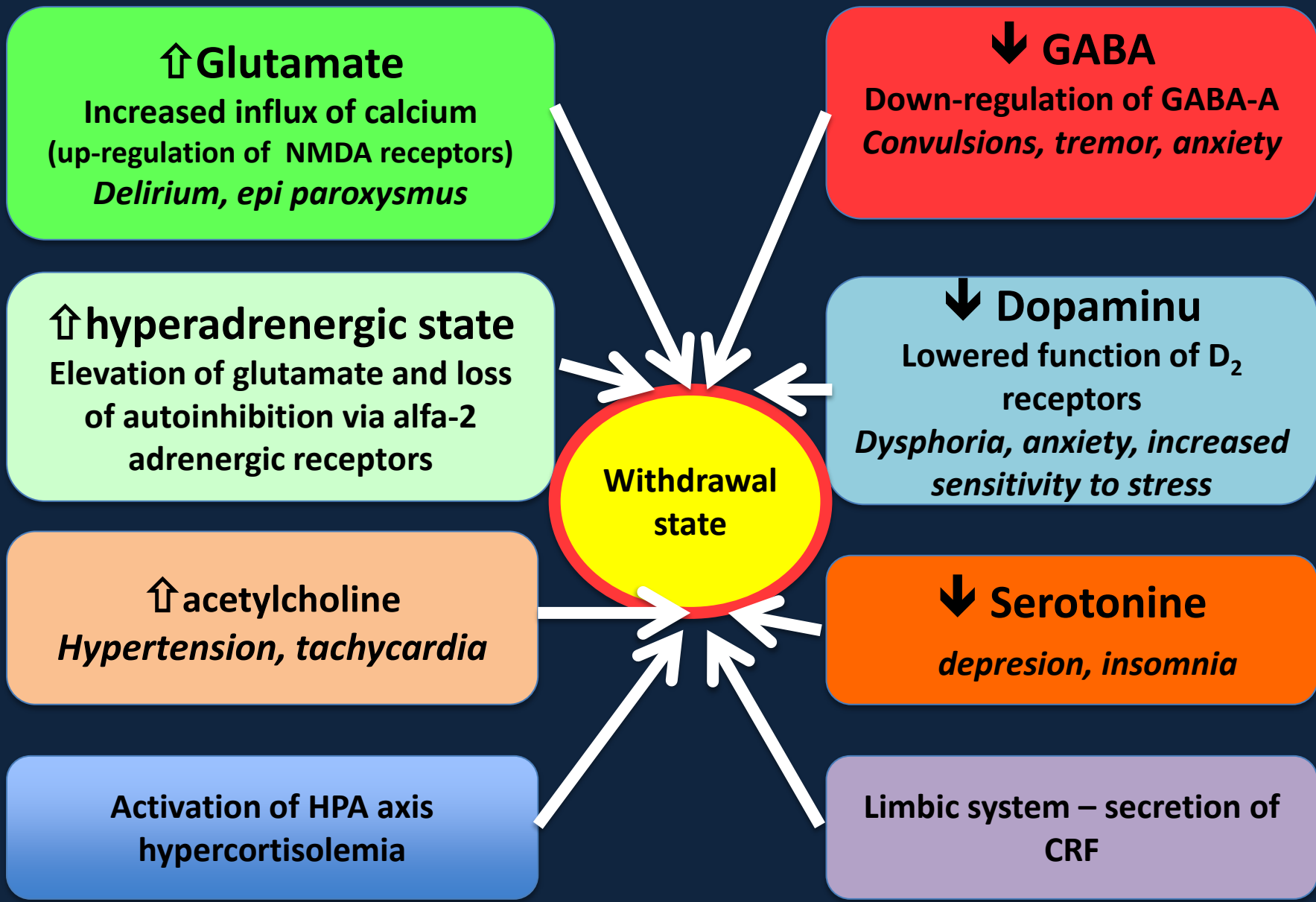
# ATTENTION !

- **Exclude other somatic cause – infection**
- **Head injury**
- **Intoxication with other substance or drug (medicinal..)**
- **Liver failure**
- **Metabolic breakdown**
- **Patient on antidiabetics - hypoglycemia**
- **Patient on psychomimetics – epi paroxysmus**

# Withdrawal state ethiology

- **LONG-TERM ABUSE** – adaptation - ↓ sensitivity and number of inhibitory GABA-A receptors and ↑ activity of glutamatergic system - ↑ number and sensitivity of NMDA receptors), to reach balance, doses of ethanol must ↑ (tolerance)
- Simultaneously **lowering of serotonergic and dopaminergic activity**
- **When we take alcohol away-** dysbalance between excitatory (Glutamatergic) and inhibitory (GABA- ergic activity) – **dominance of excitatory activity**





# Management of withdrawal state

## – basic rules

- **Alkholemia – over 2 per mil – “drunk tank”  
over 4 per mil – Intensive unit**
- **Intensive staff supervision – consciousness, changes of a state**
- **Measurement of blood pressure, pulse, temperature**
- **Environment**
- **Blood purchase – minerals, liver tests, urea, creatinin, glycemia, CRP, blood count, coagulability**
- **Questionnaires – Delirium rating scale (DRS), Clinical institute for withdrawal assessment for alcohol – revised (CIWA –Ar)**
- **ECG (if possible), pulse oxymeter**

# Environment

- **Place a patient to quiet environment, half – light**
- **Saturate needs – hydration, alimentation, self-care, communication**
- **Sometimes it is necessary to use mechanical restraint (until a patient becomes tranquille) – cave! Higher temperature, rhabdomyolysis**

Clinical Institute Withdrawal Assessment Scale for Alcohol, Revised (CIWA-Ar)

Nausea and Vomiting

- 0 – No nausea or vomiting
- 1
- 2
- 3
- 4 – Intermittent nausea with dry heaves
- 5
- 6
- 7 – Constant nausea, frequent dry heaves and vomiting

Paroxysmal Sweats

- 0 – No sweat visible
- 1 – Barely perceptible sweating, palms moist
- 2
- 3
- 4 – Beads of sweat obvious on forehead
- 5
- 6
- 7 – Drenching sweats

Agitation

- 0 – Normal activity
- 1 – Somewhat more than normal activity
- 2
- 3
- 4 – Moderate fidgety and restless
- 5
- 6
- 7 – Paces back and forth during most of the interview or constantly thrashes about

Visual Disturbances

- 0 – Not present
- 1 – Very mild photosensitivity
- 2 – Mild photosensitivity
- 3 – Moderate photosensitivity
- 4 – Moderately severe visual hallucinations
- 5 – Severe visual hallucinations
- 6 – Extreme severe visual hallucinations
- 7 – Continuous visual hallucinations

Tremor

- 0 – No tremor
- 1 – Not visible, but can be felt at finger tips
- 2
- 3
- 4 – Moderate when patient's hands extended
- 5
- 6
- 7 – Severe, even with arms not extended

Tactile Disturbances

- 0 – None
- 1 – Very mild paraesthesias
- 2 – Mild paraesthesias
- 3 – Moderate paraesthesias
- 4 – Moderately severe hallucinations
- 5 – Severe hallucinations
- 6 – Extremely severe hallucinations
- 7 – Continuous hallucinations

Headache

- 0 – Not present
- 1 – Very mild
- 2 – Mild
- 3 – Moderate
- 4 – Moderately severe
- 5 – Severe
- 6 – Very severe
- 7 – Extremely severe

Auditory Disturbances

- 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

Orientation and Clouding of the Sensorium

- 0 – Oriented and can do serial additions
- 1 – Cannot do serial additions
- 2 – Disoriented for date but not more than 2 calendar days
- 3 – Disoriented for date by more than 2 calendar days
- 4 – Disoriented for place/person

Cumulative scoring

Cumulative score	Approach
0 – 8	No medication needed
9 – 14	Medication is optional
15 – 20	Definitely needs medication
>20	Increased risk of complications



# Treatment of withdrawal state

## 1) Benzodiazepines

- diazepamum /half-time 20-100h/ - max 100mg
  - chlordiazepoxide (max 250mg/d)
  - oxazepamum in liver dysfunctions
- Max several days, to low step by step
  - CAVE: developed liver dysfunctions, severe COPD
  - Dose individually according to severity of dependence/ withdrawal signs + after intoxication + no further intoxication
  - Diazepamum 5mg=chlordiazepoxide 15mg=oxazepamum 15mg

## 2) Supplementation of minerals

## 3) Supplementation of thiamine for 5 days

## 4) Hydratation

- **According to severity – per os/infusion**
- **Lesser severity – transfer to p. o. medication**
- **Reduce a dose of bzd 10-15 mg/day**
- **Continuous monitoring of somatic state**
- **Rehydration, realimentation**
- **Motivation to a treatment of dependence**

# Other treatment psychopharmacological options

- **Clomethiazol (Heminevrin)**, cps á 300mg, 3 to 4 doses a day, e 2-4 cps, max 4800mg (16 cps)/day- lowering of dose, maximum 10 days. It can cause sedation,
- **Tiaprid** – atypical SDA  
100 mg tbl nebo 100 mg v 2ml amp., lower dose in elderly patients. 4 times per day till 1800mg/d.  
Lowers treshold for epileptic activity,  
prolongation of QTc

# Other pharmacotherapy

- **Antipsychotics – haloperidol** – only sometimes for states of agitation, prolongation of QTc.
- **Antiepileptics – carbamazepin** – unproven effect
- **Beta blockers** – lowering of some symptoms, but do not prevent epileptic seizures
- **Baklofen** – selective agonist of GABA-B receptors

# Complications

- **Agitation** – increase a dose of benzodiazepamum, deescalation, ev. Haloperidol 5-10 mg i.m., ev. very slowly 2-5mg haloperidol i.v. + restraint
- **Epi paroxysmus** – diazepamum 10mg i.v., i.m.
- **Break up of minerals + worsening of somatic state**– emergency
- **Delirium**

# Withdrawal state with delirium

- **24(48)-72 hours after last dose of alcohol**
- **Qualitative disturbance of consciousness, desorientation, worsening during night**
- **Increased suggestibility**
- **Delusions and hallucinations /visual, tactile/**
- **Vegetative hyperactivity (tachycardia, hypertension, hypertermia, sweating), mydriasis**
- **Purposeless motoric hyperactivity**
- **Paroxysmus (or not)**

# DELIRIUM TREMENS

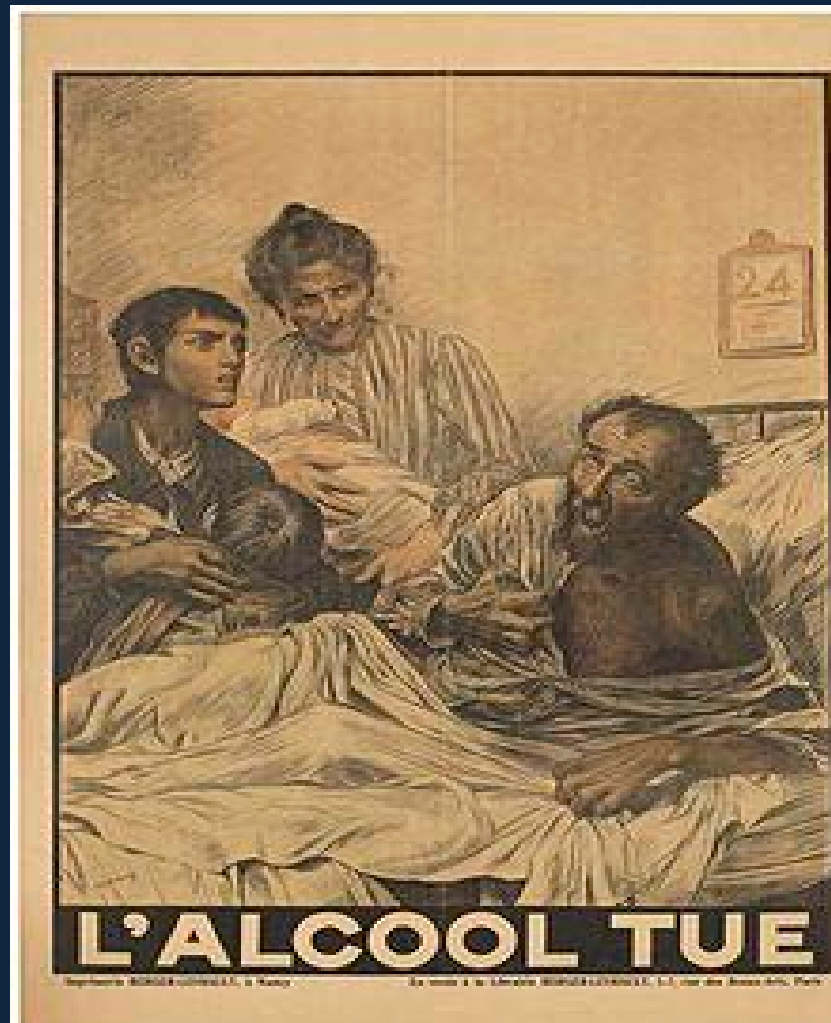
- **Mortality 5-10%! (arytmias, pneumonias, pancreatitis, hepatopatis..)**
- **Et the end amnezia**
- **Risk factors for delirium–** history of severe withdrawal state or delirium, epi paroxysmus or head – injury, older age, worse somatic state, other dependence
- **Differential diagnosis –** other delirium, alcohol hallucinosis, wernicke encephalopathy, psychosis

# Wernicke encephalopathy

- **Acute, sometimes fatal syndrom in people with alcohol dependence**
- **Deficit of thiamin**
- **oftalomoplegy** (nystagmus and parézy of oculomotoric muscles)
- **Ataxy and walking disturbances**
- **delirium** – hypoactive even coma– confusion, memory disturbances
- **Hypotermia, hypotensis, stupor, tachycardia**



# Somatic complications of alcohol dependence



# Minerals disturbances, glycaemia, dehydration

- **DEHYDRATATION** – hypertermia, vomiting, tachypnoea
- **HYPOPOTASSAEMIA** (due to renal and extrarenal loss, lowering of aldosterone....)
- **HYPOMAGNEZINÉMIA** –dysrhythmias, epi paroxysmus -substitute of MgSO<sub>4</sub>
- **Hypophosphatemia** – malnutrition – when severe, heart failure, rhabdomyolysis
- **Hyponatraemia** – carefully, (max 12 mmol/12h) – risk of pontine myelolysis
- **Hypoglycaemia** – glucosuria always with thiamin !! (risk of– wernickeův sy, akutní kardiomyopathy)

# Blood, CVS

- Hyperkoagulative state – infection, risk of DIC
- Hypokoagulative state – in hepatopathy – vit. K
  
- HYPERTENSION – beta-blocker, ACEI
- ARYTMIA – due to mineral changes

# GIT complications

- **Hepatopathy** – portal hypertension, bleeding from oesophageal varices, hepatic encephalopathy (ammonium) – lactulose, intestinal atb



- **Pancreatopathy** – elevation of sAMS, uAMS, lipases, CRP, KO, Ca, gly – parenteral alimentation, atb...

## **Kidney complication**

- Kidney failure, tuberointerstitial nephritis – due to dehydration and myoglobinuria within tremor - hydration, pharmacotherapy

## **Lung complications**

- Bronchopneumonia (aspiration, lowered immunity reactions, anaerobic agents)

# Disturbations of metabolic equilibrium

- **Metabolic acidosis** – in anaerobic metabolism, hypermetabolism, dehydration and hyposaturation. Intervention: rehydration, realimentation.
- **Alcohol ketoacidosis** – consequence of liver glycogen depletion. Intervention: realimentation, liver stabilization, parenteral nutrition.
- **Metabolic alkalosis** – in hypopotassemia, paradox aciduria; Intervention: supplementation of potassium.

# Neurological complications

- **Epi paroxysmus**
- According to Cochrane review – no proof that use of epileptics is beneficial + risk of arytmiias
- Encephaopathy, periferal neuropathy, polyneuropathy, wernicke encefalopathy

# Alcohol hallucinosis

- Hallucinations 12- 24h after withdrawal of and alcohol (x delirium later)
- Hallucinations mainly visual,also auditory or tactile
- Fade away within 24-48h
- No qualitative disturbance of consciousness.





# Farmacology of keeping of abstinence

- **Acamprosate (Campral)** : taurine analog affecting GABA centrally, slow effect (6 months). 3x day 600mg.
- **Naltrexon** – antagonist of opioid receptors, 50mg tbl, 2-2-3 tbl every other day
- **Disulfiram (Antabus)** – blocks aldehydehydrogenase, when drinking alcohol – „poisoning“ with acetaldehyde – vomiting, hypotension, arrhythmia.  
„Aversive therapy“  
Only for healthy subjects.

## 2. opiates



- **1,4 mil opiates users – stimulation of opioids receptors**
- **Illegally used - heroin, buprenorfin (subutex)**
- **Legally used – tramadol, codein, dextrometorfan (Robitussin), morfin**
- **Opium from unmaturred poppies (papaver somniferum).**
- **For 1 kg of opium - 20000 poppy heads**

# Withdrawal state in opiate dependency

- Within 6 hours after withdrawal, with methadon, buprenorphin longer (one day)
- **Eye watering, yawning, outflow from nose, muscle ache, spasmus, „goose bumps“, tachycardia, hypertension, insomnia, nausea, vomiting, mydriasis, craving, agitation**
- “Cold turkey” – it is not life-threatening

# Farmacotherapy of opiates withdrawal state

- Anxiolytics

- + substitution:

- Buprenorphin (partial agonist  $\mu$  rec and antagonist on  $\kappa$  receptors). SUBUTEX s.l., i.v. slowly decrease dose
- Buprenorphin+naloxon 4:1 - SUBOXON s.l.
- Methadone – longer half-time

# 3. Other psychoactive substances



# Cannabis

- **Long – term, dose dependent, (THC content) – schizophrenia + cognitive decline, hypobulia**
- **No withdrawal state – THC cumulates in fat tissue.**
- **Sometimes craving, sleep disturbances, irritability, hand - shaking, weakness**
- **Regime, psychotherapy, low doses of anxiolytics**

# TRANQUILLIZERS, HYPNOTICS

- Alprazolam (Neurol, Frontin, Xanax), Clonazepam (Rivotril), bromazepam (Lexaurin), diazepam, oxazepam
- Zolpidem (Hypnogen, Stilnox)
- **Similar symptoms as in alcohol withdrawal state – insomnia, irritability, tremour, risk of development of delirium.**
- **Epileptic seizures!**
- **Dose – reduction of bzd – 1. d of 30%, than 10%**
- Selection of non-benzodiazepine anxiolytics – hydroxyzin (Atarax), promethazin, buspiron aj.



# PSYCHOSTIMULANTIA

- Metamphetamin (pervitin), cocain, mefedron (4-methylmetkathionin 4-MMC) – MCAT, dron, Meow-meow, MDMA – extáze
- **Withdrawal state – fatigue, sleepiness, craving, incerease apetite, dysphoria**
- **Therapy: low doses of anxiolytics, antipsychotics, regime adjustment**
- **Long-term use of psychostimulatias – „toxic psychosis“**

# PSYCHEDELICS

- Natural – psilocybin (“mushrooms”), mescaline (from cactus peyotl), durman aj.
- Synthetic – LSD (Lyserge acid), PCP (phencyklidin), ketamin
- **No withdrawal state, sometimes psychotic microepisodes – „flash-back“**
- **Psychotherapy, regime, antipsychotics**

# Tobacco

- In the CR 30% inhabitants over 15 years old!!
- Many long-term risk factors
- **Withdrawal state – days/ weeks – craving, anxiety, increased appetite, irritability, hyposexuality, insomnia, dysphoria, depression, constipation, weakness**
- **Therapy: Nicotine substitution with progressive reduction (chewing-gums, plasters)**
- **Psychotherapy – CBT, hypnosis**

# **“Toxic psychosis”**

- **In connection with abuse of psychoactive substance**
- **Psychotic syndrome – Hallucinations, delusions, disturbance of emotions, behavior**
- **Differentiate - intoxication (longer 48 hours after intake), schizophrenia**
- **Residual psychotic disorder (alcohol jealousy, hallucinosis)**
- **Therapy – abstinence, antipsychotics**

# Conclusion

- **Case report** – 45 years old man, brought to psychiatric ward for suicidal tendencies. At admission 1,85 per mile. Regular alcohol user – 1 bottle of vodka daily. After 6 hours (0,5 per mile) – hand shakiness, nauzea,sweating, face rediness, insomnia..
- What will you do?

