Alcohol dependence

Drinking patterns
None  no alcohol in last year
Occasional no alcohol in last month
Light (males) less than 22 units / week
Light (females) less than 15 units / week
Moderate (males) 22-35 units
Moderate (female) 15-25 units
Heavy (males) 36-50 units
Heavy (female) 26-35 units
Very Heavy (male) > 50 units
Very Heavy (female) > 35 units

Recommended drinking limits
• 10 ml of absolute alcohol = 8.0 g of absolute alcohol = 1 unit
• no more than $\frac{1}{2}$ of total units should be consumed in one session
• 2 drink free days per week
• during pregnancy: 1-2 units / day a couple of days a week, but preferably nil
• 1-2 units / day has a beneficial effect on the coronary arteries

Blood alcohol levels
• one unit of alcohol can give a blood alcohol level of 15-25 mg %
• blood alcohol levels fall due to excretion at a rate of about 15-20 mg % per hour

<table>
<thead>
<tr>
<th>Blood alcohol concentration (mg %)</th>
<th>Typical effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>• enhanced sense of well-being</td>
</tr>
<tr>
<td></td>
<td>• visual reaction time reduced</td>
</tr>
<tr>
<td>40</td>
<td>• somewhat disinhibited</td>
</tr>
<tr>
<td></td>
<td>• reduced driving ability at speed</td>
</tr>
<tr>
<td>60</td>
<td>• judgement impaired</td>
</tr>
<tr>
<td>80</td>
<td>• physical coordination impaired</td>
</tr>
<tr>
<td>100</td>
<td>• evident loss of social judgement</td>
</tr>
<tr>
<td></td>
<td>• poorly coordinated</td>
</tr>
<tr>
<td>130</td>
<td>• clearly intoxicated</td>
</tr>
<tr>
<td>300</td>
<td>• coma</td>
</tr>
<tr>
<td></td>
<td>• stupor</td>
</tr>
<tr>
<td></td>
<td>• loss of bladder control</td>
</tr>
<tr>
<td>500 +</td>
<td>• coma</td>
</tr>
<tr>
<td></td>
<td>• respiratory depression, death</td>
</tr>
</tbody>
</table>
Blood, Urine, and breath alcohol equivalents

<table>
<thead>
<tr>
<th>Blood (mg / 100ml)</th>
<th>Urine (mg / 100 ml)</th>
<th>Breath (µg / 100 ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>67</td>
<td>22</td>
</tr>
<tr>
<td>80 (legal limit)</td>
<td>107</td>
<td>35</td>
</tr>
<tr>
<td>150</td>
<td>200</td>
<td>66</td>
</tr>
<tr>
<td>200</td>
<td>267</td>
<td>88</td>
</tr>
<tr>
<td>250</td>
<td>333</td>
<td>110</td>
</tr>
</tbody>
</table>

Alcohol and the brain

<table>
<thead>
<tr>
<th>Experience</th>
<th>Transmitter/ receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activation</td>
<td>NA</td>
</tr>
<tr>
<td>Euphoria/ pleasure</td>
<td>DA</td>
</tr>
<tr>
<td>Anxiolysis/ ataxia</td>
<td>GABA</td>
</tr>
<tr>
<td>Sedation/ amnesia</td>
<td>increase GABA block NMDA</td>
</tr>
<tr>
<td>Nausea</td>
<td>stimulate 5-HT₃</td>
</tr>
<tr>
<td>Withdrawal</td>
<td>increase Ca²⁺ flux decrease magnesium</td>
</tr>
<tr>
<td>reinforcing actions of alcohol</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>DA</td>
</tr>
</tbody>
</table>

Opioids
- alcohol increases concentrations of plasma endorphins
- mu and delta receptors are involved in the reinforcing effects of alcohol

GABA
- at low doses, alcohol increases the ability of GABA to open the chloride channel on GABA_A receptors
- at higher concentrations, alcohol has a direct action on the receptor, causing a prolonged opening of the channel which is GABA-independent
- this action is mimicked by barbiturates but not benzodiazepines – excessive chloride influx will result in paralysis of the neurons responsible for respiratory drive, so causing asphyxiation

Glutamate
- alcohol blocks NMDA channels, opposing the effects of glutamate, and contributes to the causation of amnesia and other cerebral depressant effects
- the brain attempts to compensate by increasing the number of NMDA channels
- once alcohol consumption drops, there is a relative excess of NMDA function, which explains the hyperexcitability of alcohol withdrawal
Harmful use of alcohol (F10.1)

- a maladaptive pattern of alcohol use:

DCR-10

A. There must be clear evidence that the substance use was responsible for (or substantially contributed to) physical or psychological harm, including impaired judgment or dysfunctional behaviour
B. The nature of the harm should be clearly identified (and specified)
C. The pattern of use has persisted for at least 1 month or has occurred repeatedly within a 12-month period
D. The disorder does not meet the criteria for any other mental or behavioural disorder related to the same drug in the same time period (except for acute intoxication)

Alcohol dependency syndrome (F10.2)


1. narrowing of repertoire
2. salience of drinking
3. tolerance
4. withdrawal symptoms
5. relief drinking
6. compulsion to drink
7. reinstatement after abstinence

DCR-10

- at least three of the following:
  A. A strong desire or sense of compulsion to drink
  B. Difficulty in controlling the amount drunk
  C. Physiological withdrawal state after drinking stops, with the possible use of alcohol to relieve this
  D. Evidence of tolerance may appear
  E. Progressive neglect of alternative pleasures and interests
  F. Persistence of drinking in spite of evidence of harmful effects

Epidemiology

Hospital admissions

- in the USA 30 % of medical and surgical cases are suffering from alcohol problems
  - 25 % of psychiatric cases, 19 % of neurology, and 12.5 % of Obstetric and Gynaecology
- alcohol accounts for 10 % of all psychiatric admissions in the UK
General population surveys

<table>
<thead>
<tr>
<th></th>
<th>Men over 15</th>
<th>Women over 15</th>
</tr>
</thead>
<tbody>
<tr>
<td>England &amp; Wales</td>
<td>14.9 units per week</td>
<td>4.0</td>
</tr>
<tr>
<td>Scotland</td>
<td>1.2</td>
<td>3.4</td>
</tr>
<tr>
<td>Northern Ireland</td>
<td>6.7</td>
<td>1.3</td>
</tr>
</tbody>
</table>

- annual consumption of 4.2 litres of absolute alcohol per capita (population surveys)
- ECA study found a 14 % lifetime prevalence of alcoholism
- M:F = 4:1
- 20-30 % of patients in general health care have alcohol-related disabilities
- 10 % of the population are totally abstinent from alcohol

Specific groups

- disproportionate rise in females
- rise in adolescents
- 35 % of homeless have alcohol disorders
- 4-6 % of medical profession abuse alcohol

- age of onset in late teens or 20s for males
- onset later in females, who are more likely to:
  - drink alone
  - delay seeking help
  - have co-morbid depression
  - have a stronger genetic predisposition
  - develop physical complications, especially cirrhosis
- higher rates in:
  - urban areas
  - divorced/ separated
  - those who manufacture, or sell alcohol
  - commercial travellers, frequent overseas travellers
  - entertainers, doctors, journalists
  - North American, Afro-Caribbean, Irish
- lower rates in:
  - ‘middle’ social groups
  - Jewish, Chinese

Aetiology

Genetic

1. *Family Studies:*
   a) 7-fold increase in risk of alcoholism among 1st degree relatives of alcoholics

2. *Twin Studies:*
   a) MZ: DZ = 70 %: 43 % for males
3. **Adoption Studies:**
   a) sons of alcoholics are 4 x more likely to be alcoholic than sons of non-alcoholic, regardless of the drinking patterns of adoptive parents
   b) sons of alcoholics raised by non-alcoholic adoptive parents are no more susceptible to other non-alcoholic adult psychiatric disorder
   c) higher rates of childhood conduct disorder in male offspring of alcoholics
   d) alcoholism and antisocial personality disorder were genetically independent disorders for both males and females

4. **Chromosomes:**
   a) recent associations between D2 dopamine receptor and alcoholism are controversial
   b) variations in allele compositions for alcohol dehydrogenase and aldehyde dehydrogenase may contribute to risk patterns of alcoholism among oriental populations

5. **Vulnerability markers:**
   a) abnormalities in P300 event-related potential associated with familial alcoholism > P300 predicts alcohol abuse (Berman et al. 1993)

6. **Risk factors:**
   a) family history

**Biochemical**
- alcohol’s reinforcing effects are modulated by dopamine, serotonin, and GABA systems
- DA antagonists, SSRIs, GABA agonists, and opioid antagonists have all been shown to reduce alcohol consumption in animal studies

1. **Dopamine:**
   a) alcohol stimulates DA release in nucleus accumbens
   b) increased DA may underlie ‘craving’

2. **5-HT:**
   a) alcohol potentiates effects of serotonin at 5-HT3 receptors
      i) increased DA release in nucleus accumbens may be via this mechanism
   b) some reports of 5-HT agonists in reducing alcohol craving

3. **MAO:**
   a) decreased platelet MAO activity is linked to type 2 alcoholism

4. **Other receptor/neuropeptides:**
   a) alcohol inhibits NMDA receptor channels in glutamate receptor
      i) possible glutamate excitotoxic model for CNS damage with alcohol
   b) potentiation of effects of GABA receptor complex

**Psychodynamic**
- intoxication is a gain to the patient, with disinhibition allowing the expression of aggression
maternal overprotection is described among some alcohol problems clinic attendees
childhood sexual abuse is more commonly reported in women alcoholics than in the general population

**Behavioural**
- models include drinking becoming a conditioned response to a wide range of circumstances
- modelling from parents, relatives, peers, etc. is clearly demonstrated
- the euphoriant effect of alcohol is an important reinforcer for continued drinking

**Stress and negative life events**
- bereavement
- separation
- impending court case

**Personality**
1. **Type 1** alcoholic – more dependent, anxious, rigid, less aggressive, more guilty, with either the mother or father an alcoholic
2. **Type 2** alcoholic – early onset, severe problems, socially detached, distractible, confident, and whose behaviour is linked to a similar pattern in the biological father
   - can be seen as alcoholism secondary to antisocial personality disorder

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Type 1</th>
<th>Type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>after age 25</td>
<td>before age 25</td>
</tr>
<tr>
<td>Gender</td>
<td>either</td>
<td>male</td>
</tr>
<tr>
<td>Antisocial traits</td>
<td>no</td>
<td>common</td>
</tr>
<tr>
<td>Type of drinking</td>
<td>binge</td>
<td>steady</td>
</tr>
<tr>
<td>Other drugs</td>
<td>rare</td>
<td>common</td>
</tr>
<tr>
<td>Guilt about drinking</td>
<td>marked</td>
<td>slight</td>
</tr>
<tr>
<td>Impulsivity</td>
<td>low</td>
<td>high</td>
</tr>
<tr>
<td>Brain 5-HT function</td>
<td>high</td>
<td>low</td>
</tr>
<tr>
<td>Mcpp responses</td>
<td>anxiety</td>
<td>high</td>
</tr>
</tbody>
</table>

**Alcohol related disabilities**

**Hepatic:**
1. may be due to toxic effects of acetaldehyde / damage to immune system by alcohol
2. women are more susceptible than men
3. **Fatty liver:**
   - a) may be present in 90% of drinkers
   - b) reversible with abstinence
4. **Alcoholic hepatitis:**
   - a) abstinence aids resolution, but cirrhosis may follow
5. **Cirrhosis:**
   - a) 10% of chronic alcoholics
b) more common in women
c) vulnerability may be due to HLA-B8 antigen, found in 25% of population
d) HLA-A28 may have a protective effect
e) fibrosis of the liver and decompensation of liver function
f) stigmata of liver disease may be present

6. Carcinoma:
   a) 15% of patients with cirrhosis go on to develop hepato-cellular carcinoma

7. Portal hypertension

Gastrointestinal:
1. Barrett’s oesophagitis
2. Oesophageal varices
3. Mallory-Weiss tears
4. Gastritis and gastric erosions
5. Peptic ulceration – 20% of alcoholics; bleeding may be exacerbated by Vitamin K deficiency secondary to cirrhosis
6. Pancreatitis – both acute and chronic
7. Gastric carcinoma
8. Possible association with colorectal carcinoma
9. Diabetes mellitus

Haematological:
1. Alcoholism is the commonest cause of macrocytosis
2. Thrombocytopenia and anaemia may also occur
3. Zieve’s syndrome is a rare form of alcoholic haemolysis

Neurological:
1. Delirium Tremens
2. Alcoholic Hallucinosis:
   a) rare conditions in which auditory hallucinations occur alone in clear consciousness
   b) usually clears in a few days, but may be followed by secondary delusional misinterpretation
   c) up to 50% go on to develop symptoms of schizophrenia (Benedetti, 1952)
3. Epilepsy of late onset (> 25 yrs) is the most common neurological complication
   a) trauma
   b) alcohol withdrawal
   c) brain damage
4. Peripheral neuropathy is probably due to thiamine deficiency (Dry Beriberi)
5. Optic atrophy:
   a) loss of visual acuity
   b) blindness associated with methanol poisoning, thiamine and B12 deficiency, and heavy tobacco smoking
6. Korsakoff’s syndrome is caused by global cortical brain impairment
7. Wernicke’s encephalopathy
8. Central pontine myelinolysis
9. Cerebellar atrophy/ degeneration
10. Widening of sulci on CT scan
11. EEG abnormalities – P300 is decreased, and other wave abnormalities have been reported in detoxified alcoholics

Cardiovascular:
1. moderate drinking is beneficial, due to changes in the lipoprotein profile
2. heavy drinking has the following effects:
   a) increase in blood pressure
   b) weakened contraction of myocardium, leading to heart failure
   c) cardiac arrhythmia
   d) cardiomyopathy

Alcohol in pregnancy
• alcohol in pregnancy associated with increased risk of:
  • stillbirth
  • neonatal mortality
  • low birth weight
  • later difficulties with attention
  • distractibility
• Foetal Alcohol syndrome (FAS):
  • incidence of 1.9 per 1000 live births in US
  • microcephaly, mental retardation, low birth weight, cleft palate, ptosis, scoliosis, abnormal dermatoglyphics, congenital heart disease, congenital renal disease
  • may occur at alcohol intake of 4-5 units per day

Social
• increased rates of:
  • physical / sexual abuse of partner
  • divorce
  • child abuse
  • later alcoholism in children

Employment
• 2 ½ times as many days off work
• decreased productivity
• increased accidents at work

Accidents
• 80% of fatal car accidents involve alcohol
• 40% of casualty trauma involves alcohol
Laboratory tests
- MCV may be raised
- GGT may be raised after a single heavy drinking bout
- CDT (carbohydrate deficient transferrin) can detect if someone has been drinking more than 7 units a day for a week
- AST > ALT in alcoholism

Psychiatric disorders associated with alcoholism
- 47% of alcoholics meet criteria for another psychiatric disorder

Affective disorders
- 70-90% of alcoholics have depressive symptoms
- depression is associated more commonly with women
- most symptoms remit in treatment, by detoxification and social support
- about 25% of completed suicides (15% in women, 45% in men) are associated with heavy drinking
  - alcoholics have at least 7 times the expected suicide rate

Anxiety
- the anxiolytic effects of alcohol wear off as tolerance develops, with a rebound effect occurring when the effects wear off
- tranquilizers are used with dual dependency resulting

Schizophrenia
- schizophrenic symptoms can occasionally be triggered by heavy drinking, which remit when the patient is detoxed
- a number of these patients go on to develop more permanent schizophrenic features

Personality disorder
- almost any personality disorder may be associated with alcohol abuse

Morbid jealousy
- may be associated with an alcoholic paranoid state

Delirium tremens
- risk develops when intake is 12 units per day
- used to have a 30% mortality
- 1-4 days after withdrawal
- trauma or infection present from outset in up to 50% of cases
- biochemical evidence of liver damage in up to 90%
- classic triad of:
  1. clouding of consciousness and confusion
     - patient is disorientated
  2. vivid hallucinations
     - usually visual (rats, insects, Lilliputian) or tactile
3. marked tremor
- primary disorder of reticular activating system – suggested by inattention, overarousal, insomnia, and overactivity
- REM rebound, with REM sleep occupying whole of sleep time
- marked autonomic hyperactivity
- epileptic fits are common

Marchiafava-Bignami disease
- presents with:
  - ataxia
  - dysarthria
  - epilepsy
  - severe impairment of consciousness
- due to extensive demyelination of the corpus callosum, the optic tracts, and the cerebellar peduncles

Central Pontine Myelinolysis
- consists of demyelination involving the pyramidal tracts within the pons
- presents with rapid onset of:
  - pseudobulbar palsy
  - quadriplegia
  - loss of pain sensation in the limbs and trunk
  - vomiting, confusion, and coma are common

Alcoholic Amblyopia
- caused by a retrobulbar neuritis
- presents as a painless bilateral loss of vision over 1-2 weeks, in association with alcohol misuse
- the majority of patients are also smokers
- thiamine deficiency has been strongly implicated - the condition responds to treatment with B-vitamins

Alcoholic dementia
- mild cognitive deficits frequent, but reversible with abstinence
- dementia rarely occurs before 40 years
- associated with CT and MRI evidence of ‘atrophy’

Treatment
- none of the following have any proven efficacy in the treatment of alcohol misuse:
  1. Antabuse
  2. Group therapy
3. Individual counselling
4. In-patient detoxification
5. Alcoholics anonymous

Pharmacotherapy
1. **NALTREXONE**
   a) is an opioid antagonist
   b) is more effective than placebo in reducing the number of relapses and lowering consumption
   c) the main action seems to reduce the likelihood that a lapse would lead to a relapse, probably by reducing the reinforcing actions of alcohol

2. **ACAMPROSATE**
   a) proven efficacy in relapse prevention
   b) pharmacodynamic actions are those of reducing endogenous excitatory neurotransmitters and enhancing GABA transmission
   c) probably acts by reducing the reinforcement caused by endogenous opioids

3. **BUSPIRONE**
   a) is a 5-HT₁A agonist
   b) can improve outcome in anxious alcoholics
Alcohol and Wernicke-Korsakoff syndrome

Biochemistry

Thiamine (Vitamin B₁)
- co-enzyme involved three major enzyme systems:
  - pyruvate dehydrogenase (energy production - involved in Kreb’s cycle)
  - transketolase (maintenance of myelin sheaths in the nervous system)
    - exists in two or more forms in different patients
  - 2-oxo-glutarate dehydrogenase (synthesis of Acetylcholine, GABA, and glutamate)
- recommended daily amount is 1.5 mg (more required in alcoholism)
- body stores:
  - liver 4 mg
  - total body 30 mg
- absorption:
  - by active transport across basal membrane of enterocytes
  - displays saturable (Michaelis-Menten) kinetics
  - energy-dependent and is therefore compromised in deficient states
  - an alcoholic will absorb about 0 - 1.3 mg of a 10 mg dose - increased doses will not result in increased absorption
- excretion:
  - rapid clearance
  - excreted in urine

Ethanol
- increases Mg²⁺ excretion (co-factor in similar enzymes to thiamine)
- damages apo-enzyme of which thiamine is a co-enzyme
- interferes with the active uptake of thiamine

Types of alcohol
- caloric content of two bottles of whisky is equal to the daily requirement
- beer and port provide the highest carbohydrate load, and therefore the highest risk to thiamine deficient alcohol abusers

Wernicke’s syndrome
- occurs in people with gradual thiamine depletion who then have an acute event (e.g. glucose load) which causes a sudden fall in thiamine
- characterized by:
  1. abrupt onset of confusion and impairment of consciousness
  2. ataxia
  3. ophthalmoplegia
• may also present with unexplained hypothermia and hypotension
• of those who get Wernicke’s, 10 % recover
  20 % die
  70 % develop Korsakoff’s

Korsakoff Psychosis

Epidemiology
• F:M = 1:1.7
• females tend to present 10-20 years earlier than men
• 1 in 9 long stay psychiatric patients have alcohol brain damage
• large increase between 1990 and 1995 - due to withdrawal of Parenterovite® from the market

Clinical features
• presentation of Korsakoff psychosis is often insidious
• features include:
  1. amnesia
  2. disorientation
  3. confabulation

Pathology
• specific topographic pattern of lesions:
  • mammillary bodies (maintenance of consciousness and waking state)
  • periventricular thalamic nuclei
  • structures in the floor of the fourth ventricle
  • involvement of the dorso-medial nucleus of the thalamus appears to be particularly associated with memory disturbance

Investigations
• SPECT scanning reveals:
  • reduced blood flow in:
    • *anterior temporal lobe* and *frontal lobe*
    • atrophy of the *thalamus* and *mamillary bodies*

Treatment & Prophylaxis
• at least 500 mg of thiamine is required for 3-5 days
• there is some evidence that ophthalmoplegia responds more rapidly than confusion
• anaphylaxis with Pabrinex is:
  • 1 in 5,000,000 for IM
  • 1 in 250,000 for IV
**Alcoholic Pellagra Encephalopathy**

- due to deficiency of niacin in association with chronic alcohol misuse
- much less common than WKS

**Clinical features**

- encephalopathic syndrome:
  - confusion
  - oppositional hypertonus
  - myoclonus
- cogwheel rigidity
- grasping and sucking reflexes
- hallucinations
- insomnia
- tremor
- ataxia
- urinary and faecal incontinence

**Treatment**

- responds rapidly to treatment with nicotinic acid

**Vitamin B₆ deficiency**

- pyridoxine is crucial co-enzyme for glutamic acid decarboxylase (GAD), the enzyme which synthesizes GABA from glutamic acid
- deficiency can result in epileptic seizures
- in nutritional seizures states, clinical response and normalization of EEG can occur within minutes of giving parental pyridoxine
Drug Misuse

Epidemiology

- % of US population who have tried cannabis = 33%; cocaine = 11%; crack = 1%
- 3.5% have used BZDs for non-medical reasons
- lifetime prevalences (ECA study, Regier et al. 1991):
  - 6.1% substance abuse (SA) disorder (excluding alcohol)
  - 13.5% alcohol abuse
  - 1.1% alcohol and other drugs
  - 3.2% substance abuse co-morbidity with other mental disorders
- age, sex:
  - 80% begin SA before age 18
  - peak abuse period in 20-30s in males, 20-24 in females
  - risk lessens after 40
  - overall, M:F = 4:1
- social class:
  - lower groups over-represented
- pattern of abuse:
  - episodic use generally seen with less addictive drugs, continuous course with highly addictive drugs
  - cannabis is first drug of abuse in 70% of opiate addicts
  - 90% of opiate abusers also abuse BZDs
  - only 1/3 of opiate users in contact with treatment agencies at any time
  - average duration of use before seeking treatment = 9 years
  - average duration of IV use before seeking treatment = 4 years
- co-morbidity:
  - 70% of opiate users have another current diagnosis (affective disorder, antisocial personality disorder, anxiety disorder)
  - 87% meet lifetime criteria for another psychiatric diagnosis
  - 50% meet lifetime criteria for ≥ 2 psychiatric disorders
  - high prevalence of SA (30-60%) in schizophrenic patients
    - Vulnerability hypothesis:
      - SA may precipitate schizophrenia in predisposed individuals
    - Self-medication hypothesis:
      - SA counteracts negative symptoms and depressed mood
      - SA counteracts side-effects of treatment

Aetiology

1. Genetics:
   a) putative association of dopamine DR D₂ allele with polysubstance abuse
      may suggest vulnerability of SA
2. Pharmacological/Biochemical:
   a) abnormalities observed in many neurotransmitter systems:
      i) opiate receptor
      ii) dopamine
iii) serotonin

b) neuropharmacology of craving:
   i) may relate to ability to increase DA activity in nucleus accumbens
   ii) reinforcing effects may occur from stimulation of corticofugal DA pathways

c)  
   Behavioural theories:
   i) modelling
   ii) primary direct reinforcement (psychic effect of SA promotes continued abuse)
   iii) secondary reinforcement (interaction of environmental cues and pharmacological effects of drugs)

d) Analytic theories:
   i) regression/ fixation at oral stage of development

e) Sociocultural theories:
   i) 50% of heroin addicts from single parent/divorced families
   ii) high rates of parental alcoholism
   iii) ‘peer group activation’, e.g. ecstasy abuse

f) Access and availability:
   i) ease of availability of ‘crack’ cocaine led to increased misuse in high-risk groups – medical personnel, prostitutes

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### Drugs of abuse

<table>
<thead>
<tr>
<th>Drug</th>
<th>Pharmacology</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioids</td>
<td>• bind to opioid receptors; NALTREXONE and NALOXONE are competitive antagonists&lt;br&gt;• tolerance develops with usage; also cross-tolerance within opioid group&lt;br&gt;• withdrawal commences 4-6 hours after last dose, peaks 24-48 hours, lasts 7-10 days</td>
<td>•</td>
</tr>
<tr>
<td>Cocaine</td>
<td>• blocks reuptake of serotonin and catecholamines, especially dopamine – inhibits transporter uptake site&lt;br&gt;• various DA agonists/ autoreceptors studied for ↓ craving</td>
<td>• formication; the ‘cocaine bug’&lt;br&gt;• reduced prolactin&lt;br&gt;• increased GH levels</td>
</tr>
<tr>
<td>Amphetamines</td>
<td>• sympathomimetics</td>
<td></td>
</tr>
<tr>
<td>Hallucinogens (LSD, mescaline, psilocybin, dimethyltryptamine - DMT)</td>
<td>• sympathomimetics&lt;br&gt;• 5-HT agonists&lt;br&gt;• onset of effects in 1 hour, last 8-12 hours</td>
<td></td>
</tr>
<tr>
<td>Phenylcyclidine (PCP)</td>
<td>• receptor sites located in calcium ion channel of NMDA subtype of glutamate receptor</td>
<td></td>
</tr>
</tbody>
</table>
Cannabis (tetrahydrocannabinol)  • G-protein receptor for cannabinoids recently discovered  • onset of effect is minutes - 1 hour, lasts 6-12 hours

Barbiturates  • CNS depressants

Benzodiazepines  • bind to benzodiazepine - GABA receptor complex

Ecstasy (MDMA – 3,4 methylenedioxyamphetamine)  • neurotoxic effect on serotonin nerve terminals (stimulates 5-HT release and blocks 5-HT reuptake), especially in frontal cortex and hippocampus

Volatile substance abuse (VSA)  • CNS depressants

**Opioids**

  • exert their effect through µ receptors

**Clinical effects**

  • euphoria  
  • analgesia  
  • respiratory depression  
  • constipation  
  • reduced appetite  
  • low libido  
  • tolerance develops rapidly  
  • withdrawal symptoms (onset within 6 hours, and peak at 36-48 hours) include:  
    • intense craving  
    • restlessness  
    • insomnia  
    • pain in muscles and joints  
    • running nose and eyes  
    • sweating  
    • abdominal cramps  
    • vomiting  
    • piloerection  
    • dilated pupils  
    • disturbance of temperature control

**Barbiturates**

  • these people are usually middle aged and took the drugs as hypnotics  
  • in aqueous solution, these drugs are highly irritant  
  • tolerance develops less rapidly than to opioids – the danger exists that tolerance to the sedating effect occurs to a greater extent than tolerance to the CNS depressant effects
withdrawal is dangerous, and leads to delirium, seizures, and can result in cardiovascular collapse and death:

• anxiety
• restlessness
• disturbed sleep
• anorexia
• nausea
• vomiting, hypotension, pyrexia, tremor, seizures, disorientation, hallucinations, a la delirium tremens

Clinical features

• drunkenness, with slurred speech and incoherence
• drowsiness
• depression
• nystagmus

Hallucinogens

• a.k.a. psychotomimetics
• synthetic hallucinogens include:
  • LSD
  • DMT – dimethyl tryptamine
    • found in normal subjects’ urine
    • found in increased amounts in urine during acute psychotic episodes
  • MDMA
• natural drugs include:
  • psilocybin
  • tolerance can occur
  • withdrawal syndrome has not been described
  • dependence may occur in long term users, but is rare

Physical effects

• tachycardia
• hypertension
• dilation of the pupils

Psychological effects

• onset within 2 hours
• last 8-14 hours
• distortions or intensifications of sensory perception
• synaesthesia
• passage of time is reduced
• distortion of the body image
• panic, fears of insanity
• mood may be exhilaration, distress, or acute anxiety
Cannabis

Clinical effects
- exaggeration of the pre-existing mood
- increased enjoyment of aesthetic experiences
- distortion of the perception of time and space
- reddening of the eyes
- dry mouth
- irritation of the respiratory tract

Adverse effects
- anxiety
- mild paranoid ideation
- toxic confusional states can occur
- psychosis (rare)

Tolerance, dependence, and withdrawal
- tolerance can occur but only for those using high doses
- withdrawal can lead to irritability, nausea, insomnia, and anorexia
- dependence can occur, but only of the non-physiological type

Stimulants
- effects are due to the release of, and blocking of the reuptake of, dopamine and noradrenaline

Clinical effects
- overtalkativeness
- over-activity
- insomnia
- dryness of the lips, mouth, and nose
- anorexia
- dilated pupils
- tachycardia and hypertension – cardiac arrythmia and CVA can occur with large doses

Adverse effects
- dysphoria
- irritability
- insomnia
- confusion
- anxiety, and panic
- paranoid psychosis may be induced by repeated high doses
- stereotyped behaviour, e.g. tidying
Tolerance, dependence, and withdrawal

- tolerance is recognized
- withdrawal consists of:
  - low mood
  - decreased energy
  - depression, anxiety, lethargy, fatigue, and nightmares in some cases
  - craving can be intense
  - suicidal ideation may be present

Cocaine

- similar effects to amphetamine (see above)
- powerful positive reinforcer in animals

Pharmacology

- blocks the re-uptake of dopamine into presynaptic dopamine terminals
- leads to high levels of extracellular dopamine in the nucleus accumbens
- activation of the physiological reward system

Clinical effects

- excitement
- increased energy
- euphoria
- tachycardia, hypertension, dilated pupils

Adverse effects

- grandiose thinking, impaired judgement, sexual indiscretion
- higher doses can lead to visual and auditory hallucinations
- paranoid ideation
- violent behaviour
- formication (the ‘cocaine bug’)
- cardiac arrhythmias, MI, myocarditis, cardiomyopathy
- seizures
- respiratory arrest

Tolerance, dependence, and withdrawal

- tolerance is recognised
- withdrawal symptoms include:
  - dysphoria
  - anhedonia
  - anxiety
  - irritability
  - fatigue
  - hypersonmolence
**Phencyclidine (PCP)**

- originally developed as a dissociative anaesthetic
- related to ketamine

**Pharmacology**
- both ketamine and PCP antagonize neurotransmission at NMDA receptors

**Clinical effects**
- drunkenness
- analgesia, and even anaesthesia
- agitation
- depressed consciousness
- nystagmus
- high blood pressure

**Adverse effects**
- aggressiveness
- ataxia
- muscle rigidity
- convulsions
- hypertensive heart failure
- CVA
- malignant hyperthermia

**Tolerance, dependence, and withdrawal**
- tolerance occurs
- withdrawal symptoms are rare in humans
- dependence can occur in heavy users

**Management**

**Pharmacological treatments**

1. *Methadone*
   a) long acting opiate
   b) maintenance therapy at 20-70 mg per day
   c) less physical morbidity, slower progression of HIV infection
   d) moderate/ high dosage of METHADONE required to maintain abstinence

2. *Naltrexone*
   a) opiate antagonist
   b) used in detoxification and maintenance
   c) less acceptable to user than METHADONE

3. *Buprenorphine*
   a) mixed agonist-antagonist
   b) useful in opiate and cocaine abuse
c) withdrawal from BUPRENORPHINE may be easier than from METHADONE

4. Other agents under investigation
   a) DESIPRAMINE – may decreased craving for cocaine
   b) AMANTADINE – decreases craving
   c) AMPEROZIDE – novel antipsychotic for schizophrenia, but may reduce craving for cocaine

Psychosocial treatments
   • aims:
     • tackle underlying factors perpetuating SA
     • increase awareness
     • develop alternative coping strategies
     • foster cognitive-behavioural strategies to manage craving and eliminate reinforcing behaviours
   • psychosocial treatments may be as effective as pharmacological therapy, especially when combined with self-help groups

<table>
<thead>
<tr>
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<th>Improvement at 6 months</th>
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<tbody>
<tr>
<td>1 counselling session per month</td>
<td>25 %</td>
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<tr>
<td>1 counselling session per week</td>
<td>60 %</td>
</tr>
<tr>
<td>1 counselling session per week plus family/ psychiatric intervention</td>
<td>&gt; 60 %</td>
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Prognosis
   • high initial relapse after treatment
   • follow-up is associated with:
     • high psychiatric morbidity
     • continued use
     • high mortality (suicide, accidents, physical complications, HIV)
   • factors associated with poor outcome:
     • early age of initial abuse
     • long history of abuse
     • IV abuse
     • early drop-out from maintenance programmes
     • antisocial personality disorder
   • 45 % of treated opiate addicts are abstinent and living in the community at 6 months
   • 85 % used opiates at some time during 6 months

Pathological gambling

Epidemiology
   • males > females (4 % attending gamblers’ anonymous are female)
• females present earlier (< 5 years)
• addiction usually begins in adolescence

Aetiology

1. **Predisposing factors:**
   a) family history of addiction
   b) parental rejection or criticism resulting in chronic low self-esteem

2. **Precipitating factors:**
   a) death of parent or relative
   b) birth of child
   c) physical illness or personal threat to life
   d) job demotion or promotion
   e) other substance abuse

Clinical features

• categorized as Habit and Impulse Disorder in ICD-10
• frequent, repeated episodes of gambling that dominate the individual’s life to the
detriment of social, occupational, material, or family commitments

• 4 phases:
  1. winning
  2. losing
  3. desperation
  4. giving up

• stress-related physical illness, depression, DSH, criminal behaviour are common in
phases 3 and 4