The Neurobiology of Opioid Addiction and its Treatment

Joshua Sonkiss, MD

Chief Medical Officer, Anchorage Community Mental Health Services

January 30, 2018
Disclosure statement

I have no financial interests to disclose.

Joshua Sonkiss MD | Anchorage Community Mental Health Services
Learning Objectives

After participating in this activity, participants will:

• Know how the reward circuit functions in opioid use disorder, including major neurotransmitter systems and their associated structures.

• Be able to define tolerance, withdrawal, dependence and addiction in terms patients and families will understand.

• Be able to apply evidence-based approaches to diagnosis and treatment of opioid use disorder.
How did we get here?

National Center for Health Statistics/CDC
Models of Addiction

• Moral—weak character
• Criminal—the war on drugs
• Recovery—a personal journey
• Social—community-oriented
• Medical—addiction as disease

Scientific basis increases moving down the list.
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.


Joshua Sonkiss MD | Anchorage
Community Mental Health Services
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?
No.

Dependence means you’ll get withdrawal symptoms when you stop using a substance.

Addiction is 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?

- Exogenous opioids bind to receptors in the VTA.
- VTA sends dopamine to the Nac.
- Dopamine in the Nac causes *intense pleasure*

The reward circuit


Joshua Sonkiss MD | Anchorage Community Mental Health Services
Dopamine increases in response to natural rewards such as food.

Joshua Sonkiss MD | Anchorage
Community Mental Health Services

Intoxicating drugs cause an exaggerated dopaminergic response.

Joshua Sonkiss MD | Anchorage
Community Mental Health Services
What sustains addiction?

Conditioning based on memories of intense pleasure

Joshua Sonkiss MD | Anchorage
Community Mental Health Services
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

Joshua Sonkiss MD | Anchorage
Community Mental Health Services
Biomedical models of addiction

• Changed set point
  Drug use causes permanent structural and chemical changes that create a new biological and behavioral baseline for the addict.
Biomedical models of addiction

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


Joshua Sonkiss MD | Anchorage
Community Mental Health Services
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.
## Decision-making in opioid users

<table>
<thead>
<tr>
<th>Opiate user status</th>
<th>Study authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current Users</td>
<td>Baldacchino, Balfour and Matthews (2014)</td>
</tr>
<tr>
<td>Current Users</td>
<td>Barry and Petry (2008)</td>
</tr>
<tr>
<td>Current Users</td>
<td>Brand, Roth-Bauer, Driessen and Munkowitsch (2008)</td>
</tr>
<tr>
<td>Current Users</td>
<td>Cheng, Lu, Han, Gonzalez-Vallejo and Su (2012)</td>
</tr>
<tr>
<td>Current Users</td>
<td>Clark, Robbins, Ersche and Snhakian (2006)</td>
</tr>
<tr>
<td>Current Users</td>
<td>Ersche et al. (2005b)</td>
</tr>
<tr>
<td>Current Users</td>
<td>Khodadadi, Dezfouli, Fakhari and Ehktiari (2009)</td>
</tr>
<tr>
<td>Current Users</td>
<td>Kirby, Petry and Bickel (1999)</td>
</tr>
<tr>
<td>Current Users</td>
<td>Lemenager et al. (2011)</td>
</tr>
<tr>
<td>Current Users</td>
<td>Ma et al. (2015)</td>
</tr>
<tr>
<td>Current Users</td>
<td>Madden, Petry, Badger and Bickel (1997)</td>
</tr>
<tr>
<td>Current Users</td>
<td>Pirastu et al. (2006)</td>
</tr>
<tr>
<td>Current Users</td>
<td>Upton, Kereestes and Stout (2012)</td>
</tr>
<tr>
<td>Ex-Users</td>
<td>Ahn and Vassileva (2016)</td>
</tr>
<tr>
<td>Ex-Users</td>
<td>Li et al. (2013)</td>
</tr>
<tr>
<td>Ex-Users</td>
<td>Sun et al. (2015b)</td>
</tr>
<tr>
<td>Ex-Users</td>
<td>Verdejo-Garcia and Perez-Garcia (2007)</td>
</tr>
<tr>
<td>Ex-Users</td>
<td>Yan et al. (2014)</td>
</tr>
<tr>
<td>Ex-Users</td>
<td>Zeng et al. (2013)</td>
</tr>
<tr>
<td>Ex-Users</td>
<td>Zhang et al. (2012)</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
</tr>
</tbody>
</table>


Joshua Sonkiss MD | Anchorage
Community Mental Health Services
Why Can’t Addicts Just Quit?

Non-Addicted Brain

Control

Saliency

Drive

Memory

NO

GO

Addicted Brain

Control

Saliency

Drive

Memory

GO

Because Addiction Changes Brain Circuits

Adapted from Volkow et al., Neuropharmacology, 2004.
Treatment implications

Why is addiction treatment evaluated differently? Both require ongoing care.

**YES!!!**
Hypertension Treatment

**NO??**
Addiction Treatment


Joshua Sonkiss MD | Anchorage Community Mental Health Services
Treatment modalities

- Peer support/recovery groups (*not treatment*)
- Psychosocial treatment
  - Individual and group counseling
  - Evidence-based therapies: CBT, DBT, MI, TSF
  - Contingency management
  - Evidence not strong for OUD

A word about detoxification

• More properly called medically-assisted or medically-managed withdrawal
• Does not treat the addiction
• 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

Types of MAT

Methadone
- Full agonist: generates effect

Buprenorphine
- Partial agonist: generates limited effect

Naltrexone
- Antagonist: blocks effect

ORT ORT Not ORT

Joshua Sonkiss MD | Anchorage
Community Mental Health Services
Full agonist

Partial agonist

Antagonist
Full Agonist Treatment (ORT)

- Methadone
  - Spectacular results since 1965
  - Full agonist
  - Long half-life reduces dopamine response*
  - Long half-life increases overdose risk
  - Specially licensed clinics
  - Effective for pain

*The goal is to feel “normal.”*
Partial Agonist Treatment (ORT)

• Buprenorphine (Suboxone, Subutex, etc.)
  ▪ Partial agonist—reduces dopamine response*
  ▪ Partial agonist—harder to overdose
  ▪ Prescribers need special training and DEA certificate, but in theory can be administered in any prescriber’s office.
  ▪ Effective for pain

*The goal is to feel “normal.”
Advantages of ORT

- Consistent evidence to support efficacy
- Better treatment retention
- Fewer overdose deaths
- Less hospitalization
- Less crime
- Cost-effective ($38 benefit per $1 spent)

Psychiatr Serv. 2014 Feb 1;65(2):146-57. doi: 10.1176
Mattick R. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence.
Cochrane Database Syst Rev. 2008 Apr 16;(2).
Zarkin GA et al. Benefits and costs of methadone treatment: results from a lifetime simulation model.
Health Econ. 2005;14(11):1133–1150
Advantages of ORT

Disadvantages of ORT

- Stigma
- Potential for abuse and diversion of medication
- Lifelong treatment for many—up to 95 percent relapse when taper attempted

Antagonist Treatment (not ORT)

• Oral or long-acting injectable naltrexone (Vivitrol)

• Advantages:
  • Blocks high from opioids
  • Avoids stigma of ORT
  • 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 precipitate withdrawal
  • Blocks opioid pain treatment
OUD and Pregnancy

ORT:

• Increases retention in treatment
• Decreases illicit opioid use
• Decreases pregnancy complications
• Improves fetal outcomes

Psychiatr Serv. 2014 Feb 1;65(2):146-57. doi: 10.1176
OUD and Pregnancy

Risks of ORT

• Medication exposure, neonatal abstinence syndrome

Versus

Risks of untreated OUD

• lack of prenatal care, increased risk of fetal growth restriction, placental abruption, fetal death, preterm labor, and intrauterine passage of meconium; engagement in high-risk activities such as prostitution, trading sex for drugs, and criminal activities; exposure to STIs, violence, loss of child custody, criminal proceedings, and incarceration


Joshua Sonkiss MD | Anchorage
Community Mental Health Services
OUD and Pregnancy

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

• Medically-supervised withdrawal is not recommended.

• XR naltrexone may be appropriate for selected patients.

Pregnant and Court-Ordered to Take Vivitrol: Is My Baby Safe?

Is Vivitrol is safe to take during pregnancy? The lack of answers might shock you.
Learning assessment

1. Which of the following is true about psychotherapy for OUD?
   a. According to recent studies, it offers little benefit when combined with MAT.
   b. Research has shown some psychosocial interventions are worse than doing nothing.
   c. Psychodynamic psychotherapy is preferred.
   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
Learning assessment

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 known treatment for pregnant women with opioid use disorder?
   a. Opioid replacement therapy
   b. Rapid detoxification
   c. Long-acting injectable naltrexone
   d. a and c only
   e. all of the above
5. Which is true about a baby born with neonatal abstinence syndrome (NAS)?
   a. The baby was born addicted.
   b. The baby has physical dependence.
   c. The baby may require a prolonged NICU stay.
   d. b and c only
   e. all of the above
Questions?

Photo by Sylvain Pedneault

Joshua Sonkiss MD | Anchorage
Community Mental Health Services