The biology of addiction and its medical treatment: an overview

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October 16, 2017
Disclosure statement

I have no relevant financial interests to disclose.

I will discuss off-label use of some medications.
Learning Objectives

After participating in this activity, practitioners should be able to:

• Explain two biomedical models for addiction.

• Name three substance use disorders for which there are evidence-based pharmacologic interventions.

• Be familiar with medications most often used to treat substance use disorders.

• Know when to refer patients for pharmacologic treatment of addiction.
Outline

• Ingredients of addiction
• Neuroanatomy of the reward circuit
• Models of cognitive impairment
• Research on executive functioning in addiction
• Pharmacologic treatment for addiction
• When to refer
## Why biology?

<table>
<thead>
<tr>
<th>DRUG OF ABUSE</th>
<th>Endogenous Neurotransmitter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>GABA</td>
</tr>
<tr>
<td>Alcohol</td>
<td>Glutamate *</td>
</tr>
<tr>
<td>Amphetamines &amp; Cocaine</td>
<td>Dopamine</td>
</tr>
<tr>
<td>Benzodiazepines &amp; GHB</td>
<td>GABA</td>
</tr>
<tr>
<td>Cannabis</td>
<td>Anandamide</td>
</tr>
<tr>
<td>Hallucinogens &amp; MDMA</td>
<td>Serotonin</td>
</tr>
<tr>
<td>Nicotine</td>
<td>Acetylcholine</td>
</tr>
<tr>
<td>Opioids</td>
<td>Endorphins</td>
</tr>
<tr>
<td>Phencyclidine &amp; Ketamine</td>
<td>Glutamate *</td>
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</tbody>
</table>
The ingredients of addiction

- Tolerance
- Withdrawal
- Dependence

- And a little something more
Tolerance

• Tolerance is the need to take more of a drug to get the same effect.
What Causes Tolerance?

• The brain makes adjustments so it functions normally when the drug is present, and abnormally when it’s not.

• Think of tolerance like driving with the brakes on—you have to push harder on the gas to get up to highway speed.
downregulation
Changes in dopamine receptor density in ventral striatum and effect on relative response natural versus drug reinforcers in cocaine addiction.

Withdrawal

is what happens when the gas pedal is all the way to the floor – and you suddenly take your other foot off the brake.
Dependence

Tolerance

+ Withdrawal

Dependence

Is dependence the same as addiction?
Is dependence the same as addiction?

No.
You need something more.

Addiction: a chronic, relapsing brain disease that is characterized by compulsive drug seeking and use, despite harmful consequences.

National Institute on Drug Abuse: www.drugabuse.gov
How does addiction get started?

Dopamine increases in response to natural rewards such as food.

Intoxicating drugs cause an exaggerated dopaminergic response.

What sustains addiction?

Conditioning based on memories of intense pleasure
What sustains addiction?

• *Salience* of drugs eclipses other stimuli, including natural consequences

Salience in the healthy brain
Salience in the addicted brain
The nicotine cycle: running away from withdrawal

The reward circuit

• Prefrontal cortex: the seat of will
  ▪ Glutamate: inhibition (though excitatory NT)
• Nucleus accumbens: the seat of pleasure
  ▪ Dopamine: desire
  ▪ Serotonin: satiety and inhibition
• Ventral tegmental area: the seat of reward
  ▪ Dopamine: pleasure
• Locus coeruleus: the seat of arousal
  ▪ Norepinephrine: sympathetic response
The reward circuit

Biomedical models of addiction

• **Changed set point**

  Opioid use causes permanent structural and chemical changes that create a new biological and behavioral baseline for the addict.

Biomedical models of addiction

• **Cognitive deficits**

Opioid use degrades prefrontal cortical inhibition of the drive to use, undermining the addicted person’s will at a neurological level.

Cognitive deficit model

Domains of cognitive impairment

• Impulsiveness
  *I’m not going to think too much deciding to get high.*

• Reward hypersensitivity
  *I want to get high more than anything else.*

• Harm hyposensitivity
  *I forgot how bad it felt the last time I went to jail.*

• Increased risk-taking
  *My probation officer probably won’t find out.*

• Outcome myopia (i.e. temporal discounting)
  *My kids might get taken away, but not right now.*
IGT and abstinence in methamphetamine users

Decision-making ability on the Iowa Gambling Task (IGT) in METH abusers at different abstinence times and healthy controls over 100 card choices.

Why Can’t Addicts Just Quit?

Because Addiction Changes Brain Circuits

Joshua Sonkiss MD | Anchorage Community Mental Health Services
Adapted from Volkow et al., Neuropharmacology, 2004.
A word about detoxification

• Not a treatment—medically-assisted withdrawal
• Useful as a bridge to psychosocial or pharmacologic treatment
• Very high relapse rates when used alone
• With opioids, elevated risk of overdose death within one month of any detox protocol

Tobacco

Causes of Annual Deaths in the US

<table>
<thead>
<tr>
<th>Cause</th>
<th>Number of Deaths (thousands)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDS</td>
<td>50</td>
</tr>
<tr>
<td>Obesity</td>
<td>50</td>
</tr>
<tr>
<td>Alcohol</td>
<td>100</td>
</tr>
<tr>
<td>Motor Vehicle</td>
<td>50</td>
</tr>
<tr>
<td>Homicide</td>
<td>50</td>
</tr>
<tr>
<td>Drug Induced</td>
<td>50</td>
</tr>
<tr>
<td>Suicide</td>
<td>200</td>
</tr>
<tr>
<td>Smoking</td>
<td>450</td>
</tr>
</tbody>
</table>

Individuals with mental illness or substance use disorders

Centers for Disease Control and Prevention, NHIS, 2007.
A road map for quitting

National Cancer Institute’s 5 As

ASK
about tobacco use

ADVISE
tobacco users to quit

ASSESS
readiness to make a quit attempt

ASSIST
with the quit attempt*

ARRANGE
Follow-up care


* One way to do this is to recommend calling the Quit Line.
The Quit Line

Ready to quit?
1800 QUIT NOW / 1-800-784-8669

How does the quit line get NRT to me?

Once you enroll in the multiple-call program, NRT is mailed directly to you. You will receive the NRT one time line up to 30 days before you are ready to quit and enroll in the program to ensure you have the NRT available to use on your quit date.

How long does the quit line program last?

A typical quit line intervention schedule will be completed within two to six months.
Medications for TUD

• Nicotine Replacement Therapy (NRT)
  - Increases quit rates by 50-70% regardless of setting
  - FDA-approved, safe
  - Patch, gum, lozenge, spray
  - Quit Line
Medications for TUD

• Bupropion (Zyban)
  ▪ Increases dopamine, norepinephrine and serotonin
  ▪ Doubles 6-month quit rate compared to placebo
  ▪ Antidepressant
  ▪ FDA-approved

• Varenicline (Chantix)
  ▪ Partly blocks nicotine receptor
  ▪ More than doubles quit rate compared to placebo
  ▪ FDA-approved
  ▪ Suicide? Psychosis?

Medications for TUD

• Nortriptyline (Pamelor)
  ▪ Tricyclic (old school) antidepressant
  ▪ Not FDA-approved

• Clonidine (Minipress)
  ▪ Blood pressure medicine
  ▪ Not FDA-approved
Medications for AUD

- Disulfiram (Antabuse)
  - “The one that makes you sick when you drink”
  - Blocks aldehyde dehydrogenase
  - Ethical concerns
  - May be effective when observed
  - Rarely used
  - FDA-approved
Medications for AUD

• Acamprosate (Campral)
  ▪ Restores balance between GABA and NMDA neurotransmission
  ▪ Reduces relapse by half compared with placebo
  ▪ 666 mg three times daily
  ▪ Reduces cravings
  ▪ FDA-approved
Acamprosate

Treatment Period*

Follow-Up Period†

% of Patients Abstinent

Sass et al., *Arch Gen Psychiatry*, 1996
Medications for AUD

• Naltrexone (Revia)
  ▪ Blocks opioid receptors
  ▪ 30-40% reduction in relapse to heavy drinking
  ▪ Reduces the pleasure associated with drinking
  ▪ Reduces cravings
  ▪ Four-week injection available (Vivitrol)
  ▪ FDA-approved

Volpicelli et al., Arch Gen Psychiatry, 1992
Emerging AUD treatments (not FDA-approved)

- **Gabapentin (Neurontin)**
  - Effective for anxiety
  - Abusable
  - May be FDA-approved soon

- **Topiramate (Topamax)**
  - “Stupamax,” “Dopamax”
  - Weight loss

- **Baclofen (Gablofen, Lioresal)**
Benzodiazepines and AUD

• Benzos include clonazepam (Klonepin), lorazepam (Ativan), alprazolam (Xanax) and many others
• Important for detox
• Cross-tolerant
• Can cause relapse
• Can cause respiratory depression/arrest
Opioids

Methadone

Full agonist: generates effect

Buprenorphine

Partial agonist: generates limited effect

Naltrexone

Antagonist: blocks effect

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Full Agonist Treatment (ORT)

- Methadone
  - Spectacular results since 1965
  - Full agonist but long half-life
  - Administered only in specially licensed methadone clinics when used for addiction treatment
  - Can be used for pain treatment
  - FDA-approved
Partial Agonist Treatment (ORT)

• Buprenorphine (Suboxone, Subutex, etc.)
  ▪ Partial agonist—harder to overdose
  ▪ Prescribers need special training and DEA certificate, but in theory can be administered in any prescriber’s office.
  ▪ Can be used for pain treatment, no special training required
  ▪ FDA-approved
Advantages of ORT

• Consistent evidence to support efficacy
• Better treatment retention
• Fewer overdose deaths
• Less hospitalization
• Cost effectiveness


Disadvantages of ORT

• Potential for abuse and diversion of medication
• Lifelong treatment for many—up to 95 percent relapse when taper attempted
• Some people see ORT as “substituting one addiction for another.”

Why use ORT?

Antagonist Treatment (not ORT)

• Oral or long-acting injectable naltrexone (Vivitrol)

• Advantages:
  • Blocks high from opioids
  • Avoids stigma of ORT (doesn’t “replace one addiction with another”)
  • Appeals to policymakers who favor abstinence
  • Can’t be abused or diverted
Antagonist Treatment (not ORT)

• Disadvantages:
  
  • Oral naltrexone no better than placebo
    Minozzi S et al, Cochrane Database Syst Rev 2011
  
  • Long-acting injectable naltrexone (Vivitrol) promising, but limited evidence
  
  • High treatment dropout rates
  
  • May interfere with pain treatment
Pregnancy and OUD

• Opioid use and opioid withdrawal have adverse effects on fetus.

• Withdrawal is usually more serious (premature delivery, stillbirth).

• Therefore, abstinence-based treatment is not recommended during pregnancy for anyone who is actively using opioids.

Pregnancy and OUD

• Opioid replacement therapy is the standard of care in pregnancy.

• Medically-assisted withdrawal is not recommended.

• Neonatal abstinence syndrome is treatable and usually resolves in several weeks.
Behavioral addictions

• Sexual addictions
  ▪ SSRI antidepressants (e.g. fluoxetine have shown benefit
  ▪ Caution with stimulants, benzodiazepines, bupropion

• Gambling addiction
  ▪ Naltrexone (Revia, Vivitrol) has shown benefit
  ▪ SSRIs have shown benefit
  ▪ Caution with stimulants, some antipsychotics
Substances with little or no evidence to support pharmacologic treatment

- Sedative-hypnotics
  - Medically managed withdrawal
- Stimulants
  - Contingency management
- Cannabis and synthetic cannabinoids
  - Counseling, 12-step
- Hallucinogens
  - Not addictive
When should you refer to an addiction medicine specialist?

- When pharmacologic treatments exist for the substance your patient is using
- When psychosocial interventions alone have not been successful
- When a patient asks for a referral
- Whenever a patient has opioid use disorder
- If your patient is pregnant
Learning assessment

1. Which of the following is true about psychosocial interventions in addiction?
   a. According to recent studies, they offer little benefit for opioid use disorder.
   b. Research has shown some psychosocial interventions are worse than doing nothing.
   c. They are the cornerstone of treatment for cannabis use disorder.
   d. a and b only
   e. all of the above
Learning assessment

2. Which of the following neurotransmitters plays a central role in all addictions?
   a. GABA
   b. Norepinephrine
   c. Serotonin
   d. Dopamine
   e. Dynorphins
3. Which of the following are true about abstinence-based treatment for OUD?
   a. It increases the risk of overdose death.
   b. It should always be tried before ORT.
   c. It works for a small minority of patients.
   d. a and c only
   e. all of the above
Learning assessment

4. What is the safest treatment for pregnant women with opioid use disorder?
   a. Opioid replacement therapy
   b. Rapid detoxification
   c. Slow detoxification
   d. a and c only
   e. all of the above
Learning assessment

5. Which of the following is true about smoking cessation drugs?

a. The Quit Line offers coaching only.
b. E-cigarettes are effective for smoking cessation.
c. Varenicline (Chantix) causes suicide.
d. NRT should never be combined with varenicline (Chantix) or bupriopion (Zyban).
e. NRT increases quit rates by 50-70% regardless of psychosocial treatment.
Questions?

Photo by Sylvain Pedneault