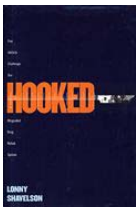
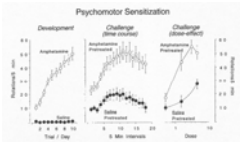


Tolerance and Dependence



Drug Tolerance is a decrease in the effect of a drug as a consequence of repeated exposure.

- Change over *repeated exposures*.
- Different effects may show different tolerance.
- Tolerance is reversible.

Mechanisms of Tolerance

- Pharmacokinetic Tolerance
  - Enzyme Induction Effects.
- Pharmacodynamic Tolerance
  - NT depletion
  - Receptor Plasticity

Receptor Plasticity and Tolerance

- Drugs that are NT *agonists* can cause receptor *downregulation*.
- Drugs that are NT *antagonists* can cause receptor *upregulation*.

Pharmacodynamic drug tolerance can also affect "normal" synaptic transmission.

- Serious side-effect of drug use.

Mechanisms of tolerance continued…

Learned Tolerance - Learned behaviors compensate for drug effects.

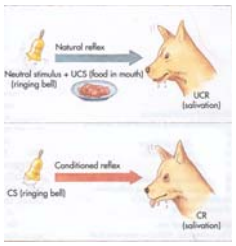
- Practice effects.
- Reward and punishment.

Context-Specific Tolerance

- Stimuli in the environment (context) become able to counteract the effects of a drug.

Pavlovian Conditioning

- A neutral stimulus paired with a biologically relevant stimulus becomes able to elicit a response.



Siegel et al. (1982) - Demonstrated that drug tolerance can be conditioned.

Group Control

15 injections of saline in distinctive room.

High dose of heroin in distinctive room on Day 16.

- Results: 96% died of overdose.

Group Same

15 injections of heroin in distinctive room.

High dose of heroin in distinctive room on Day 16.

- Results: 32% died of overdose.

Group Different

15 injections of heroin in distinctive room.

High dose of heroin in *new room* on Day 16.

- Results: 64% died of overdose.

Siegel's Theory:

- When an environment consistently *predicts* drug administration...
- … the environment begins to elicit a "compensatory" response that is opposite to the drug's effect.
- The compensatory response counteracts the drug's effect.

Siegel's theory predicts:

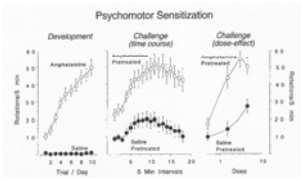
- Craving, withdrawal, and relapse.
  - "Drug environments" trigger compensatory response
  - Compensatory responses are aversive.
- Accidental overdose.

Other issues of tolerance.

- Acute tolerance
- Cross tolerance
  - Example: Cross tolerance between alcohol and valium.
- Cross tolerance can be due to
  ...pharmacokinetic,
  …pharmacodynamic,
  …or learned tolerance.

Reverse Tolerance (sensitization)

- The drug becomes more effective with repeated doses.
- E.g., marijuana, stimulant psychomotor effects, drug-induced liver disease.
- Could be due to:
  - Learning
  - Pharmacokinetics
  - Pharmacodynamics



From Anagnostaras & Robinson (1996)

Drug Dependence

- As a consequence of previous use, the individual must continue to use the drug to avoid adverse consequences.

Two types of dependence.

- Physical Dependence
  - Presence of an abstinence syndrome (withdrawal).
  - Physical symptoms relieved by drug administration.

What causes withdrawal?

Opiate administration	**Opiate Withdrawal**
Analgesia	Hyperalgesia
Euphoria	Depression
Hypothermia	Hyperthermia
Decreased BP	Increased BP
Sexual Dysfunction	Spontaneous Orgasm
Constipation	Diarrhea

Withdrawal symptoms tend to be *the opposite* of drug effects.

Homeostatic Model of Drug Withdrawal.

- Homeostasis - systems of the body keep the internal environment in an optimal state.
- Drugs interfere with normal homeostasis.
- Over time, the body adjusts to the presence of the drug and homeostasis is restored.
- When the drug is removed, homeostasis is once again disrupted.

Two types of dependence continued...

Psychological Dependence

- Strong compulsion/desire to use the drug for reasons other than to eliminate withdrawal.
  - Craving
  - Drug Seeking Behavior
  - Inability to terminate drug use.
  - Use of drug despite negative consequences.
- **Physical and psychological dependence often occur simultaneously.**

Is psychological dependence less important than physical dependence?

- Absolutely not.
- Most relapse occurs *after* physical withdrawal has terminated.

Drug Addiction - The inability to discontinue use of a drug.

Theories of Addiction

- Physical dependence model – Withdrawal symptoms serve as negative reinforcers.
  - Problems:
    - Not all psychoactive drugs support withdrawal.
    - Is the individual "cured" once withdrawal has terminated?

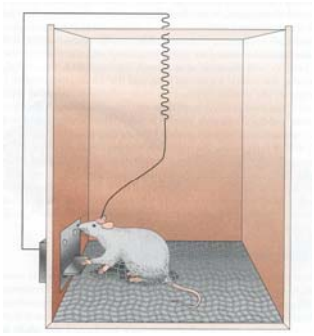
Theories of Addiction continued...

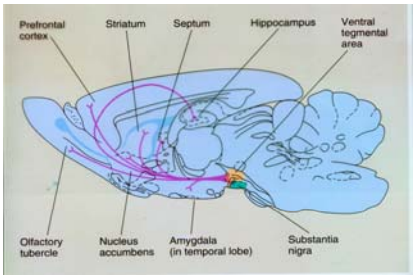
Positive Reinforcement Model

- Addiction occurs because the drug stimulates "reward centers" of the brain.
- Positive reinforcement - A behavior followed by a pleasant outcome will become more common.

Evidence for positive reinforcement model

- Drugs can serve as positive reinforcers.
  - Drug Self-Administration Paradigm
- Stimulation of "reward centers" in the brain is reinforcing.





- Nucleus Accumbens - A natural reward center in the brain.
  - Activated by dopamine.

Evidence for positive reinforcement ctd...

- Addictive drugs affect dopamine transmission in the Nucleus Accumbens.
- Lesions of Nucleus Accumbens eliminate drug self-administration of stimulants.
- Drug addictiveness seems to follow rules of effective reinforcers.
  - Saliency and Immediacy.
  - What about negative consequences?
- Social factors might also act to reinforce addictive behavior.

Problems with positive reinforcement model:

- DA seems to mediate attention not pleasure.
- Addiction without pleasure?

Incentive-Sensitization Theory of Addiction (Robinson and Berridge, 1993)

- The acts of *liking* and *wanting* a drug are different.
- Addiction occurs due to sensitization of *wanting* pathway.
  - Drug-related cues trigger *wanting* by being paired with hedonic drug effects.

Diagnosis of Substance Abuse/Dependence

- DSM IV TR

Diagnosis of *Substance Abuse Disorder*.

- At least one of the following in the last 12 months:
  - Substance related failure to meet major role obligations.
  - Substance related physically hazardous behavior.
  - Substance related legal problems.
  - Continued substance use despite negative consequences.

Diagnosis of *Substance Dependence Disorder*.

- At least 3 of the following in the last 12 months:
  - Tolerance
  - Withdrawal
  - Substance taken more/longer than intended.
  - Desire to quit or unable to quit.
  - Substance use eliminates/reduces other important activities.
  - Substance used despite negative consequences.

Approaches to treat addiction.

Stages of Treatment

- Stage 1: Detoxification
  - Elimination of drug from the body.
  - Management of physical withdrawal.
  - Medical treatment might be necessary.

Stage II: Active Treatment

- Treatment Settings:
  - Residential versus Out-Patient
- Treatment Goals:
  - Abstinence versus Controlled use.
- Treatment for comorbid disorders.

Treatment Approaches

Psychotherapy

- Group therapy (structured and unstructured).
- Behavioral Therapy
- Cognitive- Behavioral Therapy

Pharmacotherapy

- To reduce impact of withdrawal.
- To reduce likelihood of relapse.

Stage III: Aftercare

- Long-term support against relapse.
  - Options:
    - Self-help Groups
    - Psychotherapy

Does treatment work?

- About 1/3 to 2/3 of clients have positive outcomes….

…improvement rates in untreated clients are about half as high.

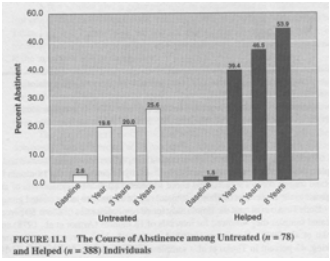


FIGURE 11.1 The Course of Abstinence among Untreated (n = 78) and Helped (n = 388) Individuals

Timko et al. (2000)