

# The Neurobiology and Pharmacology of Addiction

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# Financial Disclosures

- None
- There will be no unannounced discussion of experimental treatments or non-FDA approved medications

## Lecture Objectives

- *Describe the pharmacological properties of the principal addictive drugs and medications used in the treatment of addictive disorders; and*
- *Discuss how these drugs affect brain function.*

## Lecture Outline

- *Explain the location of the brain reward system*
- *Review basic clinical pharmacology of commonly used substances*
- *Review the treatments for opioids, nicotine, alcohol*
- *Possible effects of opioids on neuro development?*

## Principal Addictive Drugs and Sites of Action in Brain

Opiates

mu opioid receptors

Cocaine  
& Methamphetamine

dopamine, serotonin & norepinephrine  
reuptake transporters

Nicotine

acetylcholine receptors

Alcohol  
Benzodiazepines  
Barbiturates

GABA receptors

Marijuana

cannabinoid receptors

(other commonly abused drugs that you may hear about: ecstasy, hallucinogens, K2/spice, cough medicine)

**Key point #1:** addictive drugs act by binding to specific proteins in the brain and disrupt their normal function.

Some are pharmacological **agonists** (e.g. fentanyl) and activate the receptor by mimicking the endogenous transmitter (e.g. enkephalin). Some are **inhibitors** and block the transporter function (e.g. dopamine reuptake).

## What is the medical definition of Addiction?

1. Any un-approved use of an illegal or dangerous drug
2. Excessive use of any substance that impairs thinking
3. Use of any drug that causes dependence
4. None of the above



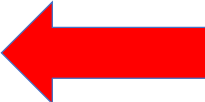

# What is the medical definition of Addiction?

**Correct Answer:** None of the above

Medical definition (DSM-V) defines 'substance use disorder' based on 11 objective criteria:

Mild	2-3/11	
Moderate	4-5/11	
Severe	+6	(Addiction)

## Diagnostic Criteria. DSM 5

1. Recurrent drug use in physically hazardous situations
2. Repeatedly unable to carry out major obligations at work, school or home due to drug use
3. Continued drug use despite social or interpersonal problems caused or exacerbated by drug use
4. Tolerance as defined by either a need for markedly increased amounts to achieve desired effect or diminished effect with continued use of the same amount
5. Withdrawal manifesting as physical syndrome or continuing use to avoid withdrawal
- 6. Using greater amounts over a longer time period than intended** 
- 7. Persistent desire or unsuccessful efforts to cut down or control drug use** 
8. Spending a lot of time obtaining, using or recovering from drug
9. Stopping or reducing important social, occupational, or recreational activities due to drug use
- 10. Persistent use of drug despite acknowledgment of harm** 
- 11. Craving or strong desire to use drug** 



Can you be addicted to chocolate?

Are you addicted to oxygen?

Can you be addicted to chocolate?

*unlikely*

Are you addicted to oxygen?

*no*

Is drug addiction a disease or a choice?

Is drug addiction a disease or a choice?

*mild substance use disorder likely a choice*





*severe substance use disorder is not a choice*

## Diagnostic Criteria. **DSM 5**

Substance Use Disorder (May 2013) mild 2-3/11, moderate 4-5/11, **severe 6-7/11**

1. Recurrent drug use in physically hazardous situations
2. Repeatedly unable to carry out major obligations at work, school or home due to drug use
3. Continued drug use despite social or interpersonal problems caused or

Addiction is an acquired brain disease that results from structural reorganization of the nervous system.

- 6. Using greater amounts over a longer time period than intended** 
- 7. Persistent desire or unsuccessful efforts to cut down or control drug use** 
8. Spending a lot of time obtaining, using or recovering from drug
9. Stopping or reducing important social, occupational, or recreational activities due to drug use
- 10. Persistent use of drug despite acknowledgment of harm** 
- 11. Craving or strong desire to use drug** 

Current opioid crisis – people are dying of respiratory depression at phenomenal rates.

*Causes are complex (but this is not the first opioid crisis):*

- Aggressive marketing by drug companies that minimized the risks
- Over prescription of opioid analgesics by providers treating acute pain
- Lack of good alternative options to treat chronic non-cancer pain
- Under appreciation by providers of the risks of abuse
- Import of very potent fentanyl (and related compounds) used to spike 'heroin'

Risk of opioid abuse is ~10-20%, but not universal. People differ in their risk, but predicting who is vulnerable is hard.

## Principal Opioid Drugs

Morphine  
Fentanyl  
Oxycodone  
Methadone  
Heroin  
Codeine  
Hydrocodone  
Tramadol / Tapentadol  
Buprenorphine  
Naloxone  
Naltrexone  
Loperamide

What are the key things to know about the pharmacology of opioids?

**Key point #1:** Opioid drugs can be distinguished by important differences in their  
Receptor Selectivity (mu, delta, kappa opioid receptors)  
Receptor affinity  
Analgesic Efficacy (partial agonists / partial antagonists)

**Key point #2:** Sustained exposure to opioids produces adverse effects  
Tolerance  
Physical dependence & Withdrawal  
Hyperalgesia  
Addiction (severe substance use disorder defined by DSM)

**Key point #3:** Opioids differ profoundly in pharmacokinetics



# Principal Opioid Drugs

## *Agonists*

Morphine  
Fentanyl  
Oxycodone  
Methadone  
Heroin

## *Partial Agonists*

Codeine  
Hydrocodone  
Tramadol / Tapentadol  
Buprenorphine

## *Antagonists*

Naloxone  
Naltrexone

## *Peripherally restricted agonists*

Loperamide

Opioids differ in efficacy



# Principal Opioid Drugs

## *Agonists*

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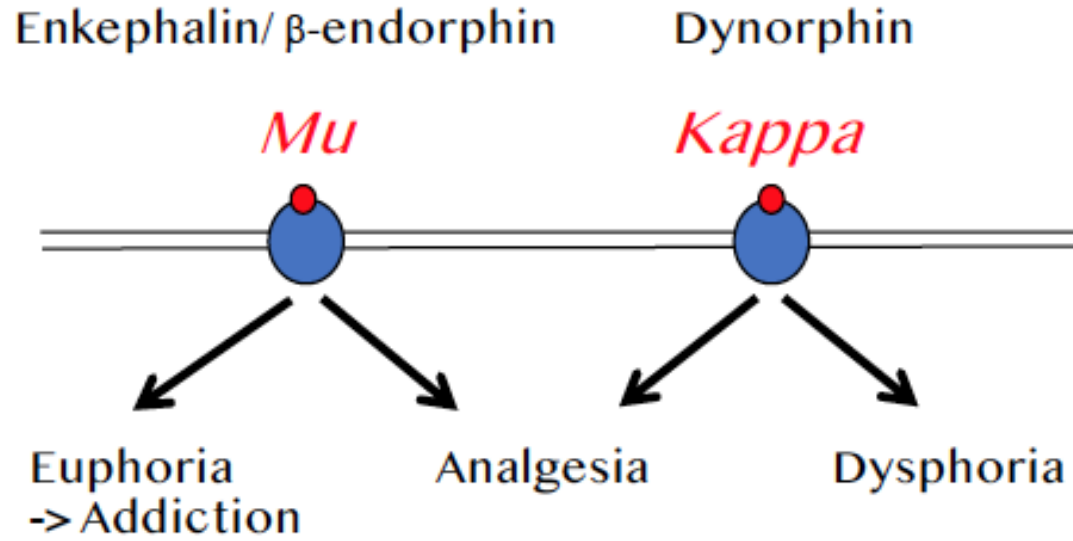
Loperamide

Opioids differ in efficacy

and pharmacokinetics



## *Multiple types of opioid receptors expressed by neurons*



- Morphine, oxycontin, heroin, & fentanyl selectively activate the mu opioid receptor*
- Less selective opioids that activate kappa receptors are dysphoric. Off-target effects of meperidine cause seizures.*

# Take home message

- Opioids activate the Mu receptor for pain relief and euphoria by mimicking the normal effects of the endogenous endorphins and enkephalins.

## Morphine

Principal opioid – central & peripheral  
mu opioid receptor agonist

- Analgesia
- Sedation
- Constipation
- Respiratory depression
- Nausea & vomiting
- Pruritus (Itching)
- Urinary retention
- Endocrine regulatory effects
- Hyperalgesia
- Tolerance & Physical dependence
- Euphoria & Addiction



Morphine impact on Mu receptors

→ Constipation

Decreases intestinal peristalsis.

GI spasm reduces propulsion. Inhibits GI secretions.

*Other smooth muscle actions:*

Contracts biliary smooth muscle,

Increases ureteral & bladder sphincter tone

Miosis – pupillary constriction



## Morphine impact on Mu receptors

➔ Respiratory depression

Principal cause of overdose death

Slowed breathing rate, minute volume, and tidal exchange

Inhibition of brainstem CO<sub>2</sub> sensors in respiratory center

- Different opioids produce different degrees of respiratory depression
- Tolerance to analgesia doesn't always match tolerance to respiratory depression
- Dose necessary to produce lethal respiratory depression not always predictable



➔ Hyperalgesia

Opioids are effective for acute pain, but can cause hyperalgesia both with increased and reduced doses.

➔ Tolerance & Physical dependence

Receptor desensitization & compensatory adaptation of the nervous system to restore homeostasis

Rebound withdrawal (**abstinence**) symptoms: rhinorrhea, lacrimation, chills, gooseflesh, muscle aches, diarrhea, yawning, anxiety, and hostility, relieved by morphine or opioids



*Neonatal opioid withdrawal syndrome*



## *Opioid Effects on Development ?*

Neonatal Intensive Care Unit (*not always necessary*)

manage withdrawal

*persistent developmental issues?*



Infants born to opioid exposed mothers have neurodevelopmental delays & smaller cerebral volumes. However the developmental delays are not significantly different from other babies of comparable **socio economic status** and other non-opioid exposures.

The NEOPAIN trial (2004) included 893 children and showed no significant overall differences in composite outcome between placebo and morphine-treated infants of very preterm age. (*VERY Different from ETOH which has no safe fetal exposure limit*)

## *Opioid Effects (con't)*

➔ Euphoria

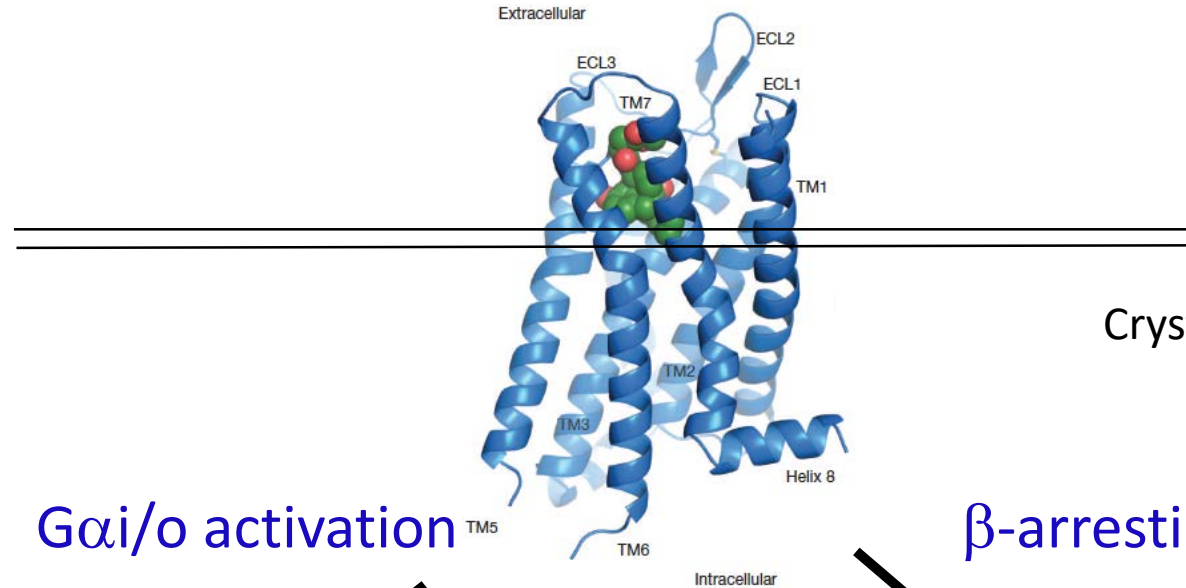
Opioids disinhibit (indirectly stimulate) the reward circuits in brain  
(midbrain dopamine systems in ventral tegmental area to striatum).

Changes in this reward circuit lead to compulsive drug use and difficulty in maintaining abstinence

➔ Addiction (Severe substance use disorder)



# Functional selectivity of *Mu* opioid ligands. – Possibly safer opioids?



Crystal structure from Manglik 2012

$G\alpha i/o$  activation

$\beta$ -arrestin activation

$G\beta\gamma$  activation of  $K^+$  channels -> hyperpolarization  
Inhibition of  $Ca^{++}$  channels -> presynaptic inhibition  
-> **analgesia**

G protein Receptor Kinase -> phospho-MOR  
 $\beta$ -arrestin binding -> **receptor desensitization**

$\beta$ -arrestin -> scaffold activation of MAP Kinase  
-> **constipation and respiratory depression**

*PZM21; Manglik 2016; SR17108, Schmid 2017; TRV130, TRV734 - Trevena*

## Risk of developing opioid use disorder

- >100 people/day are dying from opioid overdose in USA, many using multiple substances at time of death (benzo's are particularly risky).
- Unclear how recreational/prescription use progresses to addiction
- High doses and long duration of use increases risk.
- Safer alternatives to relieve *chronic pain* are needed
- More effective treatments for *co-morbid anxiety* and *depression*
- Better understanding of the *genetic* risk factors underlying drug addiction

\*Source: Shah A, Hayes CJ, Martin BC. Characteristics of Initial Prescription Episodes and Likelihood of Long-Term Opioid Use — United States, 2006–2015.

MMWR Morb Mortal Wkly Rep 2017;66:265–269. DOI:  
<http://dx.doi.org/10.15585/mmwr.mm6610a1>.

# *What are the treatments for opioid, nicotine, alcohol dependence?*

Opioids	<b>methadone</b> (long acting agonist to prevent relapse) <b>buprenorphine</b> (weak partial agonist and kappa receptor antagonist) <b>naltrexone-extended release</b> (mu receptor antagonist) <b>naloxone</b> (antagonist to prevent overdose death from respiratory depression)
Nicotine	<b>nicotine patch or gum</b> (slow release replacement) <b>bupropion</b> (Wellbutrin, Zyban) atypical antidepressant, norepinephrine,-dopamine reuptake inhibitor) <b>varenicline</b> (Chantix) high affinity partial agonist
Ethanol	acute withdrawal risk of seizures is managed by <b>carbamazepine</b> or a <b>benzodiazepine</b> <b>naltrexone</b> (mu receptor antagonist) <b>nalmefene</b> (mu receptor antagonist) <b>acamprosate</b> (glutamate receptor antagonist & GABA receptor positive allosteric modulator)

*These medication assisted treatment options complement psychosocial interventions*

## What controls the risk for developing opioid use disorder?

Not currently predictable (except with persons with history of abuse)

Absence of socially protective environmental features

Genetic component: *Impulsivity & risk taking traits*

Increased by co-morbid depression disorders: *self-medication*

Increased by *stress vulnerability*

Interactions with *chronic pain* syndromes

Neurodevelopmental vulnerabilities?

*Open research questions...*

**Chronic relapsing disorder (defined by DSM5 criteria)**

**Initiation of drug use**

**Progression to habitual use**

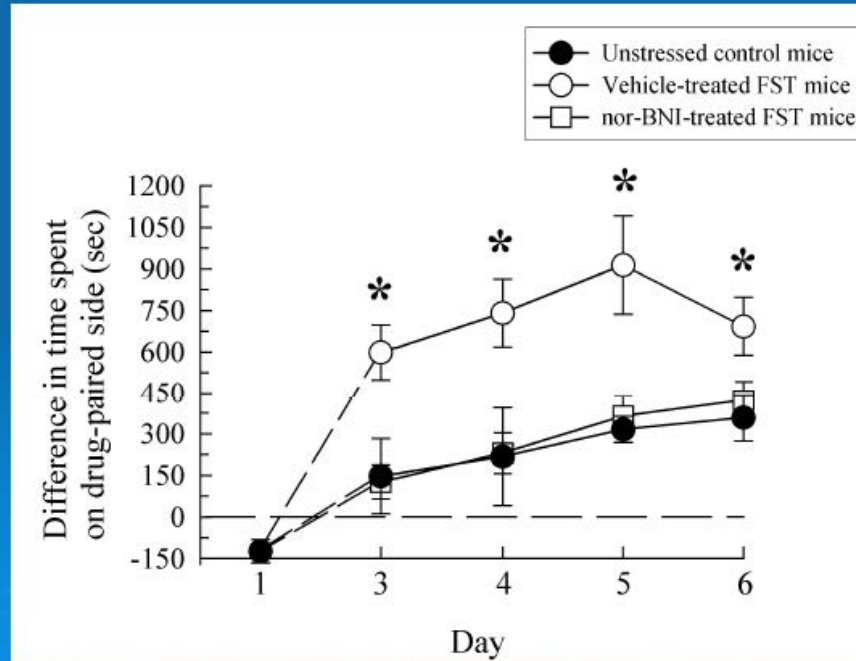
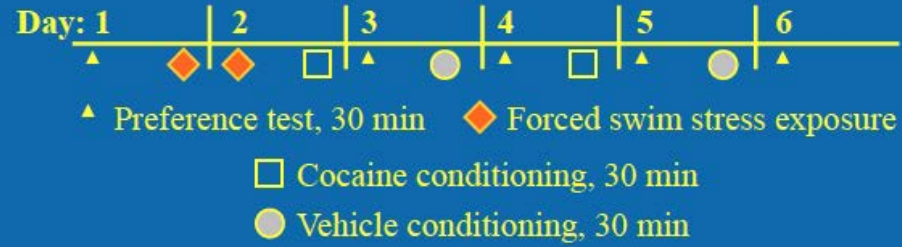
**Escalation of drug consumption**

**Multiple failed attempts of abstinence**

**Progression from recreational use to compulsive use**

**How can we understand this process and develop effective treatments?**

# How does chronic social stress increase drug addiction risk?

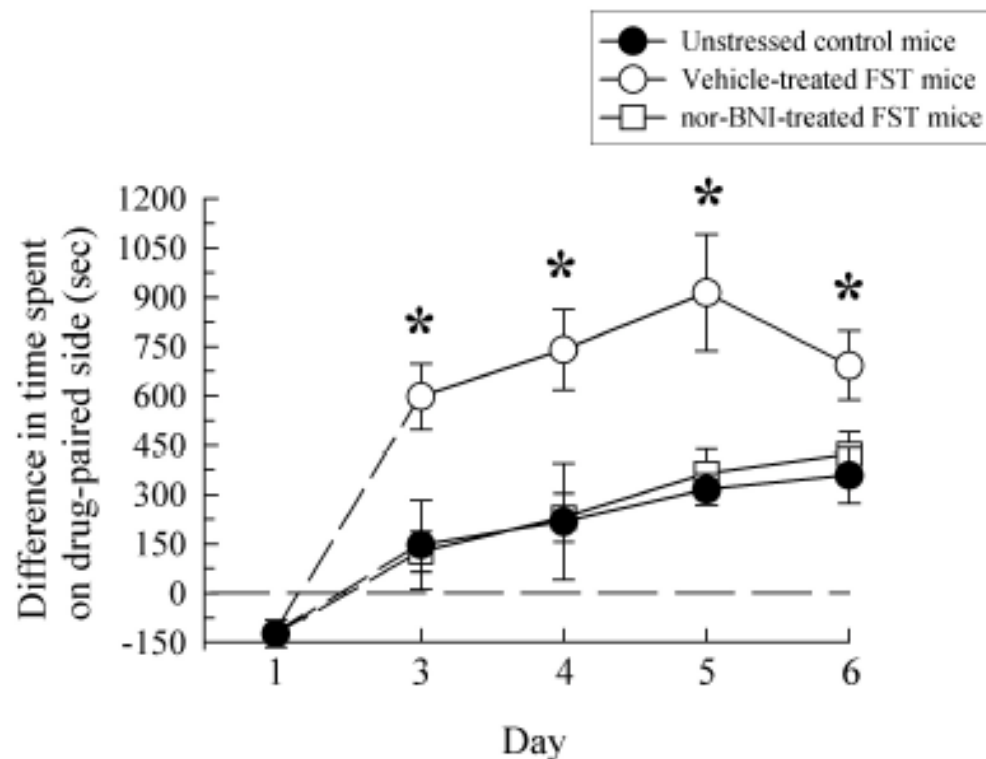


McLaughlin et al, 2003



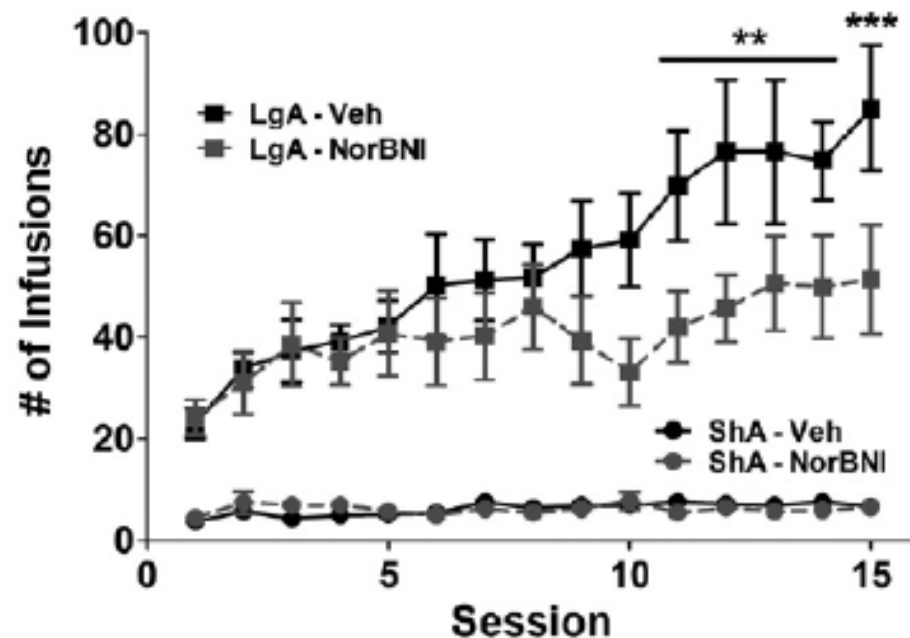
*In mice & rats...*

norBNI blocked stress  
potentiated cocaine CPP



*McLaughlin 2003*

norBNI blocked escalation of  
heroin self-administration



*Schlossburg 2013*

Stress increases the rewarding valence of drugs of abuse, promotes CPP and reinstates extinguished drug seeking behaviors.

Stress-induced dysphoria (aversion) and anxiety-like behaviors are mediated by CRF-induced activation of the dynorphin/KOR system.

norBNI specifically blocks the aversion and anxiety-like behaviors, not learning.

*How does dynorphin produce its proaddictive actions?*

# Dynorphins

Endogenous opioid peptides first detected in early 1970's  
1973 Goldstein first detected dynorphin in pituitary extracts  
1979 & 1981 Goldstein reported the sequence of dynorphin A  
1982 Numa cloned and sequenced the dynorphin precursor



Neoendorphin	YGGFLRKYP
Dynorphin A	YGGFLRRIRPKLKWDNQ
Dynorphin B	YGGFLRRQFKWT

Vertical yellow boxes highlight the YGGFLR sequence in each row, indicating the conserved N-terminal region.

Dynorphins act at kappa opioid receptors

## Kappa antagonists may have therapeutic benefit in the treatment of addiction

- Promote stress resilience – reduce stress-induced relapse
- Attenuate the dysphoria during withdrawal – reduce craving
- Will not block the euphorigenic effects of abused drugs

*Depends on the validity of the preclinical models and the role of dynorphin in human brain – additional Pet imaging necessary*

# Kappa antagonists in clinical trials

Buprenorphine (multiple trials establish therapeutic efficacy for opioids)

Buprenorphine/naltrexone for opioids/cocaine (Rothman 2000; Gerra 2006)

CURB study for cocaine dependence (Ling 2016). *Nonselective opioid drug*

CERC-501 (LY-2456302) *short acting KOR antagonist developed by Eli Lilly*

ALKS 5461 (Buprenorphine-Samidorphan) treatment resistant depression  
*developed by Alkermes*

JDTic (Buda 2015) Phase 1 trial (non-sustained ventricular tachycardia)  
*developed by Ivy Carroll at Research Triangle Institute*

PF-04455242 (Pfizer) *dropped because of toxicity*

## Why Kappa Opioid Receptor Antagonists May Fail in Clinical Trials for Addiction and Depression Treatment.

- Preclinical animal models may lack predictive validity or reproducibility
- Dynorphin may function differently in humans than in rodents
- Relapse risk, drug-craving, drug seeking behaviors by humans may not be uniquely controlled by dynorphin / KOR function
- Competitive antagonist doses may be inadequate or require frequent and high dosing increasing the probability of off target effects
- Receptor-inactivating KOR antagonists may fail to get FDA approval

## Wrap-up Summary:

- *What are the principal addictive drugs and how do they act on brain?*
- *What is the brain reward system?*
- *How do opioids differ in their clinical pharmacology?*
- *What are the treatments for opioid, nicotine, alcohol dependence?*
- *Do opioids produce lasting effects on neuro development?*

Questions?