Drugs, Addiction and Reward
Chapter 5
Psychoactive Drugs
Addiction
The Role of Genes in Addiction
Drugs, Addiction, and Reward

Figure 5.1: Honore de Balzac died of heart attack after abusing coffee

• A **drug** is any substance that changes the body or its functioning.
  • **Agonists** mimics or enhances a neurotransmitter.
  • **Antagonists** may reduce release of neurotransmitter or block receptors.
• **Psychoactive** drugs are those that have psychological effects, such as anxiety relief or hallucinations.
Psychoactive Drugs

Terms

- **Addiction** is identified by:
  - preoccupation with obtaining a drug;
  - compulsive use of the drug in spite of adverse consequences;
  - a high tendency to relapse after quitting.

- **Withdrawal**
  - negative reaction that occurs when drug use is stopped.
  - often include effects opposite of the drug itself

- **Tolerance**:
  - Person becomes less responsive to the drug, requiring increasing amounts of the drug to produce the same results
  - killed about ½ of heroin users in a long term study, and is a significant reason for overdose.
Psychoactive Drugs
An Overview

• Opiates
  • **Analgesic**: pain relief;
  • **Hypnotic**: sleep-inducing;
  • **Euphoria**: strong feelings of happiness.

• Depressants
  • **Sedation**: calming, reduces agitation and irritability
  • **Anxiolytic**: anxiety reduction
  • **Hypnotic**: sleep inducing

• Stimulants
  • Increased arousal and alertness
  • **Euphoria**

• Psychedelics
  • Perceptual distortions and hallucinations

• Marijuana
  • Temporary memory, cognitive, and IQ deficits;
  • Impaired prefrontal functioning.
Psychoactive Drugs

Opiates. Figure 5.2: Opiates are derived from the opium poppy

- Opiates have high abuse potential, since they mimic endogenous opioids (natural painkillers or analgesics called endorphins)

- Examples
  - Morphine
  - Heroin was synthesized from morphine
  - Oxycontin is a synthetic opiate, called an opioid

- Examples in Fiction
  - Wizard of Oz field of poppies
  - Game of Thrones’ “Milk of the Poppy”
Psychoactive Drugs
Opiates: The Dangers of Heroin

- **Heroin** is particularly dangerous because:
  - it produces intense euphoria
  - it crosses the blood brain barrier
  - tolerance develops rapidly, increasing the chance of overdose.

- Conditioned or learned **tolerance** also is a problem.
  - A learned association develops between tolerance and the environment in which it develops.
  - When a drug is taken in a different setting, it is more likely to result in an overdose.

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Psychoactive Drugs
Opiates and Endorphins

• **Endorphins**
  • produce pain relief by stimulating these opioid receptors
  • and produce additional positive effects by indirectly stimulating dopamine pathways.
Psychoactive Drugs
Depressants

- **Depressants** are drugs that reduce nervous system activity.
  - **Sedation:** calming, reduces agitation and irritability
  - **Anxiolytic:** anxiety reduction
  - **Hypnotic:** sleep inducing

- **Alcohol**, or ethanol, is the most commonly used and abused depressant.
  - It has been used throughout history as a part of cultural and social practices.
  - However, controlled group drinking has been replaced by uncontrolled individual consumption.
  - It is involved in 1/3 of all U.S. traffic fatalities.
Alcohol has many effects on behavior.
- It can act as a **stimulant** by turning off cortical inhibition, reducing social constraints and anxiety.
- At higher doses alcohol produces **sedative** and **hypnotic** effects.
- In the U.S. and Canada a person is considered too impaired to drive at a blood alcohol concentration of 0.08%.

Alcohol has negative effects on health.
- Acute effects include alcohol-induced coma or death.
- In some users it increases tendencies toward aggressiveness.
- Chronic effects include liver damage and brain damage associated with Korsakoff’s syndrome.

Withdrawal is dangerous, and may produce a condition known as **delirium tremens**—hallucinations, delusions, confusion, and, in extreme cases, seizures and possible death.
Psychoactive Drugs
Depressants: Figure 5.3: An Alcoholic Brain vs. A Normal Brain
Psychoactive Drugs
Depressants: Figure 5.4: Alcohol’s effect on neurotransmitter systems

• Inhibits glutamate (excitatory transmitter).
• Acts at the alcohol part of the GABA_A receptor complex (inhibitory effects)
• The combined effect is sedation, anxiolytic, muscle relaxation, and inhibition of cognitive and motor skills.
  • Alcohol’s pleasurable effects likely due to stimulation of opiate, serotonin, and cannabinoid receptors.
Psychoactive Drugs
Depressants: Figure 5.4: Barbiturates and Benzodiazepines

- **Barbiturates**
  - Once the drug of choice for treating anxiety and insomnia.
  - At prescribed doses they are not addictive, but tolerance may lead to increased consumption, which leads to addiction and possible overdoses.
  - They can open chloride channels without GABA.

- **Benzodiazepines** are safer drugs for treating anxiety.
  - Effects due to decreased activity in a variety of systems, which are due to the enhancement of GABA activity.
  - Rohypnol has a reputation as a date rape drug.
Psychoactive Drugs

Stimulants: Figure 5.6: Advertisement for Cocaine from Around 1900

- **Stimulants** activate the central nervous system to produce arousal, increased alertness, relieves fatigue, decreased appetite, & elevated mood.
- **Cocaine:** Extracted from the coca plant,
  - Blocks dopamine & serotonin reuptake
  - Dopamine removes inhibition on lower structures

SOURCE: The National Library of Medicine
Psychoactive Drugs
Figure 5.7: A Normal Brain and a Brain on Cocaine.

- Cocaine was believed to be safe, and was found in over-the-counter medications and even in Coca Cola.
  - Freud initially praised the effects of cocaine, but reversed his opinion when he noted its dangers.
- Users have deficits in executive functions that involve the pre-frontal cortex.
- Addictive due to intense euphoria and craving during abstinence.
- Difficult to treat because many users have psychological disorders... and
- Also difficult to treat because users often abuse other drugs.

Psychoactive Drugs

• **Amphetamines** are a group of synthetic drugs that produce euphoria and increase confidence and concentration.
  • Examples include Benzedrine, Dexadrine, and methamphetamine.
  • Amphetamines increase the release of norepinephrine and dopamine.
  • Heavy use can cause symptoms that resemble schizophrenia.
  • Amphetamines have been used in weight-loss drugs, to postpone sleep, and to treat narcolepsy (a disorder of excessive daytime sleepiness).
Psychoactive Drugs

• **Nicotine** is the primary psychoactive and addictive agent in tobacco.
  • It stimulates nicotinic acetylcholine receptors.
  • In the periphery, it activates muscles and may cause twitching.
  • Centrally, it produces increased alertness and faster response to stimulation.
  • Withdrawal symptoms are mild, but they contribute to a 7% increase in workplace accidents during the United Kingdom’s “No Smoking Day.”
  • Only 20% of attempts to stop are successful after two years.
Psychoactive Drugs

Smoking

• The dangers of smoking are mostly due to the compounds in tobacco smoke, not nicotine.
  • These include
    • various cancers (damages a cancer suppressing gene)
    • Buerger’s disease (constricts blood vessels)
    • Reduced birth weight

• Smoking is the primary cause of preventable death in the world.
  • 438,000 deaths annually in the U.S.
  • 4 million worldwide
  • Freud found it easier to give up cocaine than cigars.
Psychoactive Drugs
Caffeine

- **Caffeine** is the active ingredient in coffee.
  - It produces arousal, increased alertness, and decreased sleepiness.
  - It blocks receptors for the neuromodulator adenosine, increasing the release of dopamine and acetylcholine.
  - Because adenosine has sedative and depressive effects, blocking its receptors contributes to arousal.
  - Withdrawal symptoms include headaches, fatigue, anxiety, shakiness, and craving.
Psychoactive Drugs
Psychedelics (Hallucinogens)

- **Psychedelic drugs** are compounds that cause perceptual distortions.
  - Often referred to as hallucinogenic, they are most noted for producing perceptual distortions.
  - Light, color, and details are intensified.
  - Objects may change shape, sounds may evoke visual experiences, and light may produce auditory sensations.

- **Examples**
  - LSD
  - Mushrooms
  - Mescaline
  - PCP
  - Ecstasy
Psychoactive Drugs
Psychedelics (Hallucinogens)

• Ecstasy (or MDMA) is a popular drug among young people.
  • Psychomotor stimulant at low doses (releases dopamine)
  • Hallucinatory at higher doses (releases serotonin)
  • Chronic use may cause impairment in serotonin functioning
    • Cognitive deficits such as memory loss
    • In monkeys, MDMA destroys serotonergic neurons.

• Phencyclidine (PCP):
  • Addictive through activating dopamine pathways
  • Inhibits glutamate receptors, causing “model psychosis,” with significant implications for theories of schizophrenia.
Psychoactive Drugs

Psychedelics (Hallucinogens). Fig 5.8: Brain Damage Induced by Ecstasy Use
Psychoactive Drugs

Figure 5.9: A Marijuana Plant

• **Marijuana**: dried leaves and flowers of *Cannabis sativa*.

• Delta-9-tetrahydrocannabinol (THC)
  • Binds to *endogenous* cannabinoid receptors.
  • Cannabinoids regulate presynaptic transmitters.

• Effects on Brain and Mind
  • Mildly addictive
  • Memory, cognitive, IQ deficits
  • Hippocampus, amygdala reductions (possible)
  • Impaired prefrontal functioning in offspring when smoked during pregnancy
Addiction

- **Addiction** and **withdrawal** are independent processes; they even occur in different parts of the brain.
  - The desire to avoid withdrawal symptoms does not fully explain addiction.
  - How does one explain initial drug use? Probably the euphoria associated with blocking dopamine reuptake.
  - Addicts will purposefully go through withdrawal in order to reset their tolerance level.
  - The addictiveness of a drug is not related to the severity of the withdrawal symptoms.
A hypothesized basis for addiction is reward.

**Reward** is the positive effect an object or condition (drug, food, sex, etc.) has on the user.

The **mesolimbocortical dopamine system** is usually considered the major reward system.

- Major structures are the **nucleus accumbens**, **medial forebrain bundle**, and **ventral tegmental area (VTA)**.
- Virtually all abused drugs increase dopamine in the VTA.

The dopamine system is implicated in the rewarding effects of drugs, food, sex, and **electrical stimulation of the brain (ESB)**.
Addiction

Figure 5.10: The Mesolimbocortical Dopamine System
Addiction
Drug Use as a Reinforcer

- **Reward** is an incomplete explanation of addiction.
  - Over time, dopamine release to a rewarding stimulus ceases; it returns if an expected reward is omitted.
  - Researchers suggest that dopamine signals reward and errors in prediction.
  - Detecting errors in prediction is critical to learning.
  - Errors in prediction that learning theorists consider important:
    - The reward is unexpected or better than expected.
    - The reward is omitted or is worse than expected.

- Modern theory suggests that drug use is a **reinforcer**
Addiction

• Learning produces brain changes, creating lifelong addiction
  • Learning is part of the addictive process
  • Increased dendrite length and complexity in nucleus accumbens
  • Hyperactivity in areas involved in learning and emotion during craving (when presented with drug paraphernalia).

• Additional brain changes amount to pathology
  • Malformed dendrites associated with frontal dysfunction.
# Approved medications

<table>
<thead>
<tr>
<th>Drug</th>
<th>Medication</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alcoholism</strong></td>
<td>Antabuse</td>
<td>Prevents digestion of alcohol, toxic side effects increase nausea.</td>
</tr>
<tr>
<td></td>
<td>Acamprosate, Topiramate</td>
<td>Reduce craving through G Neurotransmitters</td>
</tr>
<tr>
<td><strong>Nicotine</strong></td>
<td>Gum, Patch, Electronic cigarette</td>
<td>Reduce nicotine intake</td>
</tr>
<tr>
<td></td>
<td>Buproprion</td>
<td>Block reuptake, reducing nicotine reward and withdrawal</td>
</tr>
<tr>
<td><strong>Heroin &amp; Opiates</strong></td>
<td>Naltrexone</td>
<td>Opiate antagonist</td>
</tr>
<tr>
<td></td>
<td>Methadone</td>
<td>Opiate agonist (bad)</td>
</tr>
<tr>
<td></td>
<td>Buprenorphine</td>
<td>Opiate agonist (bad)</td>
</tr>
</tbody>
</table>
Drug addiction tends to be lifelong; several strategies have been developed to prevent relapse.

- **Agonistic** treatments mimic the drug’s effects.
  - Example: Methadone for opiate addiction, the nicotine patch.
  - These replace the drug, which helps with motivation.

- **Antagonistic** treatments block drug effects.
  - Examples: Naltrexone is used for opiate and alcohol addiction; baclofen and rimonabant interfere with the dopamine pathway.
  - Antagonistic treatments don’t replace the drug, so compliance depends on the addict’s motivation to quit.
Addiction
Aversive and Anti-Drug Treatments

- **Aversive treatments** cause an unpleasant reaction when the addict uses the drug.
  - Example: Antabuse (that blocks the enzyme *aldehyde dehydrogenase* or *ALDH*) for alcohol addiction causes immediate hangover effects.
  - Treatment compliance depends on the addict’s motivation to quit.

- **Anti-drug vaccines** stimulate the immune system to make antibodies that degrade/destroy the drug.
  - Have fewer side effects than other pharmacological treatments.
  - Have longer lasting effects than other pharmacological treatments.
Addiction
Effectiveness and Acceptance of Pharmacological Treatment

• Behavioral management for heroin addiction has a 10% to 30% success rate; combined with methadone, success rises to 60-80%.
• Pharmacological treatment is controversial due to belief that recovery should involve the exercise of will and that it is wrong to give an addict another drug, such as methadone.
• Drug treatment is cost effective: Addiction costs $544 billion a year in the U.S., but every dollar invested in treatment saves $4 to $12.
# The Role of Genes in Addiction

Table 5.2: Distinguished Characteristics of Two Types of Alcoholism

<table>
<thead>
<tr>
<th>Characteristic Features</th>
<th>Type 1 <em>(or late-onset)</em></th>
<th>Type 2 <em>(or early-onset)</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of onset (years)</td>
<td>After 25</td>
<td>Before 25</td>
</tr>
<tr>
<td>Alcohol seeking</td>
<td>Infrequent</td>
<td>Frequent</td>
</tr>
<tr>
<td>Fighting/arrests while drinking</td>
<td>Infrequent</td>
<td>Frequent</td>
</tr>
<tr>
<td>Psychological Dependence</td>
<td>Frequent</td>
<td>Infrequent</td>
</tr>
<tr>
<td>Guilt and fear about dependence</td>
<td>Frequent</td>
<td>Infrequent</td>
</tr>
<tr>
<td>Novelty Seeking</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Harm avoidance</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Reward dependence</td>
<td>High</td>
<td>Low</td>
</tr>
</tbody>
</table>

Representative heritabilities for drug abuse

- Alcoholism: 50-60%
- Hallucinogens: 50%
- Cocaine: 72%
The Role of Genes in Addiction

• Genes that contribute to addiction generally
  • are involved with neurotransmitter systems or affect how the individual responds to the drug.
  • Many addicts have reduced numbers of dopamine receptors.

• Knockout mice lacking either of two Homer genes, which regulate glutamate activity, are more susceptible to cocaine.

• Mice lacking the Clock gene release more dopamine in reward areas of the brain and are more vulnerable to cocaine’s effects.

• Individuals with the G allele for an opioid receptor report greater intoxication and are 3x more likely to have a history of alcoholism.
The Role of Genes in Addiction

- People who do not respond to the negative effects of alcohol, such as motor impairment, are 4x more likely to become alcoholic later.
  - The inheritable ability to eliminate aldehyde is associated with alcoholism and vulnerability to other drugs.
  - A genetic deficiency in the ability to metabolize nicotine protects some people from nicotine addiction.
- A number of genes are common to drug dependence and the personality characteristics associated with it—impulsivity, risk taking, novelty seeking, and stress responsiveness.
The Role of Genes in Addiction

• Genes involved in alcohol addiction alter the way the brain functions, as indicated by studies of EEG activity.
  • Increased high frequency EEG occurs in alcoholics and their offspring.
  • Alcoholics and their offspring also show a reduction in the normal “dip” in the P300 wave, which is a component of the evoked potential elicited by an environmental stimulus.

• These EEG abnormalities are not specific to alcoholism.
  • They often occur in disorders characterized by behavioral disinhibition, such as conduct disorder, antisocial behavior, and other types of drug abuse.
The Role of Genes in Addiction

Figure 5.17: Evoked Potentials in High & Low Risk Children
The Role of Genes in Addiction

- Addiction research has broad implications for understanding vulnerability and behavioral inheritance:
  - Behavior results from an interplay between environment and genetics.
  - These two forces operate differently in different subgroups and cultures.
  - It is not enough to assign relative roles to environment and heredity; we must then understand the mechanisms—the neurotransmitters, receptors, pathways, enzymes, and so on.
  - In addiction and all kinds of behavior we must look beyond appeals to willpower as explanation.