Opioid Review and MAT Clinic

January 2, 2019
Announcements
CME evaluation forms are due to Katie Stangl by Friday, Jan. 4th at 4:00pm.
Upcoming Presentations

- **January 9**\(^{th}\): Dr. Charlie Reznikoff, Benzodiazepines Part 2
- **January 16**\(^{th}\): Dr. Tom Arneson, MD with MDH’s Office of Medical Cannabis
- **January 23**\(^{rd}\): Dr. Wilson Compton, MD, PhD, Deputy Director, National Institute on Drug Abuse
- **January 30**: Follow Up- DHS Prescribing Report Card Updates, Sarah Rinn and Jeff Schiff from Minnesota DHS
- **February 13**\(^{th}\): Dr. Harold Tu, Director, Division of Oral and Maxillofacial Surgery, School of Dentistry discussing the Opioid Epidemic from a Dental Perspective
- **February 20**\(^{th}\): Richard Moldenhauer, Human Services Program Consultant/State Opioid Treatment Authority Representative | Behavioral Health Division presenting on Opioid Treatment Programs in Minnesota
If you or someone within your clinic is considering or will be starting to prescribe buprenorphine, please private message Katie. We would love to help in any way possible!

If you are interested in participating in a specific nurse or physician meeting related to MAT and/or bup, please email Katie and let her know
Interested in Learning More About NAS?

• **FREE** training from Children’s will be held at CHI St. Gabriel's Thur., February 7th from 10:00-12:00

• Please RSVP number of individuals attending and names to Katie Stangl!
Exercise Makes Me Happy
Outcomes

- Explain brain changes in opioid use/abuse
- Review brain changes with exercise
- Discuss how exercise can decrease vulnerability to SUD, help withdrawal from opioids and help prevent relapse
NORTHWOODS TRIATHLON
Co-Ed Relay
1st Place - 2018
Epigenetics

- Chromatin remodeling to regulate gene activity and expression (not dependent on gene sequence)
- Remodel structure of DNA at cell level
- Can be inherited
- Can lead to persistent vulnerability to relapse after extended abstinence
Serotonin- the “feel good” hormone

- Exercise increases serotonin especially in hippocampus and cortex
  - Improved mood
  - Mild hypnotic

Technically, the only two things you enjoy

SEROTONIN & Dopamine
Opioid Addiction
Opioid Addiction

Addiction: dopaminergic and opioidergic systems
Opioids and Dopamine

Ventral tegmental areas and nucleus accumbens = mesolimbic dopamine system
Opioids and Dopamine

VTA $\rightarrow$ dopamine $\rightarrow$ NAc
(opioid receptors – Mu primarily)
Dopamine, a signaling agent in the brain that’s crucial to memory formation, helps animals remember experiences, both positive and negative. This stamped-in memory gives animals the motivation to repeat pleasurable experiences.
Opioids and Dopamine

Dopamine reward pathway

Long term use = mesolimbic hypofunction so people use opioid to get to "normal"
Glutamate: increased levels and over stimulation $\rightarrow$ motivates more use
Opioids and Glutamate

- NMDA receptor- memory formation
- Important in “triggers”
- Indirect effects on glutamate
  - Prefrontal cortex
  - Amygdala
  - Hippocampus=all coverage on NAc
Opioids and BDNP

- BDNF: brain derived neurotropic factor
- Increases in mesolimbic structures during abstinence causing increase in drug seeking behavior
- Chromatin changes/epigenetic regulation
Opioids and ERK

ERK- extracellular signal regulated kinase

- Higher levels in NAc correlated with drug seeking
- Levels increase over abstinence periods and enhance seeking/drug craving
Opioid Addiction

1. Depletes natural endorphins
2. Explains the endorphin compensation hypothesis
Exercise
Exercise and Affect on Dopamine

Dopamine

 Increased endorphins in hypothalamus and pituitary gland- similar to opioids → favor Mu receptor, trigger dopamine reward pathway

 Levels increase in NAc
Glutamate- exercise normalizes glutamate receptors/signaling

The decrease in glutamate in the striatum and hippocampus dampens glutamatergic signaling and “triggers”
Exercise and BDNP

- Molecular mediator
- Memory consolidation (behavioral and neurophysiological levels)
- Drug associated cues and conditioned responses
Exercise and BDNF

- Exercise causes a normalized synaptic charges caused by repeated opioid use.
- Exercise normalizes BDNF in structures responsible for drug seeking.
Exercise and ERK

ERK- exercise blocks increase in phosphorylated levels of ERK therefore decreases risk of relapse
Exercise

- Increases endogenous opioids: neurons located in the ventromedial arcuate nucleus project to the hypothalamic-limbic system
  - Key role in emotional process
  - Exercise’s ability to trigger dopamine reward pathway
Exercise of Mu opioid agonists

Makes you less sensitive to Mu opioid agonists
NEUROTRANSMITTERS

**ADRENALINE**
- **fight or flight**
- produced in stressful situations. Increases heart rate and blood flow, leading to physical boost and heightened awareness.

**GABA**
- **calming**
- Calms firing nerves in the central nervous system. High levels improve focus, low levels cause anxiety. Also contributes to motor control and vision.

**NORADRENALINE**
- **concentration**
- affects attention and responding actions in the brain. Contracts blood vessels, increasing blood flow.

**ACETYLCHOLINE**
- **learning**
- Involved in thought, learning and memory. Activates muscle action in the body. Also associated with attention and awakening.

**DOPAMINE**
- **pleasure**
- feelings of pleasure, also addiction, movement and motivation. People repeat behaviors that lead to dopamine release.

**GLUTAMATE**
- **memory**
- Most common neurotransmitter. Involved in learning and memory, regulates development and creation of nerve contacts.

**SEROTONIN**
- **mood**
- contributes to well-being and happiness. Helps sleep cycle and digestive system regulation. Affected by exercise and light exposure.

**ENDORPHINS**
- **euphoria**
- Released during exercise, excitement and sex, producing well-being and euphoria, reducing pain.
How Exercise Impacts the Different Stages of Addiction
Stages of Addiction

Exercise on initiation of drug use
Initiation

Prevention: drug sampling becoming regular use
Initiation

- Exercise and activity
- Decreases cigarette and drugs in adolescence and adults
Initiation

However... team sports

Higher alcohol and smokeless tobacco use

Type of exercise and/or psychosocial interactions also influence initial drug use
Initiation

Treadmill running = increases serum Ca^{++} which then enters the brain and activates synthesis of dopamine
Initiation

- Running increases tyrosine hydroxylase
  - Tyrosine hydroxylase is the rate limiting enzyme in dopamine syntheses and dopamine production
  - Increase burst activation of dopamine neurons in VTA
Initiation

- Running increased levels of voluntary neuro-adaptive changes in the dopamine reward pathway similar to exposure to drugs of abuse
Initiation

- Excessive exercise increases vulnerability to addiction
- Exercise addiction has similar neurochemical changes in the brain similar to drugs of abuse
Progression

How exercise can prevent the progression of drug use becoming addiction
Rats with cocaine use disorder - 2 weeks abstinence

- 1 hour/day running → back to drugs
- 2 hours/day running → less drug use
- 6 hours/day running → no drugs

The more rats exercised the less likely they were to relapse after abstinence

Affect even more pronounced if female
Progression

- Running decreases glutamate concentration in the striatum and hippocampus
- Also changes in glutamate receptors, dampening glutamatergic signaling
Exercise and Withdrawal
Exercise and Withdrawal

- Withdrawal increases risk of drug use
- Exercise decreased anxiety-like behaviors in morphine dependent and withdrawing rats
Withdrawal causes a decrease in dopaminergic activity in the reward pathway resulting in:

- Anhedonia - inability to experience pleasure
- Negative Affect
- Craving
Exercise and Withdrawal

- Exercise normalizes hypofunctions in the mesolimbic system
- Increases endogenous dopamine
Exercise and Withdrawal

- Upregulate dopaminergic signaling and normalize glutamatergic signaling
- Exercise upregulates endogenous dopamine signaling and normalizes glutamatergic signaling
Relapse/Exercise
Improved outcomes when exercise begins early (<30 days) in recovery
After 30 days of withdrawal, PFC and ERK levels increase leading to increased drug seeking and trigger vulnerability.
Relapse/Exercise

- Exercise alters opioid receptors because of endogenous opioids
- Decreases sensitivity to receptor agonists
- Running benefits blocked by naloxone opioid antagonist
Narcan can induce withdrawal and symptoms similar to those in chronic opioid abusers.
Decrease sensitivity of exogenous administered opioids
Exercise shortens opioid withdrawal through release of endogenous opioid peptides
Runner High
Runner High- Another Hypothesis

- Natural endorphins don’t cross the blood brain barrier well
- Endocannabinoid (anandamide) are lipid soluble-higher levels after running
  - Blood → brain
- Mice
  - Run 5 hours → lower anxiety, lower pain with stimulus
  - Sedentary
- When endocannabinoid blocked → runners had equal pain
- Endorphin blocker → no change

HERE'S WHAT WE'RE GOING TO DO

WE ARE GOING TO RUN 13.1 MILES ... FOR FUN!!!
"Movement Is A Medicine For Creating Change In A Person's Physical, Emotional & Mental States."

Carol Welch
Exercise gives you endorphins. Endorphins make you happy. Happy people don't shoot their husbands, they just don't.