For Today

1. Demystify substance use disorders by providing the neurobiological basis of the disease, grounded in the experience of a primary care patient

2. Understand the alignment between the neurobiology of addiction and persistent pain (and trauma)

3. Provide sample strategies for enhancing healing in addiction and persistent pain
Diclosures

• I have no disclosures

• I believe this is a complex problem with many pathways to success
A Day in Primary Care...

https://www.dropbox.com/s/439hrwdz7b4rx70/CCC%201.mp4?dl=0
Substance Use Disorders

DEFINITION

NEUROBIOLOGY
Definitions of Addiction

ASAM: Addiction is a primary, chronic disease of brain reward, motivation, memory and related circuitry. Dysfunction in these circuits leads to characteristic biological, psychological, social and spiritual manifestations. This is reflected in an individual pathologically pursuing reward and/or relief by substance use and other behaviors.

http://www.asam.org/for-the-public/definition-of-addiction

Gabor Maté: Any repeated behavior, substance-related or not, in which a person feels compelled to persist, regardless of its negative impact on his or her life and the lives of others.

Gabor Mate, In the Realm of Hungry Ghosts, 2010
# DSM 5: 11 Criteria for SUDs

*Diagnosis on a Continuum of Severity*

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Mild (2-3)</th>
<th>Moderate (4-5)</th>
<th>Severe (6+)</th>
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<tr>
<td>Taking substance in larger amounts for longer than intended</td>
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<td>Wanting to cut down or stop using, but not managing to</td>
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<td>Spending a lot of time getting, using, or recovering from use</td>
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<td>Cravings and urges to use the substance</td>
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<td>Not managing to do what you should at work, home or school</td>
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<td>Continuing to use, even when it causes problems in relationships</td>
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<td>Giving up important social, occupational or recreational activities</td>
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<td>Using again and again, even when it puts you in danger</td>
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<td>Continuing to use, when you have a physical or psychological problem that could have been caused or made worse by use</td>
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<tr>
<td>Needing more of the substance to get desired effect (tolerance)*</td>
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<tr>
<td>Development of withdrawal symptoms; relieved by taking more of the substance.*</td>
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</table>

*Not counted in SUD diagnosis if symptoms of tolerance or withdrawal occur during appropriate medical treatment with prescribed medications.*
Substance Use Disorders: Chronic Illness versus Moral Failing

Asthma, Diabetes, HTN, HIV, etc.

Substance Use Disorder

Time

O'Connor, JAMA 1998
Lucas, JAIDS 2005
Review of the Neural Circuits of Addiction

Koob GF et al, 2010
Neural Circuits of the Binge/Intoxication Stage

Koob GF et al, 2010
Neural Circuits of the Withdrawal/Negative Affect Stage

Koob GF et al, 2010
Conceptual Model of Alcohol/Drug Dependence

Solomon RL, 1980
# Reward Transmitters Implicated in the Motivational Effects of Drugs of Abuse

## Positive Hedonic Effects
- **Dopamine**
- **Opioid Peptides**
- **Serotonin**
- **GABA**

## Negative Hedonic Effects of Withdrawal
- **Dopamine** – “dysphoria”
- **Opioid Peptides** – pain
- **Serotonin** – “dysphoria”
- **GABA** – anxiety, panic attacks
Anti-Reward Transmitters Implicated in the Motivation Effects of Drugs of Abuse

<table>
<thead>
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<th>Positive Hedonic Effects</th>
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<tbody>
<tr>
<td>Dynorphin – “dysphoria”</td>
</tr>
<tr>
<td>Corticotropin-Releasing Factor (CRF) – stress</td>
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<tr>
<td>Norepinephrine – stress</td>
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</table>

These are ACTIVATED in amygdala and ventral striatum during withdrawal.
Neural Circuits of the Preoccupation/Anticipation “Craving” Stage

Executive Dysfunction
- impulsivity
- compulsivity
- sleep disturbances
- impaired decision making

Future targets
- GABA modulators (homeostatic reseters)
- CRF₁ antagonists (stress reducers)
- Glutamate modulators (habit reducers)

Koob GF et al, 2010
Loss of Control Over Intake – Self-Medication

- Escalation of Drug Intake
- Impairment of Executive Function
- Initial Intake
- Prefrontal Cortex Abnormalities/Hypofunction
- Neuron/oligodendrocyte Death

Koob, CSAM Addiction Medicine Review Course, 2012
Allostatic Change in Emotional State Associated with Transition to Addiction

The Developmental Roots of Addiction

“We know that the majority of chronically hard-core substance-dependent adults lived, as infants and children, under conditions of severe adversity that left an indelible stamp on their development. Their predisposition to addiction was programmed in their early years. Their brains never had a chance.”

Gabor Maté, *In the Realm of Hungry Ghosts*, 2008
The Anatomy of Trauma

CNS Actions of Corticotropin-Releasing Factor (CRF)

Pituitary Gland
- CRF
- β-Endorphin

Amygdala

Medulla Oblongata
- Sympathetic Activation

Cardiac output
- Stroke volume
- Peripheral vascular resistance
- Blood glucose
- Heart rate
- Blood pressure

Adrenal Medulla
- Epinephrine
  - Gastric acid secretion
  - Gastric emptying

Corticosteroids

ACTH

Behavioral response to stressors
Behavioral activation
Inescapable powerlessness

A “blow out” of your fight or flight system

“The result of exposure to an inescapably stressful event that overwhelms a person’s coping mechanism” – Bessel Van der Kolk
Impact of Insecure Attachments

Insecure Attachments/Lack of Attuned Parent:

Impact brain profoundly
People are seen as source of terror, neglect or ambivalence
Poor self-esteem
Difficulties self-regulating
Low frustration tolerance
Proportionately less positive affect
Inadequate development of neurological and psychological self-regulation system
Increased likelihood to look outside oneself for emotional soothing

Oswaldo Guayasamin
Addiction as Attunement-seeking behavior

A “normal” response to current and past adversity:

- Self soothing
- Stimulates internal and external responses
- Replaces the healthy attunement that should have been derived from the caregiver
Understanding Addictive Behaviors

Differentiate between the disease model vs a normal response to pain

Propose a paradigm shift in thinking about patients through lens of attachment, attunement and trauma

Not “Why the addiction,” but “Why the pain?”

Not “What’s wrong with you?” but “What happened for you?”
Emotion and Reward in Persistent Pain

LESSONS FROM THE FIELD OF ADDICTION MEDICINE
Reward learning processes may contribute to persistence and amplification of pain.

Hashmi JA et al, 2013
The Reward System in Pain

A Quick Decision-Making Process:

1. Dopamine neurons from **Ventral Tegmental Area** estimate value of reward/relief-seeking opportunity

2. **Nucleus Accumbens (NAc)** listens, makes decision to go for it

3. **Frontal cortex** also receives information from VTA, can inhibit NAc, but is slow

** The larger the dopamine input, the more likely you are to do that behavior
So What’s the Problem?

- The reward system is crucial for survival; if out of balance, it takes over: impulsivity, search for immediate gratification, unable to tolerate distress
- Addictive drugs and search for pain relief can dump tons of dopamine into these circuits
- Addictive drugs increase activity in these neurons, or prolong actions of neurotransmitters they release
- New research show pain relief activates these neurons to drive habitual relief seeking

Navratilova E et al, 2012
Example: The Couch

Pain will shape reward learning circuits:

- VTA detects the couch as opportunity for relief, NAc says “go for it!”
- Back pain gets better, and your brain listens: “I got reward!”
- Your brain will refer that relief back to the laying down, reinforce its as new context
- However, the next time you lie down, you may not get as much reward
- If you try something else, you might get more dopamine the next time

People with pain are attracted to quick relief (lying down, guarding, help-seeking, self-medication), but not necessarily recovery.
What Happens Over Time?

Chronic dopamine firing reshapes these circuits, making them very fast and hard to control.

**Accelerator:**
D1 receptor

**Brakes:**
D2 receptor

**D1 Receptors:** Dopamine in the receptors tells Nucleus Accumbens to say “Yes!”

**D2 Receptors:** Activation of these receptors slows decision-making; allows frontal cortex time to step in
Too Much Accelerator is a Bad Thing

When DA neurons are chronically over-active, they activate D1 receptors

◦ D1 pathway becomes more efficient, speeding up decisions to seek relief

◦ **Activate anti-reward circuits (dynorphin, CRF, NE)**

◦ Increase stress response and worsen mood – both amplify pain signals

◦ Pain severity increases and relief-seeking behaviors become compulsive

◦ Desensitizes D2 receptors (your brakes)
Clinical Implications for Pain (and Addiction) Recovery

In both chronic pain and addiction, interventions that increase D2 pathway activity facilitate recovery

- Need just enough DA to activate D2 receptors, get some inhibition but not knock them out
- Consistent low level DA input to build back inhibition
- Lots of tiny opportunities for little reward

The tiny things in life are what make life good, and allow D2 receptors to give your brain time to make a choice.
Clinical Implications for Pain and Addiction Recovery

In both chronic pain and addiction, same brain healing process

Reduce exposure to huge dopamine signals:
- Limit use of addictive drugs or medications, junk food, fast-acting analgesics, tobacco
- Buprenorphine is reasonable option; no burst of high DA signal
- Prevent desensitization of D2 pathway

Increase exposure to small rewards:
- Social reinforcement, problem-solving, effective emotional coping, small goal achievement (especially exercise/activity)
- Increase activity of D2 pathway
Summary

Persistent Pain as an Addiction-Like State

- Both addiction and pain-relief seeking behaviors **activate, and over-stress, the reward system**

- In both addiction and pain, **when the reward system is over-activated, anti-reward neurotransmitters in the limbic system are enhanced**

- In both addiction and chronic pain, **the executive function of the pre-frontal cortex is impaired**

- Healing process involves re-wiring the frontal cortex to the limbic system and ventral striatum

- Posit that healing from trauma involves similar mechanisms
Thank you!

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