SELF-ADMINISTRATION

positive

equal

negative

unequal

continuous

increase

Opioids

Ethanol
<table>
<thead>
<tr>
<th>Drug</th>
<th>Psychic Dependence</th>
<th>Physical Dependence</th>
<th>Tolerance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine &amp; Derivatives</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Barbiturate-like</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Amphetamine-like</td>
<td>++</td>
<td>(+)</td>
<td>+++</td>
</tr>
<tr>
<td>Cannabis (Marijuana)</td>
<td>+</td>
<td>Ø</td>
<td>(+)</td>
</tr>
<tr>
<td>Cocaine</td>
<td>+++</td>
<td>(+)</td>
<td>(+)</td>
</tr>
<tr>
<td>Ethanol</td>
<td>++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>LSD-mescalain</td>
<td>+</td>
<td>Ø</td>
<td>+++</td>
</tr>
<tr>
<td>Smoking (nicotine)</td>
<td>++</td>
<td>(+)</td>
<td>(+)</td>
</tr>
</tbody>
</table>
GABA$_A$ receptors

Benzodiazepines
Agonists
Antagonists
Inverse agonists

GABA
Barbiturates
Alcohol

Extracellular
Membrane
Intracellular
NMDA receptors

Cyttoplasmic side

Extracellular side

Polyamine site

Glutamate recognition site

Zn$^{2+}$ site

Glycine site

PCP site

Mg$^{2+}$ site

Na$^+$

Ca$^{2+}$

K$^+$

ethanol
decrease of the NMDA-stimulated DA release
Ethanol intoxication

↓ NMDA (+)

↓ voltage-sensitive Ca\(^{2+}\)-channels (+)

↑ GABA\(_A\) (-)

output ↓↓↓↓

Ethanol dependence

↑ NMDA (+)

↑ voltage-sensitive Ca\(^{2+}\)-channels (+)

↓ GABA\(_A\) (-)

output ↑↑↑↑
EFFECT of ACUTE ETHANOL

- enhanced action of 5-HT and acetylcholine
- activation of cation channels
EFFECT of ETHANOL on the 5-HT-ergic SYSTEM

**acute**
- increase of 5-HT function

**chronic**
- gradual decrease of 5-HT function

**at withdrawal**
- decreased 5-HT-ergic function

↓

alcohol craving

alcoholists corrects the serotonergic hypofunction by „self-medication”
Pharmacokinetic parameters of ethanol

**Absorption**
- topically - weak
- orally – complete (from the stomach)

**Distribution**
- in the whole body
- $V_d$ - 68 % of the body weight in man
  - 55 % in women

**Metabolism**
- >90% is metabolised
- „O“ order kinetic
- 100 mg/kg/hour (0.015%/hour)
- enzyme-induction, hepatic disease affects it

**Excretion**
- lung, kidney, breast milk, perspiration
METABOLISM of ETHANOL

%o

1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0

0 1 2 3 4 5 6 30 60 90 120 150 180 210 240 min hours

1.2 g/kg
0.8 g/kg
0.4 g/kg
Ethanol $\text{CH}_3\text{CH}_2\text{OH}$

Acetaldehyde $\text{CH}_3\text{CHO}$

Acetate $\text{CH}_3\text{COO}^-$

Alcohol dehydrogenase

MEOS

Aldehyde dehydrogenase

NAD$^+$

NADH

NADPH + O$_2$

NADPH$^+$

MEOS microsomal ethanol-oxidizing system

- In case of higher ethanol concentration, activity of MEOS increases.
- In chronic alcoholists, activity of MEOS increases.
- Ethanol clearance increases.
Phase of excitation

0.5-1.5 %

increased blood flow of the skin (flush)
increased respiration
increased motor activity
lack of inhibitions
agressivity
Phase of depression

1.2-2.5 %

stupor
sleepiness (falling asleep with ease, awakening with ease)
symptoms of deficiency in walking, in speech
perception disorders
slow, impeded reactions
Narcosis

> 2.5 %

deep sleeping
unconsciousness
superficial respiration, respiratory depression
dilated pupils (usually)
areflexia
Asphyxia

-4%o

shock
loss of thermoregulation
respiratory stop
death
OTHER EFFECTS

Effects on the heart

myocardial contractivity ↓

Effects on the smooth muscle

vasodilation

(CNS effect and acetaldehyde-induced direct effect)

Effects on the uterus

relaxation
Consequences of chronic ethanol consumption I

liver alcoholic fatty liver (reversible) alcoholic hepatitis cirrhosis

pancreas chronic pancreatitis

GI gastritis anaemia, protein malnutrition diarrhea vitamine deficiencies
Consequences of chronic ethanol consumption II

**neurotixicity**  generalised symmetric peripheral nerve injury
  ataxia
dementia
Wernicke - Korsakoff syndrome
  (B₁ deficiency)

**cardiovascular system**
dilated cardiomyopathy with ventricular hypertrophy and fibrosis
arrhythmias
  (at withdrawal also!)
hypertension
Consequences of chronic ethanol consumption III

- secondary aldosteronism
- hypoglycaemia (rare)
- increased risk of infection
- increased risk of cancer (mouth, esophagus, liver)
Fetal alcohol syndrome
(alcohol abuse during pregnancy)

- intrauterin growing ↓
- microcephaly
- poor coordination
- flattened face
- in very serious cases congenital heart defect
- mental retardation
- apoptotic neurodegeneration
- abnormal neuronal and glial migration
Tolerance
(relatively moderate to the lethal dose!)

Physical dependence

withdrawal symptoms depend on

- daily dose
- frequency of consumption
- period of chronic alcohol consumption
ALCOHOL WITHDRAWAL SYMPTOMS I

insomnia
anxiety
tremor (moderate)
nausea

more marked tremor
increased intensity of the starting symptoms
sweating
muscle cramps
vomiting
hyperreflexia
hypertension, orthostatic hypotension
nightmares
EEG symptoms
(hallucination)
persistent hallucination  desorientation
paranoia  agitation
collapse  delirium
hyperthermia  acute cardiovascular
convulsion  collapse
## COMPARISON of WITHDRAWAL SYMPTOMS of OPIOIDS and DEPRESSANTS (similarities)

<table>
<thead>
<tr>
<th>OPIOID</th>
<th>ETHANOL</th>
</tr>
</thead>
<tbody>
<tr>
<td>anxiey, dysphoria</td>
<td>anxiey, dysphoria</td>
</tr>
<tr>
<td>craving</td>
<td>craving</td>
</tr>
<tr>
<td>insomnia</td>
<td>insomnia</td>
</tr>
<tr>
<td>nausea, vomiting</td>
<td>nausea, vomiting</td>
</tr>
<tr>
<td>hyperpyrexia</td>
<td>hyperpyrexia</td>
</tr>
</tbody>
</table>
## COMPARISON of WITHDRAWAL SYMPTOMS of OPIOIDS and DEPRESSANTS (differences)

<table>
<thead>
<tr>
<th>OPIOID</th>
<th>ETHANOL</th>
</tr>
</thead>
<tbody>
<tr>
<td>lacrimation</td>
<td>tremor</td>
</tr>
<tr>
<td>nasal discharge</td>
<td>hyperreflexia</td>
</tr>
<tr>
<td>yawing</td>
<td>delirium</td>
</tr>
<tr>
<td>piloerection</td>
<td>seizures</td>
</tr>
<tr>
<td>sweating</td>
<td></td>
</tr>
<tr>
<td>mydriasis</td>
<td></td>
</tr>
<tr>
<td>abdominal pain</td>
<td></td>
</tr>
<tr>
<td>tachicardia</td>
<td></td>
</tr>
<tr>
<td>hypertension</td>
<td></td>
</tr>
<tr>
<td>involuntary</td>
<td></td>
</tr>
<tr>
<td>movements</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DEATH</td>
</tr>
</tbody>
</table>
TREATMENT OF DELIRIUM TREMENS

- clomethiazol i.v. infusion (risk of respiratory depression)
- benzodiazepines (substitutional therapy)
- $B_1$ vitamine (infusion 500 mg)
- fluid replacement
- balance of electrolites ($K^+$, $Mg^{++}$, $P$)
TREATMENT OF DELIRIUM TREMENS II

- osmotherapy (prophylactic treatment of edema)
- neuroleptics (tiapride, haloperidol)
- antibiotics
- prophylactic treatment of arrhythmia
DRUG INTERACTIONS with ALCOHOL

ADDITION of CENTRAL EFFECTS

sedative - hypnotics, anxyolitics
anticonvulsants,
antidepressants,

ALCOHOL CHANGES the METABOLISM of

phenytoine, tolbutamide, etc.
acetaminophen – risk of hepatotoxicity

HYPOGLYCEMIA – in diabetic patients

UNUSUAL ADVERSE EFFECTS with

metronidazole, cephalosporines,
oral antidiabetics,
(inhibition of aldehyd dehydrogenase)
Therapeutical usage of Ethanol

- decrease of body temperature
- irreversible nerve-blockade (injection)
- antiseptic (topical)
- anxyoliytic
- appetite enhancer
- methanol and ethyleneglycol intoxication
- premature labour
THERAPY of ALCOHOLISM I

Ethanol $\text{CH}_3\text{CH}_2\text{OH}$

$\text{NAD}^+$ + $\text{NADH}$

Acetaldehyde $\text{CH}_3\text{CHO}$

$\text{NADPH} + \text{O}_2$ + $\text{NADPH}^+$

Acetate $\text{CH}_3\text{COO}^-$

MEOS = microsomal ethanol-oxidizing system

MEOS

Alcohol dehydrogenase

Aldehyde dehydrogenase

Disulfiram

MEOS = microsomal ethanol-oxidizing system
**DISULFIRAM**

usual dose 250 mg/day – in the evening

inhibition of acetylaldehyde dehydrogenase

Symptoms in case of alcohol consumption

- nausea, vomiting
- tachycardya
- headache, migraine, dizziness
- dyspnoe
- collapse

Contraindicated in diabetes mellitus

angina
THERAPY of ALCOHOLIC PATIENTS II

(drugs used for preventing the relapse in alcoholic patients)

**Opioid antagonists**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Usual Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naltrexone</td>
<td>50 mg/day</td>
</tr>
<tr>
<td>Nalmafen</td>
<td>25 mg/day</td>
</tr>
</tbody>
</table>

only after detoxification (for 3 months)

**Gamma-hydroxibutyric acid**

for treatment of acute withdrawal symptoms (for 7 days)
ACAMPROSATE (Ca acetyl-homotaurinate)  

- increases the number of GABA binding sites in animal experiments  
- decreases the EAA transmitter function in animal experiments  
- acts first of all on the central withdrawal symptoms (tremor, anxiety)  

usual dose 3 X 600 mg/day
Block the cascade of alcohol dependence

1. Desire for alcohol positive craving
2. Acute drinking
3. Dopamine release
4. Chronic drinking
5. Withdrawal drug abstinence
6. Relapse

Drugs:
- Naltrexone, Nalmafen
- Ondansetron 5-HT3 antagonist
- Topiramate antiepileptic
- Acamprosate
- Disulfiram
COCAIN + ETHANOL

Cocaine plasma cc. ↑ (by 30%)

Ethanol → vasodilatation → absorption of cocaine is better

First-pass liver metabolism ↓

Ethanol plasma cc. ↓ (by 10%)

Cocaine → vasoconstriction ↓

Decreased absorption of ethanol?
COCAIN + ETHANOL II

euphoria ↑

paranoia, agitation ↓

withdrawal dysphoria ↓

cardiovascular effects ↑

toxicity ↑
COCAIN + ETHANOL III

coca-ethylene metabolite

its $t_{1/2}$ is about double of cocaine

it acts the same way as cocaine

in animal experiments it is self-administrated