The Neuroscience of Addiction

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Learning Objectives

- Overview of the negative consequences of alcohol and drugs and society’s attitude
- Neurobiology of addiction
- Neurobiology of alcohol dependence
  - Neuroscience based treatments
- Neurobiology of opioid dependence
  - Neuroscience based treatments
Although they restricted themselves to one drink at lunch time, Howard and Tom still found they were not at their most productive in the afternoons.
Economic Costs of Drug Abuse

Figure 1
Overall Cost of Drug Abuse, 1992-1998
(in billions of dollars)
Scientists are discovering the chemical secret to

HOW WE GET ADDICTED

...and how we might get cured
Changing Attitudes About Addiction

- The past:
  - Addiction as a moral failing
  - Behavior to be punished
  - Treatment is predominately non-medical, not medically necessary

- The future:
  - Addiction as a chronic brain disease (similar to other medical and psychiatric disorders)
  - Support for a genetic predisposition
  - Exposure of the brain to drugs of abuse produces long-lasting and/or permanent changes in neuronal gene expression and neurotransmitters
  - Addiction treatment is integrated into the medical system

- The present: somewhere in-between
Addiction Is a Complex Disease With Genetic & Environmental Components (Like many other diseases)

- **Environmental factors:**
  - Socioeconomic status, family, peer culture, education, occupation, individual experiences, drug experiences

- **Genetic influences**
  - Risk factors
  - Protective factors
  - Resiliency factors
Etiologic Factors in Dependence

Access

Genetic Predisposition

Environment and Stressors

+ Reinforcement

– Reinforcement

Sensitization/Learning/Neuroadaptation

Abuse/Dependence

How do drugs and alcohol work?
How do drugs and alcohol work?

They mimic or block normal physiology.
Neurochemical Systems and Drugs of Abuse

- **Glutamate** Excitatory Input
- **Acetylcholine** Neuron
- **Enkephalin** Inhibitory Neuron
- **Dopamine Neuron**
  - μ Opioid Receptors
  - GABA Inhibitory Neuron
  - GABA-A Receptors
  - Presynaptic Opioid Receptors (μ, δ?)
  - GABA Inhibitory Feedback
  - Dopamine Receptors
  - GABA Neuron
  - REWARD
Neurochemical Systems and Drugs of Abuse

Glutamate – PCP, Ketamine, alcohol
GABA - sedatives, alcohol
Acetylcholine - nicotine

Dopamine – cocaine, stimulants
Enkephalin - opiates, alcohol

Acetylcholine Neuron
Enkephalin Inhibitory Neuron
GABA Inhibitory Neuron
GABA-A Receptors
Presynaptic Opioid Receptors (μ, δ?)
Dopamine Neuron
Nicotinic Receptors
μ Opioid Receptors
GABA Inhibitory Feedback

Glutamate Excitatory Input
Dopamine Neurons
GABA Neuron
REWARD

PCP, Ketamine, alcohol
GABA
Acetylcholine
Dopamine
Enkephalin
Opioid
Limbic Drive vs. Cortical Thinking Structures
Limbic Drive vs. Cortical Thinking Structures

- Decision Making: Rx = Counseling
- Drive: Rx = Pharmacotherapy
Rehabilitation Psychosocial Treatments

- Brief intervention
- Supportive counseling
- Motivational interviewing
- Cognitive-behavioral therapies
- Community reinforcement
- Desensitization (cue reactivity) therapies
- Marital/family therapy
- Self-help/12-step programs
- Inpatient/residential rehabilitation
- Therapeutic community
- Intensive outpatient
Why people use Alcohol - Reward

I feel sorry for people who don’t drink. When they wake up in the morning, that’s as good as they’re going to feel all day”.

Frank Sinatra

"God only made water, but man made wine." -- Victor Hugo

“Beer is proof that God loves us and wants us to be happy.”

Benjamin Franklin
Why people use Alcohol - Relief

“Alcohol is the anesthesia by which we endure the operation of life.”

George Bernard Shaw

“Always remember that I have taken more out of alcohol than alcohol has taken out of me.”

Winston Churchill

“I tried to drown my sorrows, but the bastards learned how to swim…”

Frieda Kahlo
Ethanol is a Drug With Complex Pharmacodynamics

- Ethanol has no single mechanism of action (ie, no one active site)
- High doses nonspecifically disrupt membrane functioning (“fluidization”)
- Low doses act on membrane proteins (receptors, transporters, etc), binding to hydrophobic pockets or displacing water
- Individuals differ in their sensitivity to alcohol effects based on genetic differences

Alcohol Affects Diverse Neurotransmitter Systems

- **Neurotransmitters and receptors**
  - Acetylcholine
  - Adenosine (A1, A2 receptors)
  - Dopamine (D1, D2, D3, D4 receptors)
  - Gamma-aminobutyric acid (GABA_A, GABA_B receptors)
  - Glutamate (NMDA, AMPA, kainate receptors)
  - Glycine
  - Norepinephrine (α, β receptors)
  - Serotonin 5-HT (several receptors, especially 5-HT_3)
  - Opioid peptides (μ, δ, κ receptors)
  - Other peptides (vasopressin, neuropeptide-Y)

- **Neurotransmitter transporters**
  - Adenosine, dopamine, 5-HT, norepinephrine

- **Voltage-gated ion channels**
  - L-type, N-type calcium channels; sodium channels

- **Second messengers**
  - G-proteins, phospholipases, protein kinases

Neuroanatomy of the Brain Reward System

Relapse and Conditioning

Repeated alcohol use causes “conditioning” to occur in brain circuits.

Brain stress response systems become dependent upon the present of drugs and alcohol. The lack of drug results anxiety, withdrawal symptoms and dysphoria (allostasis).

Drug and alcohol cues can elicit stress responses (craving) even in abstinence persons.

Prevalence of Alcohol Use

NIAAA – National Epidemiologic Survey on Alcohol and Related Conditions (NESARC)

Any Alcohol Disorder
17.6 million (8.5%)

Alcohol Abuse
9.7 million (4.7%)

Alcohol Dependence
7.9 million (3.8%)

NIAAA= National Institute on Alcohol Abuse and Alcoholism

Population Heterogeneity in Alcohol Dependence

- ~ 50% of the risk is genetic, 50% environmental
- Genetic factors both promote and protect
  - Protection: ALDH2*2, OPRM1 (118A-G), CN1
  - Promoting: GABRA2, TAS2R16
- High co-morbidity of alcoholism in certain psychiatric disorders
  - Schizophrenia, bipolar, borderline personality, panic disorder, PTSD, social phobia
Pharmacotherapy Improves Clinical Alcoholism Treatments

- Pharmacological treatments can:
  - Enhance abstinence and prevent relapse
  - Complement psychosocial interventions
- Use techniques to enhance adherence for both medications and psychosocial therapies
- Pharmacotherapies can normalize neuroadaptive changes due to chronic drug or alcohol use
<table>
<thead>
<tr>
<th>Pharmacotherapy</th>
<th>Function</th>
<th>Key Features</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Disulfiram (Antabuse®)</strong></td>
<td>Aldehyde dehydrogenase inhibitor</td>
<td>When taken with alcohol leads to nausea, dizziness, headache, flushing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Approved by FDA in 1954</td>
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<tr>
<td><strong>Naltrexone (ReVia®)</strong></td>
<td>Opioid antagonist</td>
<td>Binds to opioid receptors, thus blocking alcohol reward pathways</td>
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<td></td>
<td>Approved by FDA in 1994</td>
</tr>
<tr>
<td><strong>Acamprosate (Campral®)</strong></td>
<td>Glutamate receptor modulator</td>
<td>Helps maintain complete abstinence during post-acute withdrawal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Approved by FDA in 2004</td>
</tr>
<tr>
<td><strong>Vivitrol®</strong></td>
<td></td>
<td>Sustained-release naltrexone,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Approved by FDA in 2004</td>
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</table>
Disulfiram: Mechanism of Action

Inhibition of Aldehyde Dehydrogenase

Alcohol dehydrogenase

Ethanol → Acetaldehyde

Aldehyde dehydrogenase

Acetaldehyde → Acetate

Disulfiram

Note: Disulfiram is a pro-drug, metabolized to diethylidithiocarbamate, methyl diethylidithiocarbamate

Disulfiram Dose 250-500 mg/day
Aldehyde Dehydrogenase Inhibitors

Ethanol $\rightarrow$ Acetaldehyde $\rightarrow$ Acetate

- ALDH2*2 allele reduces risk of alcohol dependence
- Efficacy of disulfiram
  - In a 1-year double-blind study with 605 alcohol-dependent patients, disulfiram was no better than placebo for abstinence; however, older and more socially stable disulfiram-treated patients and relapsers on disulfiram drank less\(^1\)
  - In a 6-month double-blind study with 126 patients who received 200 mg disulfiram or 100 mg vitamin C under supervision, disulfiram patients had more total abstinence days, reduced weekly drinking, and lower levels of GGT compared with the vitamin C group\(^2\)
  - In a 12-week treatment study of 122 patients with combined cocaine and alcohol dependence receiving psychotherapy and either disulfiram or no medication, those receiving disulfiram were found to have better retention in treatment, as well as a longer duration of abstinence for both cocaine and alcohol use\(^3\)

GGT=gamma glutamyl transpeptidase.

Disulfiram: Safety and Tolerance

- **Adverse Events**
  - Optic neuritis, peripheral neuritis, polyneuritis
  - Multiple cases of both cholestatic and fulminant hepatitis
  - Hepatotoxicity
  - Psychosis with high doses

- **Contraindications**
  - Ischemic heart disease
  - Pregnancy

- **Drug interactions**
  - Anticoagulants
  - Phenytoin
  - Isoniazid

- Interactions with alcohol in food and OTC products
Alcohol consumption results in the release of the body’s naturally occurring opiates, endorphins.

These opiates bind to receptor sites in the brain and result in the pleasurable effects of alcohol.

Animals bred to prefer alcohol have reduced opioid peptides in their brains.

Mu-opioid receptor knockout mice do not self-administer alcohol.

Alcoholics and their family members have reduced plasma levels of beta-endorphin (an opioid peptide).

Humans with the A118G allele of the mu opioid receptor (OPRM1), which binds β-endorphin more avidly, show an increased stimulation response to intravenous ethanol.
Alcohol Increases the Activity of Endogenous Opioids (endorphins) (Effect Blocked by Naltrexone)

Adapted from Kenna et al., *Am J Health Sys Pharm* 2004;61:2272.
Naltrexone in the Treatment of Alcohol Dependence

Cumulative Relapse Rate

Cumulative Proportion With No Relapse

- Naltrexone HCL (N=35)
- Placebo (N=35)

No. of Weeks Receiving Medication

Volpicelli et al, Arch Gen Psychiatry, 1992; 49: 876-880
Naltrexone Efficacy: Meta-Analysis

Relapse to Heavy Drinking

<table>
<thead>
<tr>
<th>Study</th>
<th>Peto OR (95% CI Fixed)</th>
<th>Peto OR (95% CI Fixed)</th>
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<tbody>
<tr>
<td>Anton 1999</td>
<td>0.42 [0.21, 0.62]</td>
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<tr>
<td>Chick 2000</td>
<td>1.09 [0.59, 2.03]</td>
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<tr>
<td>Guardia 2002</td>
<td>0.39 [0.17, 0.88]</td>
<td></td>
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<tr>
<td>Heinala 2001</td>
<td>0.50 [0.19, 1.27]</td>
<td></td>
</tr>
<tr>
<td>Hersch 1998</td>
<td>1.12 [0.42, 2.98]</td>
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<tr>
<td>Kranzler 2000</td>
<td>0.94 [0.46, 1.89]</td>
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<tr>
<td>Krystal 2001</td>
<td>0.75 [0.53, 1.08]</td>
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<tr>
<td>Latt 2002</td>
<td>0.46 [0.22, 0.99]</td>
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</tr>
<tr>
<td>Monti 2001</td>
<td>0.79 [0.36, 1.72]</td>
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<tr>
<td>Morris 2001</td>
<td>0.61 [0.29, 1.30]</td>
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<tr>
<td>Oslin 1997</td>
<td>0.34 [0.09, 1.33]</td>
<td></td>
</tr>
<tr>
<td>O'Malley 1992</td>
<td>0.32 [0.15, 0.68]</td>
<td></td>
</tr>
<tr>
<td>Volpicelli 1995</td>
<td>0.38 [0.16, 0.93]</td>
<td></td>
</tr>
<tr>
<td>Volpicelli 1997</td>
<td>0.49 [0.22, 1.09]</td>
<td>0.62 [0.52, 0.75]</td>
</tr>
</tbody>
</table>

TOTAL (95% CI) 0.62 [0.52, 0.75]

Predictors of Response to Naltrexone

- Greatest benefit is derived by patients with
  - Higher levels of craving
  - Higher compliance with medication
  - Family history of alcoholism

- Family history of alcoholism
  - Associated with lower baseline plasma β-endorphin and an exaggerated response to an alcohol challenge

- The A118G allele of OPRM1
  - Associated with increased substance abuse risk, ↑β-endorphin binding and altered dopamine function. Associated with naltrexone response and EtOH stimulation

OPRM1=opioid receptor mu 1 gene.
Acamprosate Reduces Glutamate Activity

Reduction in glutamate release

Reduction in post-synaptic effects

Glutamate NMDA Receptor

mGLuR5 Receptor

Ca<sup>2+</sup>

Glutamate

Acamprosate (Campral®)
Acamprosate Efficacy: Results of a Meta-Analysis

Continuous Abstinence Rates in 17 Randomized, Placebo-Controlled Trials*

Pelc (1992)
Ladewig (1993)
Borg (1994)
Paille (1995)
Roussaux (1996)†
Sass (1996)
Whitworth (1996)
Barrias (1997)
Geerlings (1997)
Pelc (1997)†
Poldrugo (1997)
Besson (1998)
Chick (2000)
Tempesta (2000)
Gual (2001)
Kiefer (2003)†
Namkoong (2003)†
All Trials

(Relative Benefit 1.47 [95% CI: 1.29-1.69])

*Values are continuous abstinence rates at 6 months, relative benefit (RB) ratios, and their 95% confidence limits.
†Data extrapolated using LOCF.
Sustained Release Naltrexone Microspheres (VIVITROL®)

Elimination: polymer eventually metabolized and eliminated as CO₂ and H₂O

- Dean RL. *Front Biosci.* 2005;10:643-655.
- Data on File. Alkermes, Inc.
Injectable Long-Acting Naltrexone Maintains a Steady State Plasma Concentration

Not FDA approved for opioid dependence

- 380 mg IM (n=10)
- 50 mg oral (n=14)

Long-Acting Injectable Naltrexone Reduces Heavy Drinking Days

Naltrexone 380 mg vs placebo, $P=.03$; naltrexone 190 mg vs placebo, $P=.07$.

* Heavy drinking defined as $\geq 5$ drinks per day for men and $\geq 4$ drinks per day for women.

Garbutt et al., *JAMA* 2005;293:1617
Other Potential Pharmacotherapies for Alcoholism

- Ondansetron (serotonin-3 receptor antagonist)
- Topiramate (antiepileptic)
- Baclofen (Muscle relaxant)
- Dopamine antagonists (clozapine, quetiapine, aripiprazole)
- Cannabinoid (CB1) receptor antagonists
- Kudzu (traditional Chinese remedy)
- Gamma-hydroxy butyrate (GHB) (sedative)
OPIATES
Distribution of Brain Opioid Receptors
A dopaminergic pathway from the ventral tegmental area (VTA) to the nucleus accumbens (N Acc) mediates stimulatory and positive reinforcing properties of alcohol. The locus ceruleus (LC) may mediate aversive effects of opiate withdrawal. Hypothalamic (HT) structures mediate satiety.
Prevalence of Opioid Dependence

- 2.4 million Americans reported using heroin at some time in their lives, 800,010 reported current use, with 171,000 new users (NHSDA, 1997).
- Heroin snorting and smoking has become commonplace in the northeastern US.
- Synthetic narcotics such as hydromorphone, oxycodone, and meperidine have gained prominence as drugs of dependence.
Categories of Opioid Dependence

Treatment Programs

- Agonist Maintenance with Methadone, LAAM
- Partial agonist maintenance with buprenorphine
- Narcotic antagonist treatment with naltrexone
- Outpatient drug free
- Short term residential
- Long-term residential (TCs, halfway houses)
- Prisons
- Medical detoxification
- Twelve step and other self-help programs
**Opioid Substitution**

- Maintains opioid dependence, but in a harm reduction model
  - Increased opioid tolerance blocks behavioral effects of injected drugs
  - Decreases drug craving to eliminate distress of withdrawal

- Treatment is defined in the Congressional Record

- Provides behavioral counseling, vocational counseling

- Provides medical and psychiatric care
Methadone Maintenance

- Methadone is a synthetic opioid, orally active with a long half-life in the body.
- In the 1960's, Dole and Nyswander offered high-dose methadone treatment to 22 volunteer patients in a behaviorally oriented heroin-treatment program in NYC.
- Patients on methadone did better than anyone ever had done in the program—results published in the *JAMA* in 1965.
- Within 5 years, methadone maintenance clinics were commonplace.
- Has always been controversial and continues to be.
**Methadone, in adequate oral doses...**

- Lasts between 24-36 hours without euphoria, sedation, or analgesia - patients function normally without mental or physical impairment.
- Relieves narcotic craving or hunger that is believed to be a major reason for relapse.
- Establishes narcotic cross-tolerance and blockade - blocks effects of normal street doses of heroin. May require doses > 80 mg/day
- Safe medication with minimal side effects.
- Used as a lifelong therapy for some patients.
Methadone Maintenance and Criminality

Reduction in crime by years in methadone maintenance treatment.
**Buprenorphine**

- has both mu and kappa agonist and antagonist properties, high affinity for opioid receptors
- agonist properties predominate at low doses and antagonist properties predominate at high doses
- shown effective in the maintenance treatment of opiate addicts in structured treatment settings
- advantages include milder withdrawal upon discontinuation and less potential for abuse
- maintenance doses usually range from 4 mg daily to up to 16 mg daily, sublingually
Buprenorphine Binding to Brain Opiate Receptors
Partial Agonist Activity Levels

At higher doses, even when partial agonist binds all mu receptors, maximal agonist effect is never achieved.

Like full agonists, partial agonist drugs increase mu activity at lower doses.

Full Agonist (e.g. heroin)

Partial Agonist (e.g. buprenorphine)
Buprenorphine Maintenance

- A new federal law enables physicians in private practice to treat opioid dependent patients with buprenorphine maintenance.
- Physicians may treat 100 patients at one time.
- Physicians who desire to use buprenorphine must:
  1) be certified in addictions by ASAM, ABPN, or AOAAM; OR complete 8 hr of training in buprenorphine use; AND
  2) register with the Department of Health and Human Services.
Combination of Buprenorphine plus Naloxone

Sublingual buprenorphine has good bioavailability
Addition of naloxone to buprenorphine to decrease abuse potential of tablets
Combination ratio is 4 to 1 (buprenorphine to naloxone)
Buprenorphine tablet with naloxone marketed as Suboxone (2/0.5 and 8/2 mg tablets)
Buprenorphine tablet without naloxone marketed as Subutex (2 and 8 mg tablets)
Opiate Antagonist Therapy (Naltrexone)

- Naltrexone is a mu opioid antagonist – blocks the effects of morphine, heroin, etc.
- Patients require detoxification first or experience severe withdrawal
- Naltrexone is most effective in highly motivated patients (impaired professionals, probationers) and less effective in street opiate addicts.
Injectable Long-Acting Naltrexone Maintains a Steady State Plasma Concentration

Not FDA approved for opioid dependence

- 380 mg IM (n=10)
- 50 mg oral (n=14)

Addictive disorders are highly prevalent in society, are costly personally and to society.

Research has identified some of the causes of addiction and new effective treatments:

- Alcohol and drug dependence have both genetic/biological and environmental causes.
- Addictions are chronic relapsing illnesses—expect exacerbations and remissions on the road to recovery.
- Alcohol and drug dependence are treatable illnesses.
- Medications for alcoholism and drug abuse are effective treatments and work best in concert with counseling and psychosocial rehabilitation.