„Addictions“
Disorders associated with (psychoactive) substances use

Ján Pečeňák

Psychiatrická klinika LF UK
ICD-10
F10 – F19
Mental and behavioural disorders due to psychoactive substance use

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, hypnotics
F14.- Mental and behavioural disorders due to use of cocaine
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.
ICD-11 – two subgroups added

- Disorders due to substance use or addictive behaviours
  - 6C42 Disorders due to use of synthetic cannabinoids
    - K2, Spice, Black Mamba, Bombay Blue,
    - drugs: Nabilon ...
    - higher affinity for receptors, unexpected effect
  - 6C47 Disorders due to use of synthetic cathinones
    - "bath salts"
### Alcohol is the main problem

No of out-patient assessment

**SK 2017**

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<th>Diagnosis</th>
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<th>19+</th>
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| Bez zistenej psychickej poruchy  
Without detected mental disorder | 377 | 212 | 165 | 3 613 | 1 849 | 1 764 |
By far most common hospitalizations

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Structure of treated drug dependent persons by main groups of used primary drug

- **Kokain (cocaine)**: 1.0%
- **Kombinované psychoaktivne látky (combined psychoactive substances)**: 6.8%
- **Opiáty (opiates)**: 24.5%
- **Prchavé látky (volatile substances)**: 1.3%
- **Hypnotiká a sedativa (hypnotics and sedatives)**: 3.9%
- **Stimulanciá (stimulants)**: 38.4%
- **Kanabis (konope, hemp)**: 23.9%
- **Hallucinogény (hallucinogens)**: 0.2%
F1x.0 Acute intoxication
   .00 Uncomplicated
   .03 With delirium
   .07 Pathological intoxication
F1x.1 Harmful use
F1x.2 Dependence syndrome
   .25 Continuous use
   .26 Episodic use [dipsomania]
F1x.3 Withdrawal state
   .31 With convulsions
F1x.4 Withdrawal state with delirium
F1x.5 Psychotic disorder
   .52 Predominantly hallucinatory
F1x.6 Amnesic syndrome
   Korsakov
F1x.7 Residual and late-onset psychotic disorder
   .70 Flashbacks
   .71 Personality or behavior disorder (depravation)
   .73 Dementia
   .74 Other persisting cognitive impairment
   .75 Late-onset psychotic disorder
F1x.8 Other mental and behavioral disorders
F1x.9 Unspecified mental and behavioral disorder
ICD-10 criteria for dependence

Three or more of the following must have been experienced or exhibited together at some time during the previous year

1. a strong desire or sense of compulsion to take the substance;
2. difficulties in controlling substance-taking behaviour
   - onset, termination, or levels of use;
3. a physiological withdrawal state
   - when substance use has ceased or been reduced
   - use of the same (or a closely related) substance with the intention of relieving or avoiding withdrawal symptoms;
4. evidence of tolerance
   - increased doses
5. progressive neglect of alternative pleasures or interests
   - increased amount of time necessary to obtain or take the substance or to recover from its effects;
6. persisting with substance use despite clear evidence of overtly harmful consequences
   - somatic, psychological, social
### DSM-5 – overview of disorders caused by substances

<table>
<thead>
<tr>
<th>Substance</th>
<th>psychosis</th>
<th>depression</th>
<th>sleep disorders</th>
<th>delirium</th>
<th>neurocognitive d.</th>
<th>withdrawal</th>
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<tbody>
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<td>i/w</td>
<td>i/w</td>
<td>i/w</td>
<td>i/w</td>
<td>i/w/p</td>
<td>✓</td>
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<td>Cannabis</td>
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<td></td>
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<td>i/w</td>
<td>i</td>
<td>✓</td>
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<tr>
<td>Phencyclidine</td>
<td>i</td>
<td>i</td>
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<td>i</td>
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<tr>
<td>Opioids</td>
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<td>i/w</td>
<td>i/w</td>
<td></td>
<td>✓</td>
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<td>Hypnotics/</td>
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<td>i/w</td>
<td>i/w</td>
<td>i/w/p</td>
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<td>anxiolytics</td>
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<tr>
<td>Stimulants</td>
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<td>i/w</td>
<td>i/w</td>
<td></td>
<td>i</td>
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<tr>
<td>Nicotine</td>
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<td></td>
<td>✓</td>
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</table>

i = during intoxication; w = during withdrawal; p = persistent
## Mechanism of effect

<table>
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<tr>
<th>Substance</th>
<th>Mechanism</th>
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<tbody>
<tr>
<td>Alcohol</td>
<td>agonism on GABA receptors, inhibition of NMDA (but secondary up-regulation in long-term use !!!!)</td>
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<td>Opioids</td>
<td>agonism on μ-, δ- κ opioid receptors</td>
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<tr>
<td>Cocaine, amphetamines ...</td>
<td>indirect agonism od dopamine/noradrenaline receptors through releasing of neurotransmitters</td>
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<tr>
<td>stimulants</td>
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<tr>
<td>Nicotine</td>
<td>agonism on Ach receptors</td>
</tr>
<tr>
<td>Cannabis</td>
<td>agonism on CB1, CB2 receptors</td>
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<tr>
<td>Phencyclidine</td>
<td>antagonism on NMDA receptors</td>
</tr>
<tr>
<td>Hallucinogens</td>
<td>partial agonism on 5-HT2A receptors</td>
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</table>
Structures and circuits involved in substance use – nc. accumbens as the central structure in mechanism of reward

nc. accumbens – dopamine transmission

Nestler, 2001
- BZD as substitute therapy
  - flumazenil

- methadone (other opioids) as substitute therapy in heroin addiction
  - naloxone
  - naltrexone
  - buprenorphine

- antipsychotics efficient in treatment of induced psychosis

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<td>Drug</td>
<td>Detection Time</td>
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<td>Alcohol</td>
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<tr>
<td>Amphetamine</td>
<td>48–72 hours</td>
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<tr>
<td>Barbiturate</td>
<td>24 hours (short acting); 3 weeks (long acting)</td>
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<tr>
<td>Benzodiazepine</td>
<td>3 days</td>
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<tr>
<td>Cocaine</td>
<td>6–8 hours (metabolites 2–4 days)</td>
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<tr>
<td>Codeine</td>
<td>48 hours</td>
</tr>
<tr>
<td>Heroin</td>
<td>36–72 hours</td>
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<tr>
<td>Marijuana</td>
<td>2–7 days</td>
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<tr>
<td>Methadone</td>
<td>3 days</td>
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<tr>
<td>Methaqualone</td>
<td>7 days</td>
</tr>
<tr>
<td>Morphine</td>
<td>48–72 hours</td>
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</tbody>
</table>

Kaplan & Sadock’s, 2017
Alcohol concentration

Widmark Formula
\[ c = \frac{A}{(r \cdot W)} \]

- \( c \) = the blood-alcohol concentration in \( \% \)
- \( A \) = amount of alcohol consumed in g
- \( W \) = the weight in kg
- \( r \) = distribution factor = 0.7 for men 0.6 for women
Alcohol metabolism

- 7 g/h on average
- several classes of ADH

ADH – alcohol dehydrogenases
ALDH - aldehyde dehydrogenase

10 milliliters = 8 grams

½ l
5,0 % = 25 ml
~ 20 g of alcohol

2 dl
12 % = 24 ml
~ 19.2 g of alcohol

“standard drink”
most commonly
10 g of alcohol

UK 8 g

Cederbaum, 2012
Alcohol metabolism

ADH – alcohol dehydrogenases
ALDH - aldehyde dehydrogenase
Intoxications with alcohol

- complicated intoxication
  - intoxication signs of behavioral disturbances (e.g. aggression, automutilation)
  - dependent on amount of alcohol and personality characteristics/common behavior during intoxications

- palimpsest (blackout)
  - amnesia, usually not-complete

- pathological intoxication
  - could be reaction to little amount to alcohol; behavior non-congruent with personality; character of qualitative disturbance of consciousness

<table>
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<th>%</th>
<th>mg/l</th>
<th>Phase</th>
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<td>mild</td>
<td>up to 1,5 %</td>
<td>0,72</td>
<td>excitatory</td>
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<tr>
<td>moderate</td>
<td>up to 2,5 %</td>
<td>1,2</td>
<td>inhibitory</td>
</tr>
<tr>
<td>severe</td>
<td>up to 3,0 %</td>
<td>1,44</td>
<td>comatose</td>
</tr>
</tbody>
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over 3,0 % – acute, life threatening intoxication
Dependence to alcohol

- about 10+ % of population

CAGE questionnaire

C: Have you ever felt you should Cut back on your drinking?
A: Has anyone ever Annoyed you by criticizing your drinking?
G: Have you ever felt Guilty about your drinking?
E: Have you ever had a drink early in the morning as an Eye-opener?

More than two positive responses suggests possible at-risk drinking and should prompt further assessment.

- primary
  - genetics about 60%
  - different social factors

- secondary
  - self treatment (e.g. social anxiety)
Withdrawal syndrome

- tremor
- autonomous imbalance
  - sweating
  - tachycardia
  - high blood pressure
  - nauzea, vomiting
- ion imbalance
  - hypokalemia
- exhaustion
- sleep disorders
- epileptic seizures
Delirium

- delirium tremens
  - symptoms similar to withdrawal +

- disturbance of orientation

- hallucinations
  - Lilliputian – microzoopsiae
  - scenic
  - occupational delirium
  - usually hyperactive
    - if aggression, disorganized behavior, restlessness, tension - physical restraint needed

- insomnia

- amnesia
- **short term use** – inhibitory effect on NMDA receptor
  - amnestic effect?

- **long term use** – up-regulation of glutamate transmission
- **stopping of alcohol intake** – neurotoxic effect of glutamate excitatory mechanism
  - epileptic seizures
  - cell damage

Herman H.H. /Ed./: Glutamate and addiction. 2003
Treatment

- somatic symptoms/disturbances
  - hypertension
  - ion imbalance
    - potassium, sodium, magnesium
    - supplementation of vitamins
      - thiamin i.m.
      - hepatoprotectives
    - nootropics

- substitute therapy
  - benzodiazepines
    - sometimes very high dosage of diazepam – 120 mg/day and even more
      - oxazepam
  - if hallucination, restlessness, aggression
    - antipsychotics – tiaprid, haloperidol
Other psychiatric complication of alcohol dependence

- Wernicke encephalopathy / Korsakoff syndrome (psychosis)
  - Wernicke – neurological syndrome
    - acute confusional state
    - ophthalmoplegia
    - nystagmus
    - ataxic gait
  - Korsakoff
    - amnestic – confabulatory syndrome
    - thiamin deficiency supposed to be the main reason

- Paranoid psychosis/psychosis of jealousy

- Alcoholic hallucinosis
  - no disturbance of consciousness

- Alcoholic dementia
  - can be at least partially reversible
Wernicke and Kosakoff

Karl Wernicke (1848-1904).

Sergei Korsakov (1853-1900)


Wernicke encephalopathy

Fig. 1—61-year-old alcoholic man with Wernicke encephalopathy during acute phase of disease.
A, Axial T2-weighted image shows asymmetric edema of mamillary bodies (arrows).
B, Multiplanar gradient-recalled image shows blooming consistent with hemorrhage (arrow) in left mamillary body.
C, Symmetric involvement of medial thalami (arrows) is seen on T2-weighted image.
D, Contrast enhancement of mamillary bodies (arrows) is seen on T1-weighted image.

Zuccoli et al., 2010
Alcohol-related dementia: a 21st-century silent epidemic?
Susham Gupta and James Warner

Summary
Evidence suggests a J-shaped relationship between alcohol consumption and cognitive impairment and other health indicators, with low levels of consumption having better outcomes than abstention or moderate to heavy drinking. Most research to date has focused on the protective effects of drinking small amounts of alcohol. As alcohol consumption is escalating rapidly in many countries, the current cohort of young and middle-aged people may face an upsurge of alcohol-related dementia. The dangers of heavy drinking and its effect on cognition require further attention.

Declaration of interest
None.
Somatic complication

- liver
  - increased liver enzymes – mainly GMT
  - fatty liver, alcoholic hepatitis, cirrhosis
    - ascites, esophageal varices
- pancreatitis
- alcoholic cardiomyopathy
- increased MCV (the mean corpuscular volume)
- peripheral neuropathy
  - problem with gait often the reason for prolonged hospitalization
- cancers
Treatment overview

- **acute intoxication**
  - hydration, minerals, prevention of suffocation
  - no benzodiazepines; antipsychotics if needed (hyperactivity, aggression)
  - flumazenil could be tried (possible combined intoxication)

- **detoxification, withdrawal, delirium**
  - substitute therapy with BZD and other means mentioned before

- **treatment of dependence**
  - long term – at specialized departments (6 - 8 weeks)
    - regimen, tokens – points for rewards like go out, education, group psychotherapy, acceptance of being addicted, change of preferences ...
  - at communities outside the health system
  - supportive groups, Alcoholics Anonymous

- **pharmacological**
  - disulfiram
  - apomorphin (aversive therapy)
    - akamprosate
    - nalmefene (similar to morphine)
    - gabapentine, carbamazepine, n-acetylcystein, naltrexone
Anxiolytics / hypnotics / sedatives

- mainly benzodiazepines
  - in SK most common bromazepam, alprazolam
- 3Z!
  - zopiclone, zolpidem
- Gamma-hydroxybutyrate (GHB) - recreational drug (dance)
  - dissociative phenomena
- withdrawal (overlap with rebound phenomena)
  - anxiety
  - insomnia
  - paresthesia
  - flashes in peripheral vision fields
  - muscles cramps and twitching
  - tremor
  - epileptic seizure
- treatment
  - substitute therapy with long-lasting drugs – diazepam
- other psychotropic drugs with surprising addiction potential
  - quetiapine
  - tianeptine
Opioids

- opiates – natural alkaloids
  - Thomas Sydenham – opium tincture "laudanum"
    - morphine
    - codeine

- opioids
  - endogenous
    - endorphins, enkephalins, endomorphins
  - semisynthetic or synthetic
    - heroin – diacetylmorphine
  - many medicaments
    - oxycodone
    - pethidine
    - fentanyl
    - dihydrocodeine
    - tramadol

ongoing epidemic in USA
**Heroine**

- **intoxication**
  - “flash”, “rush”, followed by euphoria, sedation, calming effect, inertness ... “nodding off”
  - *miosis*

- **tolerance and dependence**
  - rapid and severe
    - from smoking to i.v. application – huge increase of tolerance, need for higher dosage
    - maintenance of use more focused on prevention of withdrawal

- **withdrawal**
  - intense (subjectively), but usually not life-threatening
    - *mydriasis*
    - symptoms like in sever cold/ influenza:
      - change of temperature - chills, profound sweating
      - piloerection – “cold turkey”
      - pain in muscles / bones / back / joints
      - diarrhea
      - rhinorrhea / tearing
    - psychomotoric instability
    - yawning
    - severe insomnia
Treatment of opioid addiction

- detoxification
  - non-specific hydration, benzodiazepines, analgesics
    - clonidine = α 2 antagonist
    - Reasec = diphenoxylate (pethidine derivate) + atropine

- substitute therapy → the aim is to manage withdrawal and harm reduction in long term treatment
  - methadone
  - buprenorphine
  - buprenorphine + naloxon = Subuxone (prevention of i.v. application of buprenorphine)

- codeine
- tramadol

- antagonists
  - naloxone - antidotum
  - naltrexone
Stimulants

Erythroxylon coca

Ephedra sinica

*Catha edulis*
britanica.com
*cathinons*
bath salts – e.g. methylone
Stimulants

- cocaine
  - crack - free base of cocaine
- methamphetamine (pervitine)

- medicaments for ADHD treatment
  - methylphenidate
  - dextroamphetamine
- modafinil - narcolepsy
Effects of stimulants

- “high”, “speed”
  - energy
  - less sleep
  - higher sexual appetency and potency
  - in some people better concentration

- harmful effect
  - anxiety
  - insomnia
  - paranoid psychosis – can be dangerous because of hyperactivity, aggression
  - tactile hallucinosis

- depravation of personality
MDMA = extasy
3,4-methylenedioxymethamphetamine

- combination of
  - stimulant
    - more on noradrenaline and serotonin than dopamine
  - hallucinogen
  - entactogen – ↑ self awareness and empathy

- vigorous physical activity (dance)
  - hyperthermia
  - electrolyte imbalance
  - arrhythmias
  - sexual risky behaviors
  - depression
  - confusion

- ongoing research on PTSD
  - willingness to discuss emotionally-charged memories
Cannabinoids

- > 100 cannabinoids in marihuana
- higher levels of THC in new “sorts” — *sinsemilla*

tetrahydrocanabidiol
approved for treatment special form of epilepsy in young children by FDA

synthetic cannabinoids

- may have hundreds times higher affinities
- unpredictable
  - K2, Spice, Joker, Black Mamba, Kush, Kronic
Cannabis

- "high"
  - altered senses
    - for example, seeing brighter colors
  - altered sense of time
  - changes in mood
  - psychosis
    - problem in "dual diagnosis", mainly schizophrenia

- withdrawal
  - craving
  - dysphoria
  - insomnia
  - decreased appetite
  - hyperemesis syndrome in long term high use

- Synthetic
Hallucinogens

- LSD (d-lysergic acid diethylamide)
- Psilocybin, psylocin
- Peyote (Mescaline)
- Ayahuasca - DMT (Dimethyltryptamine)
Dissociative

- PCP (Phencyclidine)
- Ketamine - K, Special K
- DXM (Dextromethorphan)
- Salvia divinorum
Durman

- **Datura stramonium**
  - Jimsonweed, devil's trumpet
  - Anticholinergic - atropine
Trips and bad trips

- serotonin, NMDA or μ receptors
- psychotic experiences
  - illusions, hallucinations
  - change of reality, change of time speed
  - “broaden”, “extended” consciousness
Solvents / inhalants

- toluene
- amyl nitrite, butyl nitrite
- benzene
- butane, propane
- freon
- methylene chloride
- nitrous oxide ("laughing gas"), hexane

- sudden sniffing death syndrome
- suppressed immunologic function
- hypoxia
- cell death
- “group hallucinations”