MEDICAL ASPECTS OF ADDICTION

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From Use to Addiction

Brief Use and Experimentation

How? Why? Who?

Addiction: A Chronic, Medical Illness

What are the medical interventions for this disease?
Overview

 Who
  • Epidemiology of Addiction
 Why
  • Genetics of Addiction
 How
  • Neurobiology of Addiction
 Medical Interventions
  • Medications for Craving & Withdrawal
Epidemiology of Addiction

- Psychiatric Diagnoses increase risk:
  - Bipolar – especially mania, esp. males
  - Antisocial personality disorder
  - Conduct Disorder
  - Untreated ADHD
  - Schizophrenia

- 2.5% of the population drinks 1/3 of the alcohol
Prevalence in General Population

Adults Ages 12 & Over

- Illicit Drug Disorders
- Alcohol Use Disorders
- Addictive Disorders
- Heart Disease
- Diabetes

NSDUH, 2010
www.cdc.gov
American Diabetes Assn, 2011
Epidemiology of Addiction

- Men 2x more likely to have addiction than women
- Adolescents: boys = girls
- Use more likely in those who are:
  - Young adults
  - Single or cohabitating
  - Unemployed
  - Dropped out of high school
  - Have family history or other mental illness
Current, Binge, & Heavy Alcohol Use, By Ethnicity

[Bar chart showing percent using in past month for different ethnicities: White, Black or African American, American Indian or Alaska Native, Asian, Two or More Races, Hispanic or Latino. Categories are Current Use (Not Binge), Binge Use (Not Heavy), Heavy Alcohol Use.]

Note: Due to low precision, estimates for Native Hawaiians or Other Pacific Islanders are not shown.
Dependence or Abuse:

Specific Illicit Drugs, Past Year, Aged 12 & Above
Nonmedical Use of Psychotherapeutics
Past Month Tobacco Use

- Cigarette Use: 35.4% (Less Than High School), 30.0% (High School Graduate), 13.1% (Some College), 25.4% (College Graduate)
- Cigar Use: 5.6% (Less Than High School), 6.0% (High School Graduate), 5.8% (Some College), 4.4% (College Graduate)
- Smokeless Tobacco Use: 2.8% (Less Than High School), 4.6% (High School Graduate), 3.8% (Some College), 2.5% (College Graduate)

NSDUH, 2009
Genetics of Addiction

Heritability

- Alcohol Dependence: 0.55
- Opioid Dependence: 0.45
- Stimulant Dependence: 0.45
- Nicotine Dependence: 0.55

Gelernter, Kranzler 2008
Genetics of Alcohol Dependence

Ethanol → Alcohol Dehydrogenase → Acetaldehyde → Acetaldehyde Dehydrogenase → Non-harmful metabolites

“Flush reaction”

Increased function

Decreased function

GABA$_A$ receptor, GABRA2: mediates anxiety & linked to alcohol dependence

µ Opioid Receptor Genes

- OPRM1 – linked to alcohol and opioid dependence
  - Polymorphism causes:
    - Binding of β endorphin to receptor site
    - Pleasure received from the intake of alcohol (??? Opioids)
    - Alcohol Consumption

Kosten 2008.
Nicotine Dependence Genetics

- Dopa Decarboxylase
  - Enzyme that helps in dopamine synthesis and serotonin biosynthesis
  - Variant in how this enzyme is produced that is linked to nicotine dependence
- Several other genes have been implicated in nicotine dependence genetics, but these studies need further replication

Gene-by-Environment

- 5-HTTLPR – polymorphism seen in the serotonin transporter gene
  - “short” 5-HTTLPR + Stressful life events = Greater risk of depression
  - “short” 5-HTTLPR + Stressful life events = Frequent/heavy drinking & non-Rx drug use

Genetics

- Cocaine Dependence
  - Group of genes of chrom 12 increasing risk of heavy cocaine use
  - Genes on chrom 9 in African Americans increases risk of cocaine-induced paranoia

- Opioid Dependence – certain genes on chrom 17 can increase or decrease risk of heavy opioid use

Stages of Addiction

- Preoccupation with obtaining
  Persistent physical/psychological problems
- Persistent desire
  Larger amounts taken than expected
- Binge Intoxication
- Tolerance
  Withdrawal
  Compromised social, occupational, or recreational activities
Binge/Intoxication: Reward Pathway and More

Clinical Picture:
- Acute Reward

Neurotransmitters:
- Dopamine
- Opioid Peptides
- GABA
- Serotonin
- Endocannabinoids

http://thebrain.mcgill.ca/flash/i_03_cr/i_03_cr_que/i_03_cr_que.html
Koob, 2008.
Neurobiology of Addiction

Drug-seeking behavior

- Basolateral amygdala
- Central nucleus of amygdala
- Bed nucleus of stria terminalis
- Nucleus accumbens
- Prefrontal cortex
- Motor cortex
- Thalamus
- Pallidum

Enkephalin (Enk)
Corticotropin-Releasing Factor (CRF)
Neuropeptide Y (NE)
Dopamine (DA)
β-Endorphin (β-End)

Binge Intoxication Stage

Koob, 2008
Withdrawal/Negative Affect

- Disrupted reward systems – decreases in reward neurotransmitters
  - Acute withdrawal
  - Negative motivational state
- Anti-reward systems – CRF & Norepinephrine
  - Emotional dysregulation – abnormal stress response
  - Craving

Koob 2008.
## Negative Motivational State

<table>
<thead>
<tr>
<th>Neurotransmitter</th>
<th>Functional Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ Dopamine</td>
<td>Dysphoria</td>
</tr>
<tr>
<td>↓ Serotonin</td>
<td>Dysphoria</td>
</tr>
<tr>
<td>↓ GABA</td>
<td>Anxiety, panic attacks</td>
</tr>
<tr>
<td>↓ Neuropeptide Y</td>
<td>Anti-stress</td>
</tr>
<tr>
<td>↑ Dynorphin</td>
<td>Dysphoria</td>
</tr>
<tr>
<td>↑ Norepinephrine</td>
<td>Stress</td>
</tr>
<tr>
<td>↑ Corticotropin-releasing factor</td>
<td>Stress</td>
</tr>
</tbody>
</table>

Koob 2008
Neurobiology of Addiction

Drug-seeking behavior

Withdrawal/Negative Affect Stage

Koob, 2008
Preoccupation/Anticipation

- Key element in relapse
- Relapse may or may not be associated with craving
- Craving type 1/ Reward – environmental cues induce drug use
- Craving type 2/ Relief – Internal anxiety & dysphoria cause drug use
Craving Type 1: Reward Craving

Ventral Pallidum/ Basal Ganglia

Medial Prefrontal Cortex

Nucleus Accumbens

Glutamate

Koob 2008
http://grants.hhp.coe.uh.edu/clayne/6397/Unit6_files/caudate_nucleusMRI.jpg
Reward Craving: Alcohol

GABA

GLUTAMATE

Adapted from Ikelheimer 2009
Reward Craving: Acute Alcohol Use

GABA + Alcohol

GLUTAMATE

Euphoria
Anxiety
Disinhibition

Adapted from Ikelheimer 2009
Reward Craving: Chronic Alcohol Use

GABA + Alcohol

GLUTAMATE
Reward Craving: Removal of Alcohol

GABA

GLUTAMATE

Adapted from Ikelheimer 2009
Craving Type 2: Relief Craving

- HPA Axis - CRF
- Norepinephrine

http://wikis.lib.ncsu.edu/index.php/HPA_axis
Relief Craving: Role of Norepinephrine

- Norepinephrine (NA):
  - Produced in LC
  - Stimulates wakefulness

Kosten & George, 2002
Park 2009
Relief Craving: Opioids

Mu Opioid Receptor → LC Neuron → NA → Wakefulness, Breathing, Alertness

Kosten & George, 2002
Park 2009
Relief Craving: Acute Opioid Use

- Opioids
- LC Neuron
- Sedation Slowed Breathing

Kosten & George, 2002
Park 2009
Relief Craving: Chronic Opioid Use

Opioids → LC Neuron → NA

Wakefulness, Breathing, Alertness

Kosten & George, 2002
Park 2009
Relief Craving: Removal of Opioids

- LC Neuron
- Wakefulness
- Breathing
- Alertness

Opioids

- Jittery
- Cramping
- Extra
- Awake

Kosten & George, 2002
Park 2009
Summary of Neurobiology

- Addiction occurs in 3 stages:
  - Binge/Intoxication – classic reward pathway
  - Withdrawal/Negative Affect – decreased reward neurotransmitters
  - Preoccupation/Anticipation – new set-point in anti-reward pathway & craving:
    - Glutamate
    - Norepinephrine
    - Stress response & CRF
Addictions Psychopharmacology

- Alcohol
- Nicotine
- Opiates
- Stimulants
Medications for Alcohol Dependence

- **Disulfiram** – classic flushing reaction from build-up of acetaldehyde; caution in certain populations
- **Naltrexone** – opioid antagonist; works best in those with strong family history
- **Acamprosate** – effects glutamate neurotransmission; ? efficacy
- **Carbamazepine & Divalproex** – acute withdrawal, irritability, & reduced heavy drinking days
- **Baclofen** – GABA$_B$ receptor agonist; increases days abstinent but also has some abuse potential

Ries, Fiellin 2009
Medications for Nicotine Dependence

- **Nicotine Replacement Therapy** – patches mainstay, supplement with gum/lozenges/inhalers; can combine with bupropion, nortriptyline, clonidine
- **Bupropion** – augments NA & DA; reduces craving; 30% quit rate
- **Varenicline** – partial nicotine agonist/antagonist; 44% quit rate; don’t combine with replacement therapy
- **Nortriptyline** – 2nd line but maybe as efficacious as bupropion
- **Clonidine** – alpha agonist; reduces withdrawal symptoms; 2nd line

Ries, Fiellin 2009
Medications for Opioid Dependence

- **Methadone** – gold-standard; long-acting mu opioid agonist; must be in methadone clinic
- **Buprenorphine** – partial mu opioid agonist & kappa opioid antagonist; combined with naltrexone (Suboxone); office-based treatment
- **Naltrexone** – opioid antagonist; reduces euphoria from opioids, precipitating withdrawal if taken with opioids
- **Clonidine** – reduces withdrawal symptoms only

Ries, Fiellin 2009
Medications for Stimulant Dependence

- **Cocaine Dependence**
  - Desipramine – mixed results; best for those with depression, antisocial
  - Disulfiram – aversion reaction to cocaine via dopamine beta hydroxylase; caution if still using cocaine
  - Anticonvulsants – Tiagabine, Topiramate
    - Block cocaine-induced kindling; small positive trials

- **Amphetamine Dependence**
  - Naltrexone – some positive studies
  - Bupropion – possibly, for those with lower levels of use
  - Risperidone (?) – reduced use in open-label trials
  - Modafinil – controversial but promising results in early trials

Ries, Fiellin 2009
Questions ?


http://thebrain.mcgill.ca/flash/i/i_03/i_03_cr/i_03_cr_que/i_03_cr_que.html

http://wikis.lib.ncsu.edu/index.php/HPA_axis

Ikelheimer D. Reward & Recovery. Lecture to Addiction Fellows. 2009


Morbidity and Mortality Weekly Report, Centers for Disease Control, 60 (40); 1377-1381, Oct 14, 2011. www.cdc.gov