Phenomenology Substance-Related Disorders

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Phenomenology Module, Otago Regional Psychiatry Training Formal Education, 15 April 2010.
Objectives

• Review phenomenology of substance dependence
• Neurophysiology basis for phenomenology of different substance dependence and withdrawal syndromes
Classification.

- Intoxication.
- At risk use.
  - Level of risk that will cause long term health problems.
- Harmful use or abuse.
  - Recurrent use of substances despite substances causing significant work, relationship, legal or health problems.
Dependence.

- Withdrawal.
- Drug use to avoid withdrawal
- Awareness cannot control use substance
- Narrowing of repertoire of drug use pattern
- Neglect of other pleasures or interests
- Persistent use despite harm
- Return to use substance leads to dependance pattern.
Tolerance, Dependence and Withdrawal

• **Tolerance:**
  – reduction in response to a drug after repeated administration
  – receptor/second messenger desensitization/downregulation
  – acute vs chronic tolerance
  – may lead to increased intake to get desired effects

• **Dependence:**
  – compulsive drug-taking behavior; loss of ability to control use; intrusion into normal activities; + tolerance + withdrawal

• **Withdrawal:**
  – rebound physiological effects upon cessation or reduction of drug intake
  – symptoms usually opposite to those produced by drug (e.g. insomnia, anxiety - BDZs, alcohol; sedation, depression - cocaine)
Factors Associated With Substance Dependence (1)

– Environmental Factors
  • family or peer group behavior
  • availability of other reinforcers (e.g. recreational resources)
  • job/educational opportunities
  • conditioned stimuli (environmental cues paired with drug use)

– Host Factors
  • Genes:
    – + and - for alcohol (defective ALDH genes in Orientals; reduced sensitivity to alcohol phenotype in alcoholics);
    – opioid dependence associated with 2 sites on chromosome 17 (Gerlenter, Am J Hum Gen 2006)
    – unclear for other substances
  • Antisocial or anxious traits; risk-taking
  • Prior experience/expectations
Factors Associated With Substance Dependence (2)

- **Drug Factors**
  - ease of drug availability
  - price
  - purity/potency
  - how administered (GI/intranasal/IV/inhalation)
  - PK profile (speed of onset and offset of effects)

- **Neurobiological Factors**
  - drugs of abuse/dependence have widely differing pharmacological targets
  - however all addictive drugs increase synaptic dopamine concentrations in Nucleus Accumbens (PNAS 1988, 85:5274)
  - complex interplay with other transmitter systems (e.g. glutamate, Ach, endorphins), and some intracellular changes (e.g. CREB upregulation) which may facilitate conditioning in addictive states (Nature Reviews 2001, 2:695)
Key common neurocircuitry elements in drug-seeking behavior of addiction.

## Pharmacological targets of drugs of abuse/dependence

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Receptor target</th>
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<tbody>
<tr>
<td><strong>Alcohol</strong></td>
<td>GABA-A-R (+); glutamate (-); many others</td>
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<tr>
<td><strong>Nicotine</strong></td>
<td>Nicotinic Ach R agonist</td>
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<td><strong>Stimulants (cocaine, amphetamine, etc)</strong></td>
<td>Cocaine: inhibits DA, 5HT, NE transporter; amphetamines: increased release</td>
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<td><strong>Opioids (morphine, heroin, etc)</strong></td>
<td>μ-and δ-opioid agonists</td>
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<td><strong>Some hallucinogens (e.g. PCP)</strong></td>
<td>Glutamate R antagonists</td>
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<td><strong>Cannabinoids</strong></td>
<td>CB1 R agonists</td>
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<tr>
<td><strong>Benzodiazepines and barbiturates</strong></td>
<td>GABA-A-R (+) (facilitation of Cl⁻ flux)</td>
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Dopamine Pathways in the Brain

- Substantia nigra (A9) (nigrostriatal pathway)
- Caudate/Putamen (Striatum)
- Olfactory Tubercle
- Cingulate cortex
- Frontal cortex
- Ventral tegmentum (A10) (mesolimbic pathway)
- Nucleus Accumbens
- Hypothalamus (tuberoinfundibular pathway)
- Amygdala
General Treatment Principles

- Drug use must stop (alcohol, nicotine, cocaine) OR be closely managed (opioid substitution)
- Concentrate on improving patients’ health and social functioning
- Change is slow - treatment is long-term
- Improvement may be seen as reduced use rather than abstinence
- Use Voluntary Groups extensively as well as medical/psychological management - drug treatment generally has a minor role
Alcohol (1)

- **Pharmacology:**
  - nonspecific effects on membrane fluidity
    - ↑ inhibitory (GABA-A) and ↓ excitatory (glutamate) neurotransmission; ↑ DA in VTA; complex changes in NE/5HT/endorphins
- **Acute effects:**
  - low doses: arousing effects (NE/5HT/?β-endorphin); anxiolytic
  - higher doses: sedation, in-coordination, amnesia
- **Tolerance Development:**
  - acute: e.g. loss of symptoms of acute intox. despite high BAC
  - chronic: e.g. ability to tolerate very high BAC (0.3-0.4g/dL)
    - cross tolerance to other sedatives (e.g. BDZs) - basis for w/d therapy
- **Dependence:**
  - psychological and physical (withdrawal syndrome)
Alcohol (2)

- **Withdrawal:**
  - normally: autonomic overactivity (tremor, sweating, ↑BP/HR, insomnia, nausea, anorexia, diarrhea);
    mood changes (anxiety, irritability); perceptual changes (illusions); for 2-5 days after last drink
  - severe (DTs): above+++ & confusion, visual hallucinations, seizures
  - monitor for Wernicke’s encephalopathy (confusion, ataxia, ophthalmoplegia)

- **Drug Therapy:**
  - detox: - unnecessary for mild cases (absence or mild w’d symptoms)
  - for moderate cases: benzodiazepines (e.g. chlordiazepoxide 10mg hourly until symptoms controlled;
    taper total dose by 25%/day over next 4-5 days); OK to monitor as outpatient/day patient
    - if symptoms persist beyond 4-5 days they are not alcohol w/d-related
  - severe cases: hospital admission required; in addition to above, monitor hydration, nutrition
  - thiamine 100mg/day during detox and for several months post-withdrawal
Delirium Tremens

- Marked tremor limbs, body and tongue
- Restlessness
- Loss contact reality
- Disorientation and illusions → terrifying hallucinations.
- Delusions may arise from hallucinations
- Fever, sweating, tachycardia
- Usually seen as a progression milder withdrawal.
- Rarely lasts over 4 days.
Alcoholic hallucinosis

- Hallucinations without delirium (i.e., no clouding of consciousness).
  - Often start as fragmentary, often auditory.
  - Gradually hallucinations become formed and unpleasant.
  - Can become compelling, unpleasant, with commands. May lead to suicidal ideation & acts.
  - Although looks like SCZ, patients generally do not have deterioration in function as in SCZ.
Alcohol and delusions.

- Classically, alcohol abuse was associated with delusions of Jealousy (*Othello's syndrome*).
  - This may be associated with feelings inadequacy as partner.
  - Alcohol induced erectile dysfunction
- Patient's accusations become repetitive and aggressive demands for proof may be reinforced by violence.
- Alcohol abuse not only cause, but not uncommonly associated with this.
Alcohol and depression

- Frequent co-occurrence.
- Alcohol can mask symptoms depression.
- Alcohol can disinhibit if person suicidal.

“The clinician has to distinguish those persons who are drinking to deal with their depression from the larger number who are depressed because of their drinking”
Cognitive Impairment.

- 50 – 60% alcoholic seen psychiatrist have poorer results testing than predicted by age and education.
  - Impairment of memory
  - Narrowing and rigidity of thought
  - Difficulty learning new material
  - Impairment visuospatial and visuoperceptive skills.

- Imaging shows.
  - Cortical atrophy
  - Ventricular enlargement

- Cognitive functioning improves in first few days of detoxification, and in many cases may continue to improve for up to a year, if patient remains abstinent.
Wernecke's encephalopathy.

- Triad.
  - Confusion.
  - Ataxia
  - Ocular palsy.

Patients who die from this have haemorrhages brain stem and hypothalamus.

- Identical lesions found in thiamine deficient animals.
Korsakoff's psychosis.

• If there is any cognitive impairment, best to give thiamine supplementation for at least four months.

• The syndrome.
  – Impairment in memory
  – Tendency to confabulate.
  – Peripheral neuropathy.

• Assoc. necrosis and gliosis mammillary bodies.
Physical complications.

- Hepatic failure (cirrhosis).
- Metabolic (hypoglycaemia)
- Cardiovascular risk
- Sexual impairment
- Foetal alcohol syndrome
- Trauma (including subdural if confused)
- Polyneuropathy
- Myopathy
Alcohol related social harm.

- Family disruption.
  - Up to a third of divorces involve alcohol.

- Cost (to family budget)

- Employment

- Crime
  - 60% prisoners report alcohol problems
  - Drunk driving (increasingly occurring in dependant persons)
  - 60% arrested drunkenness are dependant.
Nicotine (1)

• Pharmacology:
  – N-cholinergic agonist; activates DA release in VTA; other opioid and glucocorticoid effects

• Acute effects:
  – Combined stimulant (subjective alertness) and depressant (muscle relaxation) effects

• Tolerance Development:
  – acute (e.g. first cigarette each day has greatest effects)
  – chronic (loss of early tolerability symptoms e.g. nausea)
Nicotine (2)

- Dependence:
  - probably highest dependence liability (rapid brain entry; multiple daily reinforcements; place conditioning (e.g. smoking + food/sex/situations)
  - lowest rates of successful quitting
  - rapid reinstatement of dependence after restarting smoking

- Withdrawal:
  - irritability, impatience, hostility, anxiety, dysphoria
  - difficulty concentrating, restlessness
  - decreased heart rate; increased appetite/weight gain

- Therapy:
  - detox: nicotine replacement (gum, spray, patch)
    - steady concentrations rather than peaks and troughs - lower dependence liability; no efficacy advantage for any formulation
  - abstinence rates (15-20%) marginally > placebo (5-10%) at 6 and 12 months follow-up (e.g. JAMA 1993, 269:1268)
Amphetamines (m-AMP, d-AMP), phenmetrazine, methylphenidate

- **Pharmacology:**
  - Stimulate presynaptic release of DA, NE, 5HT

- **Acute effects:**
  - Similar to cocaine for smoked/injected AMP; after oral doses ↑ alertness, ↓ fatigue; mood elevation, ↑ self-confidence, ↑ motor and speech activity

- **Tolerance development:**
  - Rapid (e.g. to anorexic effects of oral AMP); less rapid for mood effects and psychomotor performance effects; no tolerance to autonomic effects (↑ BP)

- **Dependence:**
  - Extremely high liability

- **Withdrawal:**
  - Chronic use: dysphoria/depression; sleepiness; fatigue; craving; bradycardia
  - Symptoms improve over 1-3 weeks

- **Withdrawal treatment options:**
  - No effective drug treatments
Cocaine (1)

- **Pharmacology:**
  - Inhibits DA transporter; also NE and 5HT transporters; acute ↑ synaptic monoamine levels
  - Very rapid elimination

- **Acute effects:**
  - Increased alertness, vigilance; self confidence, sense of well-being, euphoria; HR, BP; craving (desire for more drug)
  - Involuntary movements; stereotyped behavior, paranoia, anxiety; CV toxicity

- **Tolerance Development:**
  - Rapid for euphoria; none for CV effects or craving
  - Possible sensitisation to certain toxic effects (e.g. paranoid, psychotogenic effects)

- **Dependence:**
  - Extremely high liability
Cocaine (2)

• **Withdrawal:**
  – after chronic use: dysphoria/depression; sleepiness; fatigue; craving; bradycardia
  – symptoms improve over 1-3 weeks

• **Drug treatments:**
  – No approved drug treatments
  – Recent single positive trials with disulfiram, modafinil, propranolol, topiramate, baclofen and vigabatrin – need confirmation
  – psychosocial management is mainstay of current treatment approaches
Opioids (1)

Natural: opium; morphine; Synthetic: heroin; methadone; etc...

- **Pharmacology:**
  - $\mu$ opioid agonism

- **Acute effects:**
  - analgesia; euphoria (depends on route of administration); nausea, constipation, sedation, dizziness;
  - respiratory depression; pruritis, constipation, hypotension

- **Tolerance Development:**
  - rapid for euphoria; also (but slower) tolerance to sedative, analgesic, resp. depressant, nausea s/e
  - dose escalation to injectable/smoked opioids; less with oral/long t$\frac{1}{2}$ drugs

- **Dependence:**
  - differentiate physical dependence (e.g. in patients with cancer pain) vs. full dependence syndrome in opioid addicts
  - cancer patients will tolerate slow down-titration and stopping of opioids without desire to reinstate drug use
Opioids (2)

- **Withdrawal:**
  - unpleasant but not life threatening
  - time course depends on opioid (5-10 days/heroin; 2-3wks/methadone)
  - early withdrawal: drug craving; restlessness, irritability; hyperalgesia; GI symptoms (nausea, vomiting, diarrhea, cramps); myalgia; dysphoria, anxiety, insomnia; autonomic overactivity (tachycardia, sweating, dilated pupils), yawning
  - late withdrawal: anxiety, insomnia, craving, cyclical weight changes

- **Withdrawal treatment options:**
  - nothing (cold turkey)
  - managed detox required if further drug treatment is planned

- **(1) Withdrawal to abstinence or prior to antagonist Rx:**
  - clonidine (α2-agonist 0.15mg BID - effective against autonomic symptoms) plus loperamide (peripheral opioid agonist - effective against GI symptoms)
  - no effects on myalgia or craving symptoms
  - clonidine may produce hypotension
Hallucinogens (1)

Indoleamines: LSD, DMT, psilocybin, mescaline

- **Pharmacology:**
  - $5HT_{2A}$ receptor agonism (correlates with hallucinatory potency)
  - Interactions with other 5HT receptor subtypes (questionable significance)

- **Acute effects:**
  - Highly variable; changes in mood, perception, and thought; secondary autonomic changes; trips may last from 4-12 hours

- **Tolerance Development:**
  - Frequent repeated use is uncommon - tolerance is rare
  - Tolerance to behavioral effects occurs after 3-4 daily doses

- **Dependence:**
  - May not occur

- **Treatment:**
  - Talking down; benzodiazepines (e.g. diazepam 20mg) effective; antipsychotics may intensify hallucinatory symptoms
Hallucinogens (2)

Phenethylamines: MDA, MDMA (Ecstasy), etc...

- **Pharmacology:**
  - $5HT_{2A}$ receptor agonism plus DA release; chronic use may damage 5HT neurons

- **Acute effects:**
  - changes in mood, perception, and thought; euphoria; dose-dependent autonomic effects (e.g. tachycardia, dry mouth, jaw clenching; hyperthermia)

- **Tolerance Development:**
  - to positive/euphoric effects, but not to negative effects

- **Dependence**
  - some cases reported but probably rare; behavioral changes (impulsivity, memory impairment) after chronic use; no withdrawal syndrome described

- **Treatment**
  - may not be required; symptomatic if needed (e.g. BDZs for agitation)
  - hyperthermia (5HT syndrome) is a medical emergency and requires inpatient supportive care
Hallucinogens (3)

NMDA antagonists: phencyclidine (PCP), ketamine

- **Pharmacology:**
  - Antagonist at NMDA-type glutamate receptors

- **Acute effects:**
  - Emotional withdrawal; concrete thinking; hallucinations; hostile/aggressive behavior; (higher doses) anesthesia; coma; rhabdomyolysis; hyperthermia

- **Tolerance Development:**
  - Seen in animals; not known if this occurs in man

- **Dependence**
  - Not known if this occurs; possible withdrawal syndrome (tremor, sleepiness, diarrhea, bruxism) seen in monkeys

- **Treatment**
  - Agitation/psychosis: diazepam; avoid anticholinergic antipsychotics
  - Overdose: need life support (no specific antidote) - coma may last 7-10 days
Hallucinogens (4)

Kappa-opioid agonists (Salvinorin A, cyclazocine)

- **Pharmacology:**
  - Agonist at kappa opioid receptors

- **Acute effects:**
  - Intense hallucinations/perceptual distortions; analgesia; sedation; feelings of unreality; depersonalization

- **Tolerance Development:**
  - not known

- **Dependence**
  - not known

- **Treatment**
  - None established (?naloxone/naltrexone – nonspecific opioid antagonists)
Cannabinoids (1)

Multiple natural cannabinoids in marijuana (e.g. Δ-9THC, others)

- **Pharmacology:**
  - agonists at CB1/CB2 receptors
  - CB1: G-protein-coupled receptors; high density in Cx and hippocampus; mainly expressed on GABA interneurons which express CCK (modulatory). Endogenous ligand - anandamide
  - CB1 associated with psychological and performance effects (CB2 - immune modulation)
  - very lipophilic - slow (weeks) excretion from fatty depots

- **Acute effects:**
  - (dependent on dose and prior experience) - “high”; mellowing out; impaired psychomotor performance, memory, time perception; dizziness; hunger; anxiety reactions; ?analgesia

- **Tolerance Development:**
  - seen after 3-4 doses; disappears rapidly upon abstinence
Cannabinoids (2)

• **Dependence**
  - no clear dependence syndrome identified in man (may be due to very slow elimination of THC)
  - withdrawal syndrome (restlessness, irritability, insomnia) seen after abstinence in daily heavy users
  - CB1 antagonists can precipitate w/d in animals dosed chronically with THC

• **Treatment**
  - none identified or relevant for dependence or withdrawal
  - BDZs symptomatically for acute anxiety reaction
  - Rimonabant theoretically would antagonize intoxication – could induce withdrawal in dependent tolerant subjects