

## 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 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

Blood alcohol concentration (mg %)	Typical effects
20	<ul style="list-style-type: none"> <li>• enhanced sense of well-being</li> <li>• visual reaction time reduced</li> </ul>
40	<ul style="list-style-type: none"> <li>• somewhat disinhibited</li> <li>• reduced driving ability at speed</li> </ul>
60	<ul style="list-style-type: none"> <li>• judgement impaired</li> </ul>
80	<ul style="list-style-type: none"> <li>• physical coordination impaired</li> </ul>
100	<ul style="list-style-type: none"> <li>• evident loss of social judgement</li> <li>• poorly coordinated</li> </ul>
130	<ul style="list-style-type: none"> <li>• clearly intoxicated</li> </ul>
300	<ul style="list-style-type: none"> <li>• coma</li> <li>• stupor</li> <li>• loss of bladder control</li> </ul>
500 +	<ul style="list-style-type: none"> <li>• coma</li> <li>• respiratory depression, death</li> </ul>

## Blood, Urine, and breath alcohol equivalents

<i>Blood (mg / 100ml)</i>	<i>Urine (mg / 100 ml)</i>	<i>Breath (mg / 100 ml)</i>
50	67	22
80 (legal limit)	107	35
150	200	66
200	267	88
250	333	110

## Alcohol and the brain

<b>Experience</b>	<b>Transmitter/ receptor</b>
Activation	NA DA
Euphoria/ pleasure	DA opioids 5-HT <sub>2</sub>
Anxiolysis/ ataxia	GABA
Sedation/ amnesia	increase GABA block NMDA
Nausea	stimulate 5-HT <sub>3</sub>
Withdrawal	increase Ca <sup>2+</sup> flux decrease magnesium
reinforcing actions of alcohol	NA DA

### 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<sub>A</sub> 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)**

- Edwards, G. & Gross, M. M. (1976) Alcohol Dependence: provisional description of a clinical syndrome. *British Medical Journal 1: 1058-61*

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

	<b>Men over 15</b>	<b>Women over 15</b>
England & Wales	14.9 units per week	4.0
Scotland	1.2	3.4
Northern Ireland	6.7	1.3

- 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 1<sup>st</sup> degree relatives of alcoholics
2. *Twin Studies:*
  - a) MZ: DZ = 70 %: 43 % for males

47 %: 32 % for females

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 D<sub>2</sub> 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-HT<sub>3</sub> 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

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

### 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 Hallucinosi*s:
  - 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 B<sub>12</sub> 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 1/4 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-HT<sub>1A</sub> agonist
  - b) can improve outcome in anxious alcoholics

## Alcohol and Wernicke-Korsakoff syndrome

### Biochemistry

#### Thiamine (Vitamin B<sub>1</sub>)

- co-enzyme involved three major enzyme systems:
  - pyruvate dehydrogenase (energy production - involved in Krebs'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 Mg<sup>2+</sup> 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 foecal incontinence

### **Treatment**

- responds rapidly to treatment with nicotinic acid

## **Vitamin B<sub>6</sub> 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  $\geq 2$  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 D<sub>2</sub> 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

### Drugs of abuse

Drug	Pharmacology	Symptoms
Opioids	<ul style="list-style-type: none"> <li>• bind to opioid receptors; NALTREXONE and NALOXONE are competitive antagonists</li> <li>• tolerance develops with usage; also cross-tolerance within opioid group</li> <li>• withdrawal commences 4-6 hours after last dose, peaks 24-48 hours, lasts 7-10 days</li> </ul>	<ul style="list-style-type: none"> <li>•</li> </ul>
Cocaine	<ul style="list-style-type: none"> <li>• blocks reuptake of serotonin and catecholamines, especially dopamine – inhibits transporter uptake site</li> <li>• various DA agonists/ autoreceptors studied for ↓ craving</li> </ul>	<ul style="list-style-type: none"> <li>• formication; the 'cocaine bug'</li> <li>• reduced prolactin</li> <li>• increased GH levels</li> </ul>
Amphetamines	<ul style="list-style-type: none"> <li>• sympathomimetics</li> </ul>	<ul style="list-style-type: none"> <li>•</li> </ul>
Hallucinogens (LSD, mescaline, psilocybin, dimethyltryptamine - DMT)	<ul style="list-style-type: none"> <li>• sympathomimetics</li> <li>• 5-HT agonists</li> <li>• onset of effects in 1 hour, last 8-12 hours</li> </ul>	<ul style="list-style-type: none"> <li>•</li> </ul>
Phencyclidine (PCP)	<ul style="list-style-type: none"> <li>• receptor sites located in calcium ion channel of NMDA subtype of glutamate receptor</li> </ul>	<ul style="list-style-type: none"> <li>•</li> </ul>

Cannibis (tetrahydrocannabinol)	<ul style="list-style-type: none"> <li>• G-protein receptor for cannabinoids recently discovered</li> <li>• onset of effect is minutes - 1 hour, lasts 6-12 hours</li> </ul>	•
Barbiturates	<ul style="list-style-type: none"> <li>• CNS depressants</li> </ul>	•
Benzodiazepines	<ul style="list-style-type: none"> <li>• bind to benzodiazepine - GABA receptor complex</li> </ul>	•
Ecstasy (MDMA – 3,4 methylenedioxymethamphetamine)	<ul style="list-style-type: none"> <li>• neurotoxic effect on serotonin nerve terminals (stimulates 5-HT release and blocks 5-HT reuptake), especially in frontal cortex and hippocampus</li> </ul>	•
Volatile substance abuse (VSA)	<ul style="list-style-type: none"> <li>• CNS depressants</li> </ul>	•

## Opioids

- exert their effect through  $\mu$  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 arrhythmia 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
  - hypersomnolence

## 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

	<i>Improvement at 6 months</i>
1 counselling session per month	25 %
1 counselling session per week	60 %
1 counselling session per week plus family/ psychiatric intervention	> 60 %

### 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