Alcohol use disorder: clinical features, neurobiology, and evidence-based treatment

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Harmful Substance use
ICD 11 criteria

A pattern of substance use that has caused damage to a person’s physical or mental health or has resulted in behaviour leading to harm to the health of others.

The pattern of substance use is evident over a period of at least 12 months if substance use is episodic or at least one month if use is continuous.

Harm to health of the individual occurs due to one or more of the following:

(1) behaviour related to intoxication;
(2) direct or secondary toxic effects on body organs and systems; or
(3) a harmful route of administration.
ICD-11: Dependence syndrome.

Substance dependence is a disorder of regulation of substance use arising from repeated or continuous use of substance. The characteristic feature is a strong internal drive to use substance, which is manifested by impaired ability to control use, increasing priority given to use over other activities and persistence of use despite harm or negative consequences.

2 of the following:

- **Impaired control over substance use**
  - in terms of the onset, level, circumstances or termination of use, often but not necessarily accompanied by a subjective sensation of urge or craving.

- **Substance use becomes an increasing priority in life**
  - takes precedence over other interests or enjoyments, daily activities, responsibilities, or health or personal care. Substance use takes an increasingly central role in the person’s life and relegates other areas of life to the periphery; continues despite the occurrence of problems.

- **Physiological features (indicative of neuroadaptation to the substance) as manifested by**
  - (i) tolerance, (ii) withdrawal symptoms following cessation or reduction in use of that substance or (iii) repeated use of the substance (or pharmacologically similar substance) to prevent or alleviate withdrawal symptoms.
DSM vs ICD
continuum vs separate

more individuals meet threshold for diagnosis in DSM-5 vs DSM-IV
Addiction vs dependence?

- **Addiction** - compulsive drug use despite harmful consequences, characterized by an inability to stop using a drug; failure to meet work, social, or family obligations; and, sometimes (depending on the drug), tolerance and withdrawal.

- In biology/pharmacology, **dependence** refers to a physical adaptation to a substance
  - Tolerance/withdrawal
    - Eg opioid, benzodiazepine, alcohol
    - So can be dependent and not addicted

- **Antidepressants?**
  - Withdrawal but no other features of addiction

- Confusion with terminology so be clear in how you are using either term ‘addiction’ or ‘dependence’ to other professionals and individual concerned.
Reward deficiency
(positive reinforcement)

Overcoming adverse state
eg withdrawal, anxiety
(negative reinforcement)

Impulsivity/
compulsivity

Models of Addiction:
Overlap to some extent
Natural rewards such as food, sex increase levels of a chemical – **dopamine** - in a part of the brain called ventral striatum. Drugs of abuse also increase levels of dopamine here.

Mesolimbic dopamine pathway has been referred to as the ‘pleasure-reward-motivation’ system:

A key modulator is opioid system – particularly mu opioid that mediates pleasurable effects (eg of alcohol, ‘endorphin ‘rush’); others include GABA-B, cannabinoids, glutamate etc that are targets for treatment

Addiction has been conceptualized as a ‘reward deficient’ state
Assessing function in the reward pathway with fMRI: Monetary Incentive delay task - anticipation of winning money

- Blunted activation of reward system in abstinent addicts compared with controls.
  - Blunted responses shown in 14yr olds who went on to develop problematic drug use at 16yrs (IMAGEN; Buchel et 2017)

HC=Healthy Control,  AD=abstinent alcohol dependent,  PD=abstinent polydrug (alcohol, cocaine, opiate) dependent

Paterson, Lingford-Hughes, Nutt et al
Higher activity in reward pathway is associated abstinence at follow-up:

- in abstinent addicts, those with blunted response in the brain to ‘anticipation of reward’ are more likely to relapse
  - consistent with ‘reward deficiency’ theories of addiction

Paterson, Lingford-Hughes, Nutt et al
HC=Healthy Control,  AD=abstinent alcohol dependent,  PD=abstinent polydrug (alcohol, cocaine, opiate) dependent

- DRD3 antagonism ‘normalises’ response in addiction
  - Presynaptic D3 receptor – increase dopamine
Alcohol cue reactivity

- In alcoholics: alcohol cues resulted in greater activation in ventral striatum, anterior cingulate and ventromedial prefrontal cortex.

- Cue-elicited activation of ventral striatum was most frequently correlated with behavioural measures and most frequently reduced by treatment eg naltrexone. However there is little consistency across addictions and different paradigms to assist with prediction of treatment efficacy.

Schacht et al; Courtney et al Addiction Biology
Regions of brain involved in different stages:
- binge/intoxication,
- withdrawal/negative affect,
- preoccupation/anticipation ‘craving’.

Koob & Volkow
Change from positive to negative reinforcement as addiction/dependence develops.
Neuropharmacology and brain regions associated with withdrawal and negative emotional states in addiction: targets for treatment.

The ‘reward’ system: reduced dopamine and mu opioid function

The ‘stress’ system: increased activity in many including kappa opioid (dynorphin), noradrenaline (arousal system) CRF (stress) etc

Dysregulation in amygdala is key

Heightened brain response in left amygdala in abstinent polydrug addicts to aversive vs neutral images but not in alcoholism.

Healthy vs Polydrug

Healthy vs Alcohol

Paterson et al in prep
Withdrawal: a negative emotional state
Chronic alcohol exposure results in neuroadaptations:
in absence of alcohol GABA & glutamate are no longer in balance

Upregulation of excitatory system

Reduced function in inhibitory system:
Treat with benzodiazepines to boost GABA function

NMDA receptor:
In detox: increase in Ca^{2+}: toxic leading to hyperexcitability (seizures) and cell death (atrophy)
treatment: Mg loss – replenish?; thiamine – oral or parenteral?
For relapse prevention and consider for detox: acamprosate (functional NMDA antagonist)

GABA-A receptor:
Regions of brain involved in different stages:
- binge/intoxication
- withdrawal/negative affect
- preoccupation/anticipation ‘craving’

Naltrexone: +ve
DRD3: no
Implications from neurobiology for treatment in alcoholism

Psychosocial and pharmacological treatments to

• decrease reward value of drugs
• increase value of non-drug rewards
• weaken learned associations between drug & drug cues
• strengthen frontal-striatal control
• regulate brain stress systems
• gender differences for treatment

➢ Medication is essential for some eg for detox and should always be used alongside psychosocial treatment
  ➢ Active consideration for relapse prevention in moderate-severe alcoholism
## Relapse prevention medications in alcoholism

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<td>Reduction of drinking in those who do not need a detox</td>
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**Licensed & recommended**

**Off-label**
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<td>Gabapentin, sodium oxybate, topiramate; new targets: ‘anti-stress’, appetitive hormones, inflammation</td>
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<td>Future?</td>
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Guidelines:
NICE
BAP

Coming in 2021:
‘Alcohol’ guidelines from Public Health England