VOLUME C
Pharmacological Treatment for Drug Use Disorders
Drug Treatment for Special Populations
Module 1

Drug Dependence basics

1. Drug use, addiction and dependence
2. Management of Alcohol & benzodiazepine dependence
3. Psychostimulants
4. Volatile substances, cannabis and new psychoactive substances
Workshop 2
Management of Alcohol & benzodiazepine dependence
At the end of this workshop, you will be able to:

► Distinguish between acute and chronic effects of alcohol and benzodiazepines
► Understand the medical and psychiatric dangers associated with intoxication, overdose, withdrawal and interactions with other substances
► Understand withdrawal approaches and protocols, differentiate between treatment protocols to treat intoxication and overdose
► Identify necessary treatments following detoxification
► Describe proper setting and support services needed to properly conduct withdrawal treatments
Alcohol

light beer = regular beer = wine = fortified wine = spirits

425mL = 285mL = 100mL = 60mL = 30mL
Still the most popular “drug”
- In some societies over 80% of population drinks

8% drink daily, peaking in males +60 yrs (23%), 40% drink weekly

At-risk drinking now defined as:
- risks of harm in the long term (chronic harm)
- risks of harm in the short term (acute harm)
A standard drink

Although they restricted themselves to one drink at lunch time, Alan and Roger found they were not at their most productive in the afternoons.
Alcohol: pharmacology & neurobiology
Pharmacokinetics

- Rapidly absorbed into blood by stomach (20%) and small intestine (80%)
- Metabolised by liver (95% – 99%)
  - Alcohol → acetaldehyde → acetic acid & H2O → CO2
- Distributed in body fluids (not fat)
- 1 standard drink per hour raises BAC by about 0.01–0.03 g%
- It takes 5 minutes to affect brain
- 2% excreted unchanged in sweat, breath and urine
Alcohol metabolism

![Graph showing blood alcohol concentration over time for different quantities of alcohol consumption.]

- One drink: 100 mg%
- Two drinks: 50 mg%
- Three drinks
- Four drinks
Alcohol: effects on the brain

- No single receptor. Alcohol interacts with and alters function of many different cellular components.
- Primary targets are GABA, NMDA glutamate, opiates (mu and delta) and serotonin receptors.
- Stimulates dopamine and opioid systems.
- Effects of chronic consumption are opposite to acute because of homeostatic compensation.
Alcohol: mechanism of action in VTA
## Effects of alcohol intoxication

<table>
<thead>
<tr>
<th>BAC*</th>
<th>Likely effects of intoxication</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.02–0.05 g / 100 ml</td>
<td>cheerful, relaxed, pleasant feelings of happiness and wellbeing, decreasing inhibitions, judgment increasingly impaired, increased chance of accidents, impaired coordination</td>
</tr>
<tr>
<td>0.1–0.2 g / 100 ml</td>
<td>decreased ability to appropriately interpret and react to surroundings, poor judgment, loss of ‘self-control’, slurred speech, increasingly unpredictable behaviour, labile mood, potential for aggression, ataxia</td>
</tr>
<tr>
<td>0.2–0.3 g / 100 ml</td>
<td>poor judgment, marked ataxia and slurred speech, labile mood, nausea and vomiting, double vision, memory loss</td>
</tr>
<tr>
<td>0.3–0.4 g / 100 ml</td>
<td>memory lapse, stage 1 anesthesia (sleepiness, poor response to external stimuli, oblivion), labile mood</td>
</tr>
<tr>
<td>&gt; 0.40 g / 100 ml</td>
<td>respiratory failure, coma, possible death</td>
</tr>
</tbody>
</table>
Harmful drinking & alcohol related harms
Types of problems

- Intoxication
- Dependence
  - Withdrawal
  - Craving
  - Obsessive
  - Cognitive
  - Conflict
  - Loss of control
- Regular use
Types of problems: clinical samples

- Intoxication
- Regular use
- Dependence
Risky drinking levels (for chronic harm)
Predisposing factors for high-risk drinking

► Family history of alcohol problems
► Childhood problem behaviours related to impulse control
► Poor coping responses in the face of stressful life events
► Depression, divorce or separation
► Drinking partner
► Working in a male-dominated environment
Acute harm to health associated with high-risk alcohol use

Physical injury and psychological harms and death arise from:

<table>
<thead>
<tr>
<th>Falls</th>
<th>Fires</th>
<th>Comorbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical assaults</td>
<td>Drowning</td>
<td>Dehydration</td>
</tr>
<tr>
<td>Sexual assaults</td>
<td>Child abuse</td>
<td>Sleep disturbances</td>
</tr>
<tr>
<td>Domestic violence</td>
<td>Unprotected sex leading to STDs and HIV</td>
<td>Raised blood pressure</td>
</tr>
<tr>
<td>Traffic accidents</td>
<td>Overdose</td>
<td>Shortness of breath</td>
</tr>
<tr>
<td>Occupational &amp; machinery injuries</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Chronic harms to health associated with high-risk alcohol use

► Hypertension, CVA
► Cardiomyopathy
► Peripheral neuropathy
► Impotence
► Cirrhosis and hepatic or bowel carcinomas
► Cancer of lips, mouth, throat, and esophagus
► Cancer of breast
► Foetal alcohol syndrome
Cognitive impairment may result from consumption levels of >70 grams per day

Thiamine deficiency leads to:
- Wernicke’s encephalopathy
- Korsakoff’s psychosis

Frontal lobe syndrome
Cerebellar degeneration
Trauma
Regions of the brain most vulnerable to alcohol’s effects

► **Cerebellum**
  - Damage results in a loss of balance and stumbling, and may affect cognitive functions such as memory and emotional response

► **Limbic system**
  - Damage impairs several tasks including memory and emotion

► **Cerebral cortex**
  - Damage impairs ability to think, plan, behave intelligently, and interact socially. It also impair the ability to solve problems, remember, and learn
Alcohol-induced memory loss

Teenagers (28.4%) were most likely to have a memory loss incident following drinking:
- 4.4% reported “blackouts” occurring on a weekly basis
- 10.9% reported “blackouts” on a monthly basis

Memory loss occurred after drinking for:
- 12% male drinkers aged > 40 years
- 7% female drinkers aged > 40 years
- 20% - 30% of all other age groups
Binge drinking: definitions

A pattern of drinking alcohol that brings blood alcohol concentration to 0.08gm % or above. This corresponds to consuming 5 or more drinks (male) or 4 or more drinks (female) in about 2 hour

(NIAAA, 2004)

Drinking 5 or more alcoholic drinks on the same occasion on at least 1 day in the past 30 days

(SAMHSA)
Binge drinking can lead to:

- Increased risk taking
- Poor judgement/decision making
- Misadventure/accidents
- Increased risky sexual behaviour
- Increased violence
- Suicide
Alcohol & special populations
Alcohol and young people: health risks

- Causes many deaths: 5,000 deaths/year in the USA
- Causes many injuries: 190,000 visits to A&E/year for alcohol-related injuries
- Impairs judgment: drink driving, unprotected sex and violent behavior
- Increases the risk of physical and sexual assault
- Increases risk of trouble in school or with the law
- Drinking alcohol also associated with the use of other drugs
- Increases the risk of alcohol problems later in life
- Interferes with brain development
Women are more susceptible to the effects of alcohol due to:

- Smaller physical size
- Decreased blood volume
- Lower body water to fat ratio
- Reduced ADH activity in gastric mucosa (hence reduced stomach metabolism of alcohol)

Resulting in:

- Higher brain levels of alcohol than men with the same amount consumed
- Earlier development of organ damage
- Increased risk of intoxication related harms; e.g., assault, injury
Alcohol and women: health risk

- **Liver damage**
  - women more likely to develop alcoholic hepatitis

- **Heart disease**
  - women more susceptible to alcohol related heart disease

- **Breast cancer**
  - 10% higher chance in women who consume about one drink per day
  - risk increase by another 10% for every extra drink per day
Alcohol and pregnancy

► No proven “safe” limit in pregnancy
► Binge drinking especially detrimental to fetus
► Any drinking during pregnancy puts fetus at risk for learning, behavioral problems & abnormal facial features
► May increase the risk for preterm labor
► Alcohol has been found in breast milk
Increasing prevalence of risky drinking by young women has raised concerns about foetal alcohol syndrome/effects.
Concurrent mental health problems

Alcohol may:

► Exacerbate existing mental health problems
► Interact with prescribed medications
► Reduce or exacerbate the effect of certain medications
► Reduce patient compliance with treatment regimens
Alcohol treatment: an overview
Interventions and treatment for alcohol-related problems

► Screening and assessment ➔ individualised interventions
► Brief intervention and harm reduction strategies
► Withdrawal management
► Relapse prevention/goal-setting strategies
► Controlled drinking programs
► Residential programs
► Self-help groups
Consider the patient’s:
► Perspective on drinking
► Attitudes towards drinking goals
► Significant others
► Short-term objectives

Provide:
► Information on standard drinks, risks, and risk levels
► Encouragement to identify positive alternatives to drinking
► Self-help manuals
► Follow-up session
Two steps towards BI

1. Screening
   - For example, the alcohol AUDIT, a 10-item questionnaire

2. Intervention
   - Information
   - Brief counselling
   - Advice
   - Referral (if required)
After administering the AUDIT, use “FLAGS”:

► Feedback results
► Listen to patient concerns
► Provide Alcohol education and information
► Goals of treatment – identify and plan
► Strategies discussed and implemented
## Benefits of cutting down or cutting out

- Save money  
- Be less depressed  
- Lose weight  
- Less hassles for family  
- Have more energy  
- Sleep better  
- Better physical shape

## Reduce the risk of

- Alcoholism/addiction  
- Liver disease  
- Cancer  
- Brain damage  
- High blood pressure  
- Accidents  
- Injury  
- Legal problems
### Choosing a treatment option

<table>
<thead>
<tr>
<th>Severity</th>
<th>Goal</th>
<th>Treatment options examples</th>
</tr>
</thead>
</table>
| No major lifestyle disruptions, not severely dependent | Reducing consumption / controlled (or even abstinence) | • Outpatient counselling  
• Group or individual work (skills training, relapse prevention)  
• Marital and family therapy  
• Loss and grief counselling  
• Self-help / support groups |
| Major lifestyle disruptions, significant dependence | Abstinence                                      | Above options plus:  
• Withdrawal management  
• Pharmacotherapy  
• Residential rehabilitation |
Break
Alcohol withdrawal & its management
Neurobiology of alcohol withdrawal

► Alcohol ↑ activity of GABA - inhibitory neurotransmitter and ↓ activity of NMDA (excitatory) receptors
► In turn, GABA influences other transmitter systems that are thought to contribute to the alcohol withdrawal syndrome
► Dopaminergic induction ➔ psychotic symptoms
► NMDA excitability ↓ seizure threshold
► Glutamate: ↑ noradrenergic sympathetic activity

Pharmacotherapy of withdrawal is therefore based on depressant drugs that ↑ GABA.
## Alcohol withdrawal

- **Usually occurs 6–24 hours after last drink**
  - Tremor
  - Anxiety and agitation
  - Sweating
  - Nausea and vomiting
  - Headache
  - Sensory disturbances and hallucinations

- **Severity depends on**
  - Pattern, quantity and duration of use
  - Previous withdrawal history
  - Patient expectations
  - Physical and psychological wellbeing of the patient (illness or injury)
  - Other drug use/dependence
  - The setting in which withdrawal takes place
Progress of alcohol withdrawal from time of last drink
The particular purpose of detoxification is to minimize the severity of withdrawal symptoms that occur when alcohol consumption is abruptly stopped or markedly reduced, and thereby to achieve an alcohol-free state with maximum safety and minimum discomfort to the patient.
Goals of pharmacological management of withdrawal

➤ Provide a safe withdrawal from the drug(s) of dependence and enable the patient to become drug free

➤ Provide withdrawal that is humane and protects the patient's dignity

➤ Prepare the patient for ongoing treatment of his or her substance dependence
Treatment of alcohol withdrawal is usually uneventful and the clinician has a generous margin of error within which to work. Where mistakes are made, they are usually in the related areas of insufficient prescribing and insufficient observation for the level of risk.
Repeated detox

Myth of revolving doors in addiction treatment

Those not familiar with the chronic nature of addictive disorders often characterize detoxification programs as 'revolving doors' which have little impact on the recovery process. Although it is true that many people undergo detoxification more than once and some do so many times, the assumption that little or no progress has been made is often false.

(Alling, 1992)
Repeated detoxification: patterns

Alling (1992) described a pattern in individuals who return for several detoxification episodes:

- Young people with short duration of dependence: unrealistically optimistically about ability to remain drug free after detox

- On return after several months for repeat detox: more realistic expectation about steps to remain substance free

- Subsequent relapse & return for detox: even clearer understanding of what is required to sustain recovery
Repeated detoxification: recovery

- During certain expected and predictable phases of recovery, addicted persons are at increased risk of relapse but this can happen any time in recovery.

- Relapse prevention is a legitimate area for patient education, and the relapsed patient is appropriate for clinical treatment.

- Treatment services designed precisely for this stage of the disease may facilitate the individual's return to abstinence.
Alcohol withdrawal treatment
Treatment of alcohol withdrawal symptoms

Medications for management of withdrawal

► Benzodiazepines
► Thiamine & multivitamins
► Antiemetic
► Analgesia (e.g., paracetamol)
► Antidiarrhoeal
Benzodiazepines with long half-life: Chlordiazepoxide & Diazepam are usually preferred

Lorazepam & Oxazepam tolerated well by older patients and in severe liver disease. Lorazepam is an effective anticonvulsant in preventing a secondary alcohol withdrawal seizure

Favoured by internists and hepatologists treating alcohol withdrawal in patients with severe liver failure. It has a relatively short half-life. Its metabolism is very simple and it has no metabolites
### Alcohol dosing regimen:
example Chlordiazepoxide (mg)

<table>
<thead>
<tr>
<th>Example of Chlordiazepoxide Dosing Regime for Alcohol Withdrawal (1)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Daily alcohol consumption</strong></td>
</tr>
<tr>
<td>Daily alcohol consumption</td>
</tr>
<tr>
<td>Day 1</td>
</tr>
<tr>
<td>Day 2</td>
</tr>
<tr>
<td>Day 3</td>
</tr>
<tr>
<td>Day 5</td>
</tr>
<tr>
<td>Day 6</td>
</tr>
<tr>
<td>Day 7</td>
</tr>
<tr>
<td>Day 8</td>
</tr>
<tr>
<td>Day 10</td>
</tr>
<tr>
<td>Day 11</td>
</tr>
<tr>
<td>Day 12</td>
</tr>
<tr>
<td>Day 13</td>
</tr>
</tbody>
</table>
## Sample Chlordiazepoxide withdrawal regime

<table>
<thead>
<tr>
<th>Day</th>
<th>Morning</th>
<th>Midday</th>
<th>Evening</th>
<th>Night</th>
<th>Total daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>30 mg</td>
<td>30 mg</td>
<td>30 mg</td>
<td>30 mg</td>
<td>120 mg</td>
</tr>
<tr>
<td>Day 2</td>
<td>30 mg</td>
<td>20 mg</td>
<td>20 mg</td>
<td>30 mg</td>
<td>100 mg</td>
</tr>
<tr>
<td>Day 3</td>
<td>20 mg</td>
<td>20 mg</td>
<td>20 mg</td>
<td>20 mg</td>
<td>80 mg</td>
</tr>
<tr>
<td>Day 4</td>
<td>20 mg</td>
<td>10 mg</td>
<td>10 mg</td>
<td>20 mg</td>
<td>60 mg</td>
</tr>
<tr>
<td>Day 5</td>
<td>10 mg</td>
<td>10 mg</td>
<td>10 mg</td>
<td>10 mg</td>
<td>40 mg</td>
</tr>
<tr>
<td>Day 6</td>
<td>10 mg</td>
<td>10 mg</td>
<td>0</td>
<td>10 mg</td>
<td>30 mg</td>
</tr>
<tr>
<td>Day 7</td>
<td>10 mg</td>
<td>0</td>
<td>0</td>
<td>10 mg</td>
<td>20 mg</td>
</tr>
</tbody>
</table>

For moderate severity of withdrawal start at day 3; for mild severity start at day 5.
Sample Diazepam regime for alcohol withdrawal

<table>
<thead>
<tr>
<th></th>
<th>8 am</th>
<th>12 midday</th>
<th>5 pm</th>
<th>10 pm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>10 mg</td>
<td>10 mg</td>
<td>10 mg</td>
<td>10 mg</td>
</tr>
<tr>
<td>Day 2</td>
<td>10 mg</td>
<td>5 mg</td>
<td>10 mg</td>
<td>10 mg</td>
</tr>
<tr>
<td>Day 3</td>
<td>10 mg</td>
<td>5 mg</td>
<td>5 mg</td>
<td>10 mg</td>
</tr>
<tr>
<td>Day 4</td>
<td>5 mg</td>
<td>5 mg</td>
<td>5 mg</td>
<td>5 mg</td>
</tr>
<tr>
<td>Day 5</td>
<td>5 mg</td>
<td>–</td>
<td>5 mg</td>
<td>5 mg</td>
</tr>
<tr>
<td>Day 6</td>
<td>5 mg</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Day 7</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Day 8</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>
Management of withdrawal complication delirium tremens (DTs)

- In DTs oral Lorazepam is first-line treatment
- If symptoms persist or oral route unsuitable, give parenteral Lorazepam, Haloperidol or Olanzapine
- If DTs develop during treatment for acute alcohol withdrawal, review withdrawal drug regimen
Management of withdrawal complication seizures

- Use quick-acting Benzodiazepine – Lorazepam, to reduce further seizures
- If seizures develop in a person during treatment for withdrawal, review the withdrawal drug regimen
- Do not offer phenytoin to treat alcohol withdrawal seizures
Management of withdrawal complication
Wernicke's encephalopathy (WE)

► Healthy & uncomplicated patients:
  oral thiamine >300 mg/day

► High risk of WE:
  prophylactic parenteral (IM or IV) treatment with 250 mg Thiamine, once daily for 3–5 days or until no further improvement seen

► WE:
  parenteral thiamine (i.m. or i.v.) of >500 for 3–5 days, followed by 250 mg once daily for a further 3–5 days depending on response
Alcohol: post withdrawal management pharmacotherapy
Post-withdrawal management

► Treatment options/goals:
  – Retain in treatment, ongoing management for RP
  – Seek referral to structured day programmes / residential rehabilitation units

► Considerations:
  – Patient’s choice and circumstances, clinical considerations and availability
  – Severity of problems and social support

► Pharmacotherapies:
  – Acamprosate
  – Naltrexone
  – Disulfiram
Pharmacotherapies to
manage relapse & promote abstinence

- Few medications are effective in reducing relapse after successful alcohol withdrawal.
- These are to be used as part of a comprehensive psychosocial treatment plan (CBT, behavioural therapies / social network and environment-based therapies) focused specifically on alcohol misuse.
- The most common medications used for relapse prevention are described in the next few slides.
Pharmacotherapies to manage relapse & promote abstinence

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acamprosate</td>
<td>666mg TDS</td>
<td>If Body Weight ≥ 60 kg</td>
</tr>
<tr>
<td></td>
<td>666mg mane &amp; 333mg @ midday &amp; 333mg nocte</td>
<td>If Body Weight &lt; 60 Kg</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>50mg/day</td>
<td>Start at 25 mg</td>
</tr>
<tr>
<td>Disulfiram</td>
<td>200mg/day</td>
<td>Max 500mg/day</td>
</tr>
<tr>
<td>Combination of above</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Acamprosate

Glutamate antagonism

Acamprosate

GABA agonism
# Acamprosate

| What it does | Referred to as anti-craving medication  
abstinence after detox  
heavy drinking’ if relapsed  
Does not interact with alcohol, does not cause dependence  
Correction of Glutamate–GABA imbalance  
alcohol dependence esp. withdrawal associated with ↑ glutamatergic system. Acamprosate can↓ this |
| Commence | As soon as possible after abstinence achieved  
BAP recommendation is to start during detox (neuroprotective effect) |
| Treatment time | 1 year. Stop, if drinking persists x 4–6 weeks. |
| Side effects | Nausea & vomiting, diarrhoea, abdominal pain, fluctuation in libido, pruritus, maculopapular skin rash, (which may last the first 1–2 weeks only), rarely bullous skin reaction |
| Contra-indications | Severe liver and renal impairment (serum creatinine>120micromol/L), pregnancy, lactation |
Naltrexone

Naltrexone

μ-opioid antagonism
## Naltrexone

| What it does                                                                 | • Reduces lapse to relapse  
|                                                                            | • Reduces alcohol’s rewarding effects and motivation to drink (craving)  
|                                                                            | • Possibly lowers levels of impulsivity  
|                                                                            | • Does not interact with alcohol  
|                                                                            | • Not known to cause dependence |
| Commence                                                                   | Soon after alcohol withdrawal  
| Treatment time                                                             | Up to 6 months, or longer for those benefiting from the drug who want to continue with it. Stop if drinking persists 4–6 weeks after starting the drug.  
| Side effects                                                                | Nausea, vomiting, abdominal pain, diarrhoea, constipation, reduced appetite, increased thirst, chest pain, anxiety, sleep disorders, headache etc. (refer to Summaries of Product Characteristics at [www.medicines.org.uk/emc](http://www.medicines.org.uk/emc) for full list of side effects) |
| Contra-indications                                                        | Currently dependent on opioid, severe hepatic impairment, acute hepatitis, hepatic failure, severe renal impairment, lactation  
| Cautions                                                                   | LFTS before and during treatment. Pregnancy(use only if benefit outweighs risk). Avoid concomitant use of Opioid but increased dose of opioid analgesic may be required for pain. Warn patients of risk of acute opioid intoxication if they over-dose in attempt to overcome opioid receptor blockade |
Acamprosate or Naltrexone

► Acamprosate is more effective in preventing a lapse, whereas Naltrexone was is better in preventing a lapse from becoming a relapse.

(Rosner et al., 2008)
## Disulfiram (Antabuse)

| What it does | • Aldehyde dehydrogenase blocker ➔ Acetaldehyde accumulation if alcohol consumed ➔ very unpleasant reaction. This deters people from drinking.  
• Blocks dopamine-b-hydroxylase in the brain, ↑dopamine and ↓NA. This may contribute to its effects.  
• Useful in alcoholism as well as cocaine addiction. |
| Commence | > 24 hours after last drink |
| Treatment time | Supervise: 2-weekly x first 2/12, monthly x 4/12, 6 monthly thereafter |
| Side effects | Initially drowsiness & fatigue, nausea, vomiting, halitosis, reduced libido, rarely psychotic reactions, allergic dermatitis, peripheral neuritis, hepatic cell damage |
| Contra-indications | Cardiac failure, coronary artery disease or CVA, hypertension, psychosis, severe personality disorder, suicide risk. Avoid in first trimester of pregnancy, lactation. |
| Cautions | Respiratory disease, diabetes mellitus, epilepsy, acute porphyria, hepatic impairment, renal impairment |
Disulfiram blocks Aldehyde Dehydrogenase, causing accumulation of Acetaldehyde if alcohol consumed, resulting in a very unpleasant reaction. Symptoms include:

► Flushing, headache, palpitation, tachycardia
► Nausea and dizziness, vomiting, chest pain, palpitations
► Large doses of alcohol may cause hypotension, arrhythmia & collapse
Disulfiram: other factors to consider

- Best results with supervised ingestion
- Test liver function, U&Es before treatment
- Warn about rapid and unpredictable onset of the rare complication of hepatotoxicity
- Symptoms of Alcohol-Disulfiram reaction can occur within 10mts of consuming alcohol
- Small amounts of alcohol (ingredient of other oral medication, toiletries, mouth wash etc.) sufficient to precipitate a reaction
- Alcohol should be avoided for at least 1 week after stopping treatment
Let’s think!

Case study

► How will you respond as a doctor?
► If alcohol use continues, how can harm be reduced?

Meg, a 47-year-old woman, always has alcohol on her breath and frequently falls. She moved into the suburb a few months ago and is well known at the local liquor shop and hotel. She denied alcohol use until a recent fracture and hospital admission. Since her discharge, she has started drinking again, mostly spirits. She presents to you late one afternoon seeking benzodiazepines.
Where are we so far?

► What are the effects of alcohol on the human body and brain?
► Is there a difference in effects and consequences of alcohol use between men and women?
► How to manage alcohol withdrawal?
► What are the risks associated with alcohol use?
► What options are there for the long-term management of alcohol dependency?
Break
Benzodiazepines
Benzodiazepine (BZD)

“Benzodiazepines: the opium of the masses”

(2) basic 5-phenyl-1,4-benzodiazepine skeleton
Benzodiazepines enhance the effect of GABA, which is an inhibitory neurotransmitter.

They are hence used as tranquilizers, hypnotics, anticonvulsants & centrally acting muscle relaxants.

Over 50 of these are marketed globally for clinical use.

35 of these are subject to international control under the 1971 Convention on Psychotropic Substances.
Benzodiazepine misuse

- Benzodiazepine misuse is widespread globally
- Illicit Benzodiazepines are generally diverted from legitimated sources
- Alprazolam and Diazepam are among the most diverted & misused psychotropic substances
- Combination products, e.g. Chlordiazepoxide-Amitriptyline & Chlordiazepoxide-Clidiniumbromide also appear on the illicit market
Benzodiazepine formulations

- Benzodiazepines are formulated mainly as capsules and tablets
- Some are available as injectable solutions
- Diazepam, the most traded and widely available benzodiazepine, can be found as capsules, tablets, aqueous or polyethylene glycol solutions for injection, syrups and suppositories
Benzodiazepines under international control

The information related to each of the 35 benzodiazepines currently under international control, can be found in:

The Multilingual Dictionary of Narcotic Drugs and Psychotropical Substances under International Control

- Includes synonyms
- Includes different trade names for the relevant substances
- Provides information on their control status
Benzodiazepines: history and clinical properties
### Benzodiazepines: history

<table>
<thead>
<tr>
<th><strong>1950s</strong></th>
<th>Invented by Swiss chemists who identified its sedative effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1950s–60s</strong></td>
<td>Chlordiazepoxide (Librium) marketed as a safer alternative to barbiturates; along with newer benzodiazepines (BZDs), promoted as having no dependence-inducing properties!</td>
</tr>
<tr>
<td><strong>1970s–80s</strong></td>
<td>BZDs most commonly prescribed drug class in the world</td>
</tr>
<tr>
<td><strong>1990s on</strong></td>
<td>Some decline in the number of prescriptions due to problems related to dependence and reduced therapeutic value. Generally safer than barbiturates; problems are with longer term and polydrug use</td>
</tr>
<tr>
<td><strong>1998</strong></td>
<td>8.89 million prescriptions dispensed</td>
</tr>
</tbody>
</table>
General medical/psychiatric indications for benzodiazepine use

- Anxiolytic – chronic/phobic anxiety & panic attacks
- Sedative and hypnotic – sleep disturbance & anaesthesia/premedication
- Anticonvulsant – status epilepticus, myoclonic & photic epilepsy
- Muscle relaxant – muscle spasm/spasticity
- Alcohol withdrawal
Let’s think!

Case study

► What would be an appropriate plan and treatment option for Shirley?

After the recent and unexpected death of her husband from an MI, Shirley, aged 62, presented for you to check her cardiac state as she fears a similar fate to her husband’s.

She is afraid to go out alone, and she fears going to sleep as she is scared she will not wake up. She experiences occasional non-radiating chest pain. She has been taking sleeping tablets for several years and finds that they are now no longer working.
BZDs are one of the most prescribed drugs

4% of all prescriptions from general practitioners are for benzodiazepines (BZDs)

Predictors for BZD prescription include:
- being female
- being elderly
- being an established patient
- attending a busy doctor, or a doctor in inner urban area

Over 40% of prescriptions given to people > 70 years old

Night time use tends to increase with age

58% of current users report daily use for > 6 months
BZDs and long term use

- Long-term use is common and associated with:
  - Altered use patterns (from night-time to daytime use)
  - Excessive sedation
  - Cognitive impairment
  - Increased risk of accidents
  - Adverse sleep effects
  - Dependence and withdrawal (even at therapeutic doses)

- BZDs have an additive effect with alcohol / other CNS depressants, increasing the risk of harm

- BZDs have limited long-term efficacy
BZD and illicit drug use

- Illicit BZD use is usually oral, although around 5% are likely to inject (usually males)
- Often 2\textsuperscript{nd} drug of choice for illicit drug users, as BZDs assist withdrawal from opioids, stimulants, and alcohol
- Estimated around 70% of people using > 50 mg per day are polydrug users, who tend to:
  - Be younger
  - Have higher daily doses and higher lifetime exposure
  - Use in combination with other CNS depressants to increase intoxication
  - Prefer fast-acting BZDs (diazepam, flunitrazepam)
  - May convert form to enable injection
# Benzodiazepines: half-life

<table>
<thead>
<tr>
<th>Benzodiazepines</th>
<th>Half-life (hrs) 2 [active metabolite]</th>
<th>Appr. Equivalent Oral dosages (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprazolam (Xanax, Xanor, Tafil)</td>
<td>6-12</td>
<td>0.5</td>
</tr>
<tr>
<td>Diazepam (Valium)</td>
<td>20-100 [36-200]</td>
<td>10</td>
</tr>
<tr>
<td>Clonazepam (Klonopin, Rivotril)</td>
<td>18-50</td>
<td>0.5</td>
</tr>
</tbody>
</table>
Pharmacodynamics

- Rapidly absorbed orally (slower rate of absorption IM)
- Lipid soluble – differences determine rate of passage through blood brain barrier, i.e.,
  - ↑ lipophilic → ↑ speed of onset
- Duration of action variable –
  - ↑ lipophilic → ↓ duration of action due to distribution in adipose tissue
Metabolism

- Metabolised in the liver – mostly oxidative transformation prior to conjugation with glucuronic acid for urinary excretion

- Elimination half life (drug & active metabolites) ranges from 8 – >60 hours, if short half life & no active metabolites, it rapidly attains steady state with minimal accumulation
Benzodiazepines (BZD) are ‘allosteric modulators’ of GABA-A receptors.

Binding of BZD increases affinity of the receptor for GABA, which causes receptor ‘opening’ to allow the passage of chloride ions through the membrane.

This results in neuronal hyper-polarization and reduced excitability of the target cell.

Unlike barbiturates at high doses, benzodiazepines do not mimic the effects of GABA and do not activate chloride channels directly.

Specific neuronal membrane receptors for BZD closely associated with synaptic GABA receptors.

Receptors distributed through CNS, concentrated in reticular formation & limbic systems, also peripheral binding sites.
Benzodiazepines: short term & long term effects
# Effects: low dose

## Short term:

- Sedation
- Anxiety relief
- Anticonvulsant properties
- Can usually attend daily business (though should not drive in first 2 weeks of treatment)

## Other effects:

- Drowsiness, lethargy, fatigue
- Impaired concentration, coordination, memory
- Reduced ability to think and learn
- Clumsiness, ataxia
- Depression
- Mood swings
- Blurred vision and/or vertigo
- Light-headedness
- Nausea, constipation, dry mouth, loss of appetite
Effects: high dose

**Short term:**
- Sedation
- Intoxication
- Drowsiness

**Other effects:**
- Paradoxical excitement
- Mood swings
- Hostile and erratic behaviour

**Toxicity:**
- Performance deficits
- Emotional blunting
- Muscle weakness
- Sensitivity
- Potentiates other drugs
- Euphoria, hypomania
Drug + alcohol interactions

- CNS depressants, e.g., benzodiazepines
  - Confusion, depressed respiration

- Antipsychotics, antidepressants
  - Decreased metabolism, toxicity & CNS depression

- Opioid analgesics, antihistamines (some)
  - CNS depression

- Hypoglycaemics (chlorpropamide), metronidazole, cephalosporins (some)
  - Facial flushing, headache
Benzodiazepine overdose
Benzodiazepines are the most commonly implicated drug in overdose cases.

On their own, unlikely to cause death despite causing respiratory depression.

Serious/potentially fatal implications when used in combination with other CNS depressants such as opioids or alcohol.
Overdose response

Overdose depresses the conscious state and respiratory system. Airway management and assisted ventilation is necessary.

**Flumazenil®**

- A BZD antagonist which reverses BZD overdose, though contraindicated outside the emergency department
- Precipitates seizures in:
  - chronic BZD users
  - pre-existing epilepsy
  - tricyclic antidepressant users
  - concurrent amphetamine or cocaine users
# Flumazenil

<table>
<thead>
<tr>
<th>What it does</th>
<th>Benzodiazepine antagonist</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Reversal of central sedative effect of Benzodiazepines</td>
</tr>
<tr>
<td></td>
<td>• May prevent need for ventilation in patients with severe respiratory disorders</td>
</tr>
</tbody>
</table>

| Contraindication | Life threatening condition controlled by benzodiazepines (Raised ICT, status epilepticus), breast feeding. It can be hazardous in mixed overdoses involving Tricyclic anti depressants or in benzodiazepine dependent patients |

| Side effects | Nausea & vomiting, palpitation, anxiety, fear, transienthypertension, tachycardia, flushing, agitation, convulsions, dizziness, sensory disturbance, chills, sweating |

| Caution    | • To be used on expert advice only |
|           | • Short acting effect-repeat doses may be necessary |
|           | • May precipitate withdrawal symptoms in those dependent on benzodiazepines |
|           | • Risk of convulsions in those who are on prolonged benzodiazepine therapy for epilepsy |
|           | • Risk of recurrence of panic disorder |
|           | • Head injury, elderly, children |
Benzodiazepine dependence: assessment & management
Benzodiazepine assessment

► Review BZD medication
  – Initial reasons for use
  – Type of BZD, response to, and patterns of use
  – Side-effects reported or observed
  – Current / past withdrawal history and symptoms

► Obtain physical history (concurrent medical problems)

► Mental health history (e.g., depression)

► Other drug (and alcohol/prescription drug) use

► Discuss options
  – Risks of continued and prolonged use
  – Withdrawal potential/risks, management options
Two groups of patients are especially likely to develop dependence:

▸ Low dose dependence occurs among women and elderly prescribed low doses over long time periods (up to 40% experience withdrawal symptoms)

▸ High dose dependence occurs among polydrug users
Benzodiazepine withdrawal

- 40% of people on long-term therapeutic BZD doses will experience withdrawal if abruptly ceased
- Symptoms occur within 2 “short-acting” to 7 day “long-acting” forms
- BZD withdrawal:
  - Is not life-threatening & usually protracted
  - Initial symptoms / problems re-emerge on cessation
  - Issues usually more complicated on cessation
- Seizures uncommon (unless high dose use or abrupt withdrawal, + alcohol use)
- Two main groups of users:
  - Prescribed (older women)
  - High level, erratic polydrug use
Severity of withdrawal is dependent on:

- Pattern and extent of use (duration, quantity, type (half-life))
- Withdrawal experience (prior symptoms, success, complications)
- Coexisting physical / mental health problems
3 Areas of BZD withdrawal

► Anxiety and anxiety-related symptoms
  – Anxiety, panic attacks, hyperventilation, tremor
  – Sleep disturbance, muscle spasms, anorexia, weight loss
  – Visual disturbance, sweating
  – Dysphoria

► Perceptual distortions
  – Hypersensitivity to stimuli
  – Abnormal body sensations
  – Depersonalisation/derealisation

► Major events
  – Seizures (grand mal type)
  – Precipitation of psychosis
Withdrawal management

- Obtain an accurate consumption history
- Calculate diazepam equivalent and substitute. Reduce gradually over 6–8 weeks (or longer, e.g., 3–4 months)
- Reduce dose by a fixed rate at weekly intervals (usually 10%–20% initially, then 5%–10% / week, or slower when dose at 15 mg or less)
- Supervision of long-term BZD reductions (3-4 months)
- Dose at regular times
- Regularly review and titrate dose to match symptoms
- If symptoms re-emerge, dose may be plateaued for 1–2 weeks, or increased before reduction resumed
- Provide support, not pharmacological alternatives for conditions such as insomnia and anxiety
Consider outpatient withdrawal management:
► If willing, committed, compliant and has adequate social supports
► If taking < 50 mg diazepam equivalent or therapeutic doses
► If no previous history of complicated withdrawal
► If able to attend weekly reviews

Develop an individualised withdrawal plan considering:
► Psychosocial factors
► Coping skills
► Previous attempts
► Counselling/referral needs
Benzodiazepine withdrawal management – sample regimes
Withdrawal from Diazepam
40mg daily sample regimen

<table>
<thead>
<tr>
<th>Stage</th>
<th>Morning (mg)</th>
<th>Night (mg)</th>
<th>Total Daily Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting dosage</td>
<td>20</td>
<td>20</td>
<td>40 mg</td>
</tr>
<tr>
<td>Stage 1 (1-2 weeks)</td>
<td>18</td>
<td>20</td>
<td>38mg</td>
</tr>
<tr>
<td>Stage 2 (1-2 weeks)</td>
<td>18</td>
<td>18</td>
<td>36mg</td>
</tr>
<tr>
<td>Stage 3 (1-2 weeks)</td>
<td>16</td>
<td>18</td>
<td>34mg</td>
</tr>
<tr>
<td>Stage 4 (1-2 weeks)</td>
<td>16</td>
<td>16</td>
<td>32mg</td>
</tr>
<tr>
<td>Stage 5 (1-2 weeks)</td>
<td>14</td>
<td>16</td>
<td>30mg</td>
</tr>
<tr>
<td>Stage 6 (1-2 weeks)</td>
<td>14</td>
<td>14</td>
<td>24mg</td>
</tr>
<tr>
<td>Stage 7 (1-2 weeks)</td>
<td>12</td>
<td>14</td>
<td>22mg</td>
</tr>
<tr>
<td>Stage 8 (1-2 weeks)</td>
<td>12</td>
<td>12</td>
<td>20mg</td>
</tr>
<tr>
<td>Stage 9 (1-2 weeks)</td>
<td>10</td>
<td>12</td>
<td>18mg</td>
</tr>
<tr>
<td>Stage 10 (1-2 weeks)</td>
<td>10</td>
<td>10</td>
<td>16mg</td>
</tr>
<tr>
<td>Stage 11 (1-2 weeks)</td>
<td>8</td>
<td>10</td>
<td>18mg</td>
</tr>
<tr>
<td>Stage 12 (1-2 weeks)</td>
<td>8</td>
<td>8</td>
<td>16mg</td>
</tr>
<tr>
<td>Stage 13 (1-2 weeks)</td>
<td>6</td>
<td>8</td>
<td>14mg</td>
</tr>
<tr>
<td>Stage 14 (1-2 weeks)</td>
<td>5</td>
<td>8</td>
<td>13mg</td>
</tr>
<tr>
<td>Stage 15 (1-2 weeks)</td>
<td>4</td>
<td>8</td>
<td>12mg</td>
</tr>
<tr>
<td>Stage 16 (1-2 weeks)</td>
<td>3</td>
<td>8</td>
<td>11mg</td>
</tr>
<tr>
<td>Stage 17 (1-2 weeks)</td>
<td>2</td>
<td>8</td>
<td>10mg</td>
</tr>
<tr>
<td>Stage 18 (1-2 weeks)</td>
<td>1</td>
<td>8</td>
<td>9mg</td>
</tr>
<tr>
<td>Stage 19 (1-2 weeks)</td>
<td>**</td>
<td>8</td>
<td>8mg</td>
</tr>
<tr>
<td>Stage 20 (1-2 weeks)</td>
<td>**</td>
<td>7</td>
<td>7mg</td>
</tr>
<tr>
<td>Stage 21 (1-2 weeks)</td>
<td>**</td>
<td>6</td>
<td>6mg</td>
</tr>
<tr>
<td>Stage 22 (1-2 weeks)</td>
<td>**</td>
<td>5</td>
<td>5mg</td>
</tr>
<tr>
<td>Stage 23 (1-2 weeks)</td>
<td>**</td>
<td>4</td>
<td>4mg</td>
</tr>
<tr>
<td>Stage 24 (1-2 weeks)</td>
<td>**</td>
<td>3</td>
<td>3mg</td>
</tr>
<tr>
<td>Stage 25 (1-2 weeks)</td>
<td>**</td>
<td>2</td>
<td>2mg</td>
</tr>
<tr>
<td>Stage 26 (1-2 weeks)</td>
<td>**</td>
<td>1</td>
<td>1mg</td>
</tr>
</tbody>
</table>
Withdrawal from short acting BZD (Lorazepam) by switching to Diazepam

<table>
<thead>
<tr>
<th>Stage</th>
<th>Morning</th>
<th>Midday/Afternoon</th>
<th>Evening/Night</th>
<th>Daily Diazepam Equivalent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting dosage</td>
<td>Lorazepam 1mg</td>
<td>Lorazepam 1mg</td>
<td>Lorazepam 1mg</td>
<td>30 mg</td>
</tr>
<tr>
<td>Stage 1 (1 week)</td>
<td>Lorazepam 1mg</td>
<td>Lorazepam 1mg</td>
<td>Lorazepam 0.5mg</td>
<td>30 mg</td>
</tr>
<tr>
<td>Stage 2 (1 week)</td>
<td>Lorazepam 0.5mg</td>
<td>Lorazepam 1mg</td>
<td>Lorazepam 0.5mg</td>
<td>30 mg</td>
</tr>
<tr>
<td>Stage 3 (1 week)</td>
<td>Lorazepam 0.5mg</td>
<td>Lorazepam 0.5mg</td>
<td>Lorazepam 0.5mg</td>
<td>30 mg</td>
</tr>
<tr>
<td>Stage 4 (1 week)</td>
<td>Lorazepam 0.5mg</td>
<td>Lorazepam 0.5mg</td>
<td>Stop Lorazepam diazepam 10mg</td>
<td>30 mg</td>
</tr>
<tr>
<td>Stage 5 (1 week)</td>
<td>Stop Lorazepam diazepam 10mg</td>
<td>Lorazepam 0.5mg</td>
<td>Diazepam 10mg</td>
<td>30 mg</td>
</tr>
<tr>
<td>Stage 6 (1 week)</td>
<td>Diazepam 10mg</td>
<td>Stop Lorazepam diazepam 10mg</td>
<td>Diazepam 10mg</td>
<td>30 mg</td>
</tr>
<tr>
<td>Stage 7 (1-2weeks)</td>
<td>Diazepam 10mg</td>
<td>Diazepam 10mg</td>
<td>Diazepam 8mg</td>
<td>28mg</td>
</tr>
<tr>
<td>Stage 8 (1-2weeks)</td>
<td>Diazepam 8mg</td>
<td>Diazepam 8mg</td>
<td>Diazepam 10mg</td>
<td>26mg</td>
</tr>
<tr>
<td>Stage 9 (1-2weeks)</td>
<td>Diazepam 8mg</td>
<td>Diazepam 8mg</td>
<td>Diazepam 10mg</td>
<td>24mg</td>
</tr>
<tr>
<td>Stage 10 (1-2weeks)</td>
<td>Diazepam 6mg</td>
<td>Diazepam 6mg</td>
<td>Diazepam 10mg</td>
<td>22mg</td>
</tr>
<tr>
<td>Stage 11 (1-2weeks)</td>
<td>Diazepam 6mg</td>
<td>Diazepam 6mg</td>
<td>Diazepam 10mg</td>
<td>20mg</td>
</tr>
<tr>
<td>Stage 12 (1-2weeks)</td>
<td>Diazepam 6mg</td>
<td>Diazepam 2mg</td>
<td>Diazepam 10mg</td>
<td>18mg</td>
</tr>
<tr>
<td>Stage 13 (1-2weeks)</td>
<td>Diazepam 6mg</td>
<td>Stop Diazepam</td>
<td>Diazepam 10mg</td>
<td>16mg</td>
</tr>
<tr>
<td>Stage 14 (1-2weeks)</td>
<td>Diazepam 5mg</td>
<td>**</td>
<td>Diazepam 10mg</td>
<td>15mg</td>
</tr>
<tr>
<td>Stage 15 (1-2weeks)</td>
<td>Diazepam 4mg</td>
<td>**</td>
<td>Diazepam 10mg</td>
<td>14mg</td>
</tr>
<tr>
<td>Stage 16 (1-2weeks)</td>
<td>Diazepam 3mg</td>
<td>**</td>
<td>Diazepam 10mg</td>
<td>13mg</td>
</tr>
<tr>
<td>Stage 17 (1-2weeks)</td>
<td>Diazepam 2mg</td>
<td>**</td>
<td>Diazepam 10mg</td>
<td>12mg</td>
</tr>
<tr>
<td>Stage 18 (1-2weeks)</td>
<td>Diazepam 1mg</td>
<td>**</td>
<td>Diazepam 10mg</td>
<td>11mg</td>
</tr>
<tr>
<td>Stage 19 (1-2weeks)</td>
<td>Stop Diazepam</td>
<td>**</td>
<td>Diazepam 10mg</td>
<td>10mg</td>
</tr>
</tbody>
</table>

Continue reducing night time diazepam by 1 mg every 1-2 weeks
Lorazepam 3mg ≈ 30mg Diazepam
## Withdrawal from Nitrazepam (Mogadon)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Bedtime doze</th>
<th>Dose of Nitrazepam approx. equivalent to Dose of Diazepam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting dosage</td>
<td>Nitrazepam 10mg</td>
<td></td>
</tr>
<tr>
<td>Stage 1 (1 week)</td>
<td>Nitrazepam 5mg</td>
<td></td>
</tr>
<tr>
<td>Stage 2 (1 week)</td>
<td>Diazepam 5mg</td>
<td></td>
</tr>
<tr>
<td>Stage 3 (1-2 weeks)</td>
<td>Diazepam 9mg</td>
<td></td>
</tr>
<tr>
<td>Stage 4 (1-2 weeks)</td>
<td>Diazepam 8mg</td>
<td></td>
</tr>
<tr>
<td>Stage 5 (1-2 weeks)</td>
<td>Diazepam 7mg</td>
<td></td>
</tr>
<tr>
<td>Stage 6 (1-2 weeks)</td>
<td>Diazepam 6mg</td>
<td></td>
</tr>
<tr>
<td>Stage 7 (1-2 weeks)</td>
<td>Diazepam 5mg</td>
<td></td>
</tr>
<tr>
<td>Stage 8 (1-2 weeks)</td>
<td>Diazepam 4mg</td>
<td></td>
</tr>
<tr>
<td>Stage 9 (1-2 weeks)</td>
<td>Diazepam 3mg</td>
<td></td>
</tr>
<tr>
<td>Stage 10 (1-2 weeks)</td>
<td>Diazepam 2mg</td>
<td></td>
</tr>
<tr>
<td>Stage 11 (1-2 weeks)</td>
<td>Diazepam 1mg</td>
<td></td>
</tr>
<tr>
<td>Stage 12</td>
<td>Stop Diazepam</td>
<td></td>
</tr>
</tbody>
</table>
Inpatient withdrawal management is necessary if the patient:

► Is using > 50 mg diazepam equivalent for >14 days
► Has a history of alcohol or other drug use or dependence
► Has concurrent medical or psychiatric problem
► Has a history of withdrawal seizures
► If significant symptoms are predicted
► Is in an unstable social situation
► Has previous poor compliance/doubtful motivation
► Is in concurrent methadone stabilisation
Drug interactions

BZDs either potentiate/increase effects or interfere with metabolism or absorption of:

► Alcohol
► Antidepressants and antihistamines
► Disulfiram, cimetidine, erythromycin
► Anticonvulsants
► Anticoagulants, oral diabetic agents
► Cisapride
Questions
Wrap-up

► What are acute and what are chronic effects of alcohol and benzodiazepines?

► What are main differences between protocols to treat intoxication and overdose?

► What is the main approach in withdrawal protocols?

► What kind of treatments can follow detoxification?
Thank you for your time!
End of workshop 2