PSYC1022: The Psychology of Addiction

Topic 7: Withdrawal & Tolerance (I)

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Outline:

- Diagnostic Definition (DSM-5)
- Tolerance:
  - Receptor desensitisation & down-regulation
  - Behavioural tolerance
- Withdrawal:
  - Alcohol
  - Stimulants: Cocaine & Methamphetamine
  - Opiates
  - Cannabis
  - Nicotine

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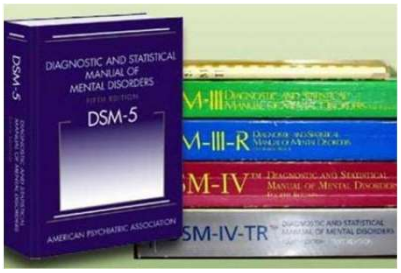
Diagnostic Definition

Diagnostic & Statistical Manual of Mental Disorders 5th Edition (APA, 2013)

- Handbook for the standardisation of psychiatric diagnosis & classification
- Treatment providers/researchers use to identify individuals who cross the boundary (from 'normality') to be diagnosed with a particular mental disorder

- Substance Use Disorder:
  - Alcohol, sedatives, cannabis, stimulants, tobacco, hallucinogens, opioids



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Diagnostic Definition

DSM-5 (2013) 11 symptoms of substance use (generally):

NB: Severity ranges from mild (2-3 symptoms) to severe (6 or more symptoms)

1. Substance is often taken in larger amounts or over a longer period than was intended
2. Persistent desire or unsuccessful efforts to cut down or control substance use
3. Significant time spent trying to obtain the substance, or recovering from its effects
4. Craving, or a strong desire/urge to use the substance
5. Recurrent substance use resulting in a failure to fulfil major role obligations
6. Continued substance use despite recurrent social or interpersonal problems caused or related to the substance
7. Important social, occupational, or recreational activities are given up or reduced because of substance use
8. Recurrent substance use in situations in which it is physically hazardous
9. Continuing substance use despite knowledge that it is likely to cause or exacerbate a physical or psychological problem
10. **Tolerance:**
    i. A need to increase substance dose to achieve intoxication or desired effect
    ii. A diminished effect with the same amount of the substance
11. **Withdrawal:**
    i. Having experienced the characteristic withdrawal syndrome for the substance
    ii. The substance (or a related substance) is taken to relieve or avoid withdrawal symptoms

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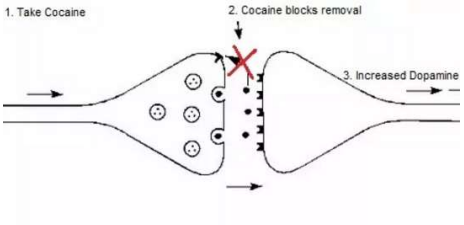
Tolerance: Receptor desensitisation & down-regulation

To remain healthy neurons need to fire with a certain frequency. Too frequent/infrequent firing can result in neurotoxicity. Cellular mechanisms exist to modify various states to balance firing rate/synaptic communication within optimal limits.

Drugs of abuse cause super-optimal states of synaptic communication which can lead to cell death

- if the drug acts on inhibitory receptors, the cell will under-fire
- if the drug acts on excitatory receptors, the cell will over-fire



Quora, 2013

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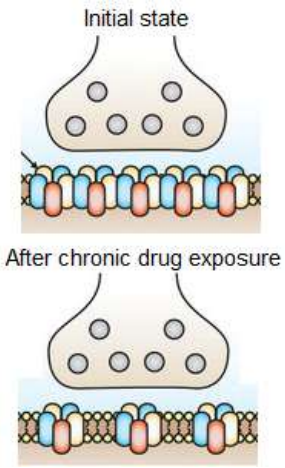
Tolerance: Receptor desensitization & down-regulation

Two mechanisms neurons employ to protect themselves from super-optimal receptor binding resulting from chronic drug exposure are:

- **Desensitisation:** the number of receptors on the cell membrane remains constant but the associated ion channels become insensitive such that binding to the receptor has no impact on the excitation or inhibition of the cell.
- **Down-regulation:** is where there is a decrease in the number of receptors such that neurotransmitter release or drug presence has less effect on the excitation or inhibition of the cell.



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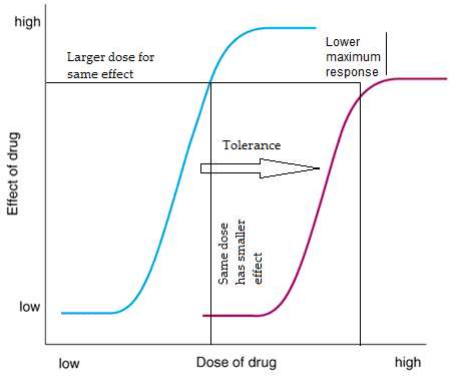
Behavioural Tolerance

As a result of desensitization & down-regulation there is a reduction in the response to the drug

- Tolerance is represented as a shift to the right in the dose-response curve
  - A larger dose is required to achieve the same effect
  - The same dose yields a smaller effect
  - Lower maximum response to the drug because the upper limit of the cells firing rate is capped by desensitization & down-regulation.



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Withdrawal

Receptor desensitization & down-regulation occur to optimize the level of binding when a drug is chronically present

- As a consequence, abstinence from the drug will result in the opposite problem: supra-optimal (low) level of binding
- Supra-optimal binding will occur in the same neurotransmitter systems to which the drug binds
- Thus, withdrawal will produce the *opposite* responses to acute drug administration.

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Withdrawal: Alcohol

Alcohol acts upon various neurotransmitter systems, to collectively produce a broad state of relaxation & euphoria.
By contrast, the adaptation to chronic alcohol exposure shows the opposite psychological effects, over-excitation & dysphoria.

Neurotransmitter	Acute cellular effects	Chronic cellular effects	Behavioral effects
Glutamate	Receptor antagonism and reduces release	——	Memory loss
	——	Up-regulation of receptors and rebound increase in release	Rebound hyperexcitability of the abstinence syndrome
	——	Extreme hyperexcitability and massive Ca^{2+} influx (rebound)	Brain damage
GABA	Acutely enhances GABA-induced Cl^- influx to hyperpolarize	——	Sedative effects: anxiety reduction, sedation, incoordination, memory impairment
	——	Neuroadaptive decrease in GABA function without change in receptor number	Tolerance and signs of hyperexcitability during withdrawal (seizures, tremors)
Dopamine	Acute increase in transmission in mesolimbic tract	——	Reinforcement
	——	Chronic effects show reduced firing rate, release, metabolism	Negative affect as a sign of withdrawal
Opioids	Acute increase in endogenous opioid synthesis and release	——	Reinforcement
	——	Neuroadaptive decrease in endorphin levels	Dysphoria

PSYCHOPHARMACOLOGY, Table 9.3 © 2005 Sinauer Associates, Inc.

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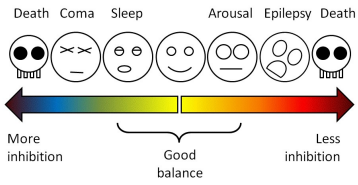
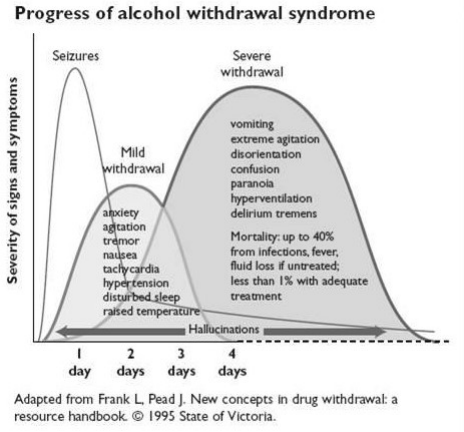
Withdrawal: Alcohol

The over-excitation of brain activity resulting from decreased GABA (less inhibition) & increased glutamate (more excitation) following alcohol withdrawal can be life-threatening & neurotoxic in its own right, so treatments for alcohol dependence are increasingly using self-paced alcohol reduction programs to negate these harms prior to full abstinence (Craig et al.).

Excitation / Inhibition balance





Adapted from Frank L, Pead J. New concepts in drug withdrawal: a resource handbook. © 1995 State of Victoria.

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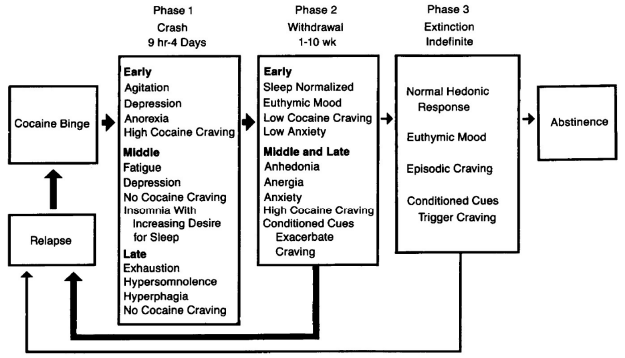
Withdrawal: Stimulants

Stimulants increase the activity of DA (reward) & 5-HT (positive mood) producing a state of motivation, euphoria & confidence. Accordingly, the withdrawal syndrome is marked by a loss of motivation, depression & anxiety.



Gawin (1986)

Duration and intensity of symptoms vary based on binge characteristics and diagnosis. Binges range from under four hours duration to six or more days. High cocaine craving early in phase 1 continues for up to 20 hours, but usually lasts less than six, and is followed by period of noncraving with similar duration in next subphase (middle-phase 1). Substantial craving then returns only after lag of up to five or more days, during phase 2. (See text for details and time course of other symptoms.)

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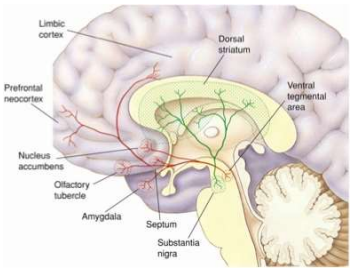
Withdrawal: Stimulants

Given that stimulants activate mesolimbic DA neurons, withdrawal should be characterized by a decrease in activity in these cells.

- Ackerman & White (1992): recorded the number of DA cells within the VTA that were spontaneously active during the recording period
- Compared rats that had been withdrawn for 10-14 days following 2 weeks of repeated treatment with either cocaine or saline.
- the number of cells found to be active was reduced by 49% in the cocaine withdrawn rats.
- Reduced DA activity thought to contribute to cocaine withdrawal syndrome, in particular, the loss of motivation.



	Cells/track
Saline	1.39
Cocaine	0.81

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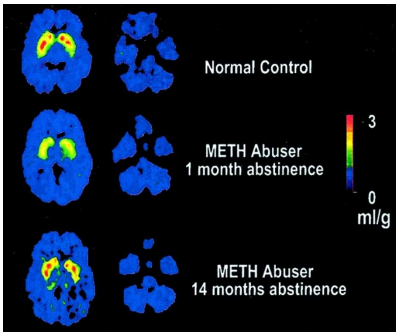
Withdrawal: Stimulants

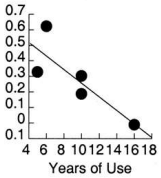
In humans, withdrawal from meth is similarly marked by a loss of DA activity in the mesolimbic pathway.

Volkow et al. (2001): meth users underwent brain imaging following 1 and 14 months abstinence.

- compared to normal controls, meth abusers showed reduced DA activity (red colour) at one month abstinence, but showed some recovery by 14 months abstinence.
- Note, the level of recovery was less in meth abusers with a longer history of meth abuse, suggesting a persistent desensitization or down regulation of DA receptors with longer drug use.



Recovery of striatal dopamine activity from 1 to 14 months abstinence



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Withdrawal: Opiates

Opiates primarily act on the endorphin & DA systems, to produce analgesia, euphoria & reward.

The withdrawal syndrome is correspondingly characterised by pain, dysphoria & loss of motivation.

Acute action	Withdrawal sign
Analgesia	Pain and irritability
Respiratory depression	Panting and yawning
Euphoria	Dysphoria and depression
Relaxation and sleep	Restlessness and insomnia
Tranquilization	Fearfulness and hostility
Decreased blood pressure	Increased blood pressure
Constipation	Diarrhea
Pupil constriction	Pupil dilation
Hypothermia	Hyperthermia
Drying of secretions	Tearing, runny nose
Reduced sex drive	Spontaneous ejaculation
Flushed and warm skin	Chilliness and "gooseflesh"

PSYCHOPHARMACOLOGY, Table 10.2

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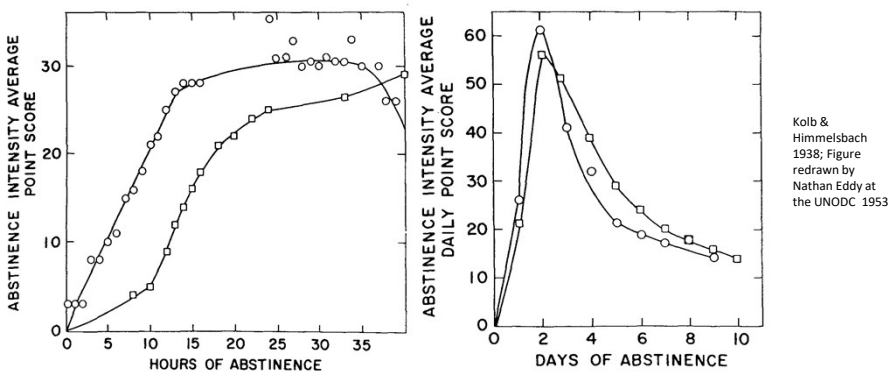
Withdrawal: Opiates

Opiate withdrawal increases rapidly following abstinence peaking around Day 2 & then declines. But withdrawal is not fully abated by 10 days post-abstinence.

- Some have suggested that negative mood or depression is a permanent, or very persistent, psychological condition of ex-opiate addicts, presumably resulting from irreversible desensitization or down-regulation of opioid &/or DA receptors (Koob & Le Moal 2001).



Kolb & Himmelsbach 1938; Figure redrawn by Nathan Eddy at the UNODC 1953

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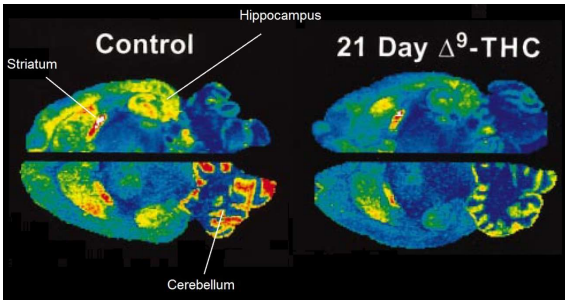
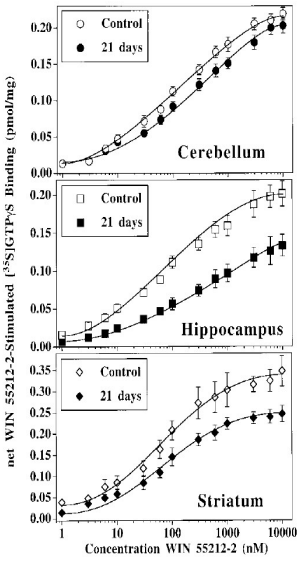
Withdrawal: Cannabis

Breivogel et al. (1999): pretreated rats with THC for 21 days. Found desensitization & down-regulation of CB1 in the cerebellum, hippocampus & striatum.

- Note the S shaped function relating dose of the drug to the amount of receptor binding is both shifted to the right & has a lower maximum (tolerance).





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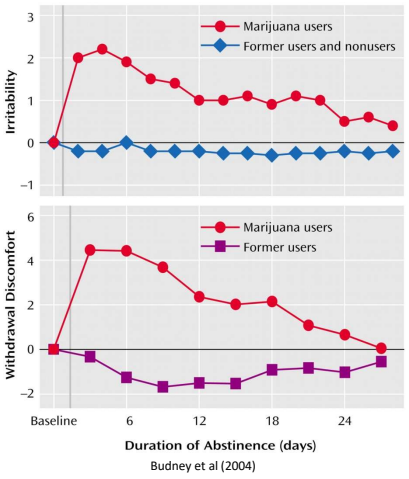
Withdrawal: Cannabis

Endocannabinoid system involved in retrograde inhibition of neurotransmission, damping synaptic communication broadly across the brain and creating a sense of calm.

- Withdrawal is marked by anger, anxiety & sleep disturbance.
- In heavy marijuana users, withdrawal symptoms last around 27 days, peaking at 1 week after abstinence

Common symptoms
Anger or aggression
Decreased appetite or weight loss
Irritability
Nervousness/anxiety
Restlessness
Sleep difficulties, including strange dreams
Less common symptoms/equivocal symptoms
Chills
Depressed mood
Stomach pain
Shakiness
Sweating



Budney et al (2004)

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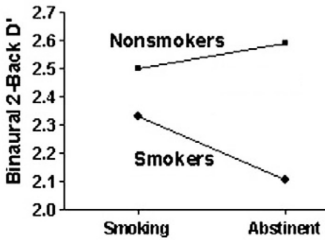
Withdrawal: Nicotine

Nicotine primarily acts upon Ach receptors (cognitive enhancement) & DA (reward).

- Nicotine withdrawal syndrome is characterised by impaired cognition, depression & anxiety

Jacobsen et al. (2005): compared smokers & non-smokers performance on a "2-back task" (assesses sustained attention & memory).

- Smokers performed worse than non-smokers (consistent with a pre-existing cognitive impairment or toxic damage)
- Importantly, abstinence increased this cognitive impairment in smokers, suggesting that nicotine withdrawal is characterised by a cognitive deficit, compared to the acute cognitive enhancing effects of nicotine.



Jacobsen et al. (2005)

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