Objectives

1. Definitions of Drug Addiction

2. Understand the Dopamine Hypothesis of addiction

3. Understand definitions of drug tolerance, sensitization, and dependence

4. Mechanism of action of opioids & psychostimulants
Drug Addiction

• Modern views have focused on 3 types of drug use: 1) occasional, controlled or social use; 2) drug abuse or harmful use; 3) drug addiction

• Official definition by the American Association of Psychiatry: Addiction is a chronic relapsing disease that is characterized by:
  1) Compulsion to seek and take the drug
  2) Loss of control in limiting intake
  3) Emergence of a negative emotional state when access to the drug is prevented (defined as dependence).

• Dependence versus addiction—Is there a difference?
Drug Addiction

• 200 million people, or 5% of the global population, consumed illicit drugs at least once in the last 12 months (2005 UN world drug report).

• 22.5 million Americans aged 12 or older experienced substance dependence in 2004 (The US Department of Health). About 21.1 million people needed but did not get treatment for their addiction in the US alone.

• In the US: Illicit drugs cost society $161 Billions per year (Office of National Drug Control Policy, 2001).
Drug Addiction

Estimated prevalence among 15-54 years old of drugs of abuse

<table>
<thead>
<tr>
<th>Ever used</th>
<th>Dependence among</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobacco</td>
<td>75.6%</td>
</tr>
<tr>
<td>Alcohol</td>
<td>91.5%</td>
</tr>
<tr>
<td>Cocaine</td>
<td>16.2%</td>
</tr>
<tr>
<td>Heroin</td>
<td>1.5%</td>
</tr>
<tr>
<td>Cannabis</td>
<td>46.3%</td>
</tr>
<tr>
<td></td>
<td>31.9%</td>
</tr>
<tr>
<td></td>
<td>15.4%</td>
</tr>
<tr>
<td></td>
<td>16.7%</td>
</tr>
<tr>
<td></td>
<td>23.1%</td>
</tr>
<tr>
<td></td>
<td>14.7%</td>
</tr>
</tbody>
</table>
Drug addiction

Euphoria, Activation of the reward pathway
Positive reinforcement

5-30%

Addictive drug

Neuroadaptations (withdrawal, tolerance, sensitization)
Dysregulation of reward pathway
Negative reinforcement

Loss of control, Denial

Stress
Drug related cues
Drugs

Novelty seeking,
Sensation seeking
Failed impulse suppression

Craving, relapse
Characterized by:

- Compulsive Behavior
- Continued abuse of drugs despite negative consequences
- Persistent changes in the brain’s structure and function

What is Addiction?
Addiction is a Brain Disease
Addiction is Like Other Diseases...

- It is preventable
- It changes biology

**Decreased Brain Metabolism in Drug Abuser**

Healthy Brain

Diseased Brain/Cocaine Abuser

**Decreased Heart Metabolism in Heart Disease Patient**

Healthy Heart
The Dopamine Hypothesis of Drug Addiction

This hypothesis states that drugs of abuse act through mechanisms involving the brain neurotransmitter dopamine and the neural systems that regulate it.

Addictive drugs may act on dopamine systems either:

- **Directly** - Psychostimulants (Amphetamine & Cocaine)
- **Indirectly** - Nicotine, Morphine / Heroin, Alcohol, & Barbiturates
The ventral tegmental area (VTA)-accumbens dopamine system is strongly implicated in mediating drug reward.
<table>
<thead>
<tr>
<th></th>
<th>D₁-like receptor family</th>
<th>D₂-like receptor family</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Amino Acids</strong></td>
<td>D₁ 446 (h)</td>
<td>D₂/₅D₃/₄ 415/443 (h)</td>
</tr>
<tr>
<td></td>
<td>D₅ 477 (h)</td>
<td>D₃ 400 (h)</td>
</tr>
<tr>
<td><strong>G-protein</strong></td>
<td>Gₛ</td>
<td>Gi/o</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gi/o</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gi/o</td>
</tr>
<tr>
<td><strong>Second messengers</strong></td>
<td>AC</td>
<td>AC</td>
</tr>
<tr>
<td></td>
<td>AC</td>
<td>AC</td>
</tr>
<tr>
<td></td>
<td>AC</td>
<td>AC</td>
</tr>
<tr>
<td><strong>DA Affinity</strong></td>
<td>µM</td>
<td>µM</td>
</tr>
<tr>
<td></td>
<td>µM</td>
<td>nM</td>
</tr>
<tr>
<td></td>
<td>µM</td>
<td>µM</td>
</tr>
<tr>
<td><strong>Agonists</strong></td>
<td>SKF-38393</td>
<td>(+)PHNO</td>
</tr>
<tr>
<td></td>
<td>SKF-38393</td>
<td>7-OH-DPAT PD-168,077</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PD-128,907</td>
</tr>
<tr>
<td><strong>Antagonists</strong></td>
<td>SCH-23390</td>
<td>raclopride</td>
</tr>
<tr>
<td></td>
<td>SCH-23390</td>
<td>(+)S14297</td>
</tr>
<tr>
<td></td>
<td></td>
<td>L-745870</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GR-103,691</td>
</tr>
</tbody>
</table>
**D1 and D2 Neurons**

- Projection neurons in the Nucleus Accumbens (NAc) and dorsal striatum
- ~95% of the neurons in NAc and dStr
### Mesocorticolimbic Dopamine

#### The Neuropeptide of “Reward”? (NAC)

<table>
<thead>
<tr>
<th>“Reward”</th>
<th>Dopamine Release (NAC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOOD, SEX</td>
<td>50-100%</td>
</tr>
<tr>
<td>ETHANOL</td>
<td>125-200%</td>
</tr>
<tr>
<td>CANNABIS [THC]</td>
<td>125-175%</td>
</tr>
<tr>
<td>NICOTINE</td>
<td>225%</td>
</tr>
<tr>
<td>MORPHINE/HEROIN</td>
<td>150-300%</td>
</tr>
<tr>
<td>COCAINE</td>
<td>400%</td>
</tr>
<tr>
<td>AMPHETAMINE</td>
<td>1000%</td>
</tr>
</tbody>
</table>

*R. Wise et al., 2000*
What is Addiction in a rodent!? 
The Dopamine Hypothesis of Drug Addiction
Evidences for the implication of DA in drug addiction

• Rats will self-administer amphetamine or cocaine directly into the Nucleus Accumbens (NAc). More is self-administered if DA receptors are partially blocked.
• If dopamine is depleted by 6-OH-DA lesions or the NAc is destroyed then rats no longer self-administer amphetamine or cocaine.
• Withdrawal from several drugs (psychostimulants, alcohol, nicotine and opiates) is associated with a reduction in DA levels in the NAc.
To Feel Good
To have novel: feelings, sensations, experiences AND to share them

To Feel Better
To lessen: anxiety, worries, fears, depression, hopelessness
Voluntary intake

tolerance
sensitization
dependence

‘Involuntary’ intake

compulsive intake

cravings
relapse

obsession
**Tolerance** - The diminishing effect of a drug after repeated administration at the same dose or to the need for an increase in dose to produce the same effect

- Tolerance may develop to some but **not all** effects of a drug

- Tolerance frequently develops to the **analgesic**, **euphoric** and **respiratory** depressant effects of opioids.

- In general there is **NO** tolerance to the pupillary constriction effects of opioids

**Two “types” of tolerance**

1) **Pharmacokinetic**-increased drug metabolism

2) **Pharmacodynamic**-adaptations of the neuronal elements that respond to drugs initially (this is a key contributor to the neurobiology of addiction)
Sensitization—also referred to as “reverse tolerance”. This occurs when repeated administration of the same drug (at the same dose) elicits an escalating effect.
Dependence is defined as the adaptive state develops in response to repeated drug administration. This state is generally unmasked during withdrawal-which occurs when drug taking is stopped.

Dependence from long-term drug (Opioids) use may have both somatic components which are manifested by:

**physical symptoms**
- Increased pain
- Diarrhea
- Hyperventilation

**Emotional component**
- Increased irritability
- Insomnia
- Dysphoria
- Anhedonia
Physical dependence is not a useful diagnosis of addiction because they do not occur with may commonly abused drugs (i.e. cocaine and amphetamine). Moreover, physical dependence can occur with drugs not abused (i.e. propanolol, clonidine).
BAYER
PHARMACEUTICAL PRODUCTS.

We are now sending to Physicians throughout the United States literature and samples of
ASPIRIN
The substitute for the Salicylates, agreeable of taste, free from unpleasant after-effects.

HEROIN
The Sedative for Coughs.

HEROIN HYDROCHLORIDE
Its water-soluble salt.
You will have call for them. Order a supply from your jobber.

Write for literature to
FARBENFABRIKEN OF ELBERFELD CO.
40 Stone Street, New York.

MRS. WINSLOW'S
SOOTHING SYRUP

FOR CHILDREN TEETHING

COUGH

THE PROBLEM

HAS BEEN SOLVED

by the pharmaceutical compound known as

GLYCO-HEROIN (Smith)

The remedy obtained with Glyco-Heroin (Smith) is the all-inclusive and one of cough is answered by someone of the world, and there are no other compounds in the world that are prepared for the use of the world. Scientifically Compounded. Scientifically Concentrated.

GLYCO-HEROIN (Smith) simply acts upon its virtues before the production, ready to prove its efficacy to all who are interested in the art of
How Big is the problem?

After Marijuana, Prescription and Over-the-Counter Medications* Account for Most of the Commonly Abused Drugs

Prevalence of Past-Year Drug Use Among 12th Graders

Categories are not mutually exclusive

Percent

Marijuana/Hashish 34.8
Vicodin* 8.0
Cough Medicine* 6.6
Adderall* 6.5
Tranquilizers* 5.6
Salvia 5.5
Hallucinogens 5.5
OxyContin* 5.1
Sedatives* 4.8
MDMA (Ecstasy) 4.5
Inhalants 3.6
Cocaine (any form) 2.9
Ritalin* 2.7

*Nonmedical Use

Source: University of Michigan, 2010 Monitoring the Future Study
FDA News Release

FDA moves quickly to approve easy-to-use nasal spray to treat opioid overdose

Naloxone in nasal spray form provides important new alternative for family members, first responders

For Immediate Release
November 18, 2015

Today the U.S. Food and Drug Administration approved Narcan nasal spray, the first FDA-approved nasal spray version of naloxone hydrochloride, a life-saving medication that can stop or reverse the effects of an opioid overdose. Opioids are a class of drugs that include prescription medications such as oxycodone, hydrocodone, and morphine, as well as the illegal drug heroin.

Drug overdose deaths, driven largely by prescription drug overdoses, are now the leading cause of injury death in the United States – surpassing motor vehicle crashes. In 2013, the Centers for Disease Control and Prevention reported the number of drug overdose deaths had steadily increased for more than a decade. When someone overdoses on an opioid, it can be difficult to awaken the person, and breathing may become shallow or stop – leading to death if there is no medical intervention. If naloxone is administered quickly, it can counter the overdose effects, usually within two minutes.

"Combating the opioid abuse epidemic is a top priority for the FDA," said Stephen Ostroff, M.D., acting commissioner, Food and Drug Administration. "We cannot stand by while Americans are dying. While naloxone will not solve the underlying problems of the opioid epidemic, we are speeding to review new formulations that will ultimately save lives that might otherwise be lost to drug addiction and overdose."

Until this approval, naloxone was only approved in injectable forms, most commonly delivered by syringe or auto-injector. Many first responders and primary caregivers, however, feel a nasal spray formulation of naloxone is easier to deliver, and eliminates the risk of a contaminated needle stick. As a result, there has been widespread use of unapproved naloxone kits that combine an injectable formulation of naloxone with an...
SAMHSA: Pain Medication Abuse a Common Path to Heroin
Experts Say This Pattern Likely Driving Heroin Resurgence

Bridget M. Kuehn, MSJ

The New England Journal of Medicine

SPECIAL ARTICLE

Trends in Opioid Analgesic Abuse and Mortality in the United States

C Survey of Key Informants’ Patients Program

Rate of Heroin Use per 100,000 Population

Rate of OxyContin Abuse per 100,000 Population

No. of Persons Reporting Heroin Use in Past Month

Release of reformulated OxyContin
# Mechanisms of Action

## Table 1: Acute actions of some drugs of abuse

<table>
<thead>
<tr>
<th>Drug</th>
<th>Action</th>
<th>Receptor signalling mechanism</th>
</tr>
</thead>
<tbody>
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<td>Opiates</td>
<td>Agonist at μ-, δ- and κ-opioid receptors*</td>
<td>$G_i$</td>
</tr>
<tr>
<td>Cocaine</td>
<td>Indirect agonist at dopamine receptors by inhibiting dopamine transporters‡</td>
<td>$G_i$ and $G_s$</td>
</tr>
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<td>Amphetamine</td>
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</tr>
<tr>
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<td>Unknown</td>
<td></td>
</tr>
</tbody>
</table>
Opioids

Opiates
  – alkaloids found in the opium poppy for example Opium, Morphine, and Codine

Heroin = diacetylmorphine
  • addition of two acetyl groups to morphine
    – ~ 10x more potent than morphine
    – pharmacological effect usually thought to be identical to morphine
Types of Opioids

Endogenous Opioid that bind to specific opiate receptor

- Endorphins- *mu receptors*
- Enkephalins- *delta receptors*
- Dynorphins- *kappa*

**Endorphins**
- *discrete*
- *hypothalamic - endocrine related*

**Enkephalins and Dynorphins**
- *wide distribution, local circuit and short axon projections*
• The reinforcing actions of heroin and morphine appear to be mediated by the mu opiate receptor subtype located at the in the VTA.

VTA → accumbens DA system

β-endorphin

GABA

Ventral tegmental area (VTA)

“Disinhibition”

Nucleus accumbens

Ventral pallidum

Mesolimbic dopamine

DA

OPIATES AND DOPAMINE
Opioids: G protein linked-- affecting
* Activate mu (µ); delta (σ), or kappa (κ) receptors
* Opioid receptors are members of the 7 Trans-membrane, G protein- coupled receptor superfamily
  * Ion channel state
  * Intracellular Ca2+ levels
  * Protein phosphorylations states

Two well-defined opioid actions:
* Reduce neurotransmitter release; by closing a voltage-gated Ca2+ channel on presynaptic neuronal terminals
* Inhibit postsynaptic neurons by increasing K+ channel conductance
β-arrestin produces GPCR tolerance in a series of resolvable steps

- GPCR-PO4 activates β-arrestin
- Newly exposed β-arr domain binds GPCR
- GPCR- β-arr prevents G-protein association
- GPCR- β-arr complex is internalized by a dynamin and clathrin dependent mechanism
**LOCUS COERULEUS (LC)**

LC is a discrete, compact, homogeneous nucleus, consisting of almost exclusively Nor Epinephrine (NE) neurons. LC neurons express the three main classes of opioid receptors: MOR, DOR, and KOR with distinct distribution, although, as with the VTA, MOR is most directly implicated in opiate dependence and addiction.
**Acutely:**

**Morphine inhibits LC firing – sedation**

There is a Decrease in cAMP

Noradrenergic neuron in the locus coeruleus

- Neuron hyperpolarized and NE release inhibited
- Cell excitability inhibited
- µOR
- K⁺

Modified from C. Chavkin University of Washington
**Chronically Compensatory increase in LC activation increased excitatory drive**

There is a **Increase in cAMP & the transcription factor CREB**

**Tolerance**

- **Excitatory drive**
- **μOR**
- **cAMP**
- **CREB**

Receptor desensitization

- Normal Excitability restored

*Modified from C. Chavkin University of Washington*
Clonidine, an $\alpha_2$-adrenergic receptor agonist, is effective at reducing nervous system hyperactivity associated with acute opiate withdrawal.

Clonidine, an $\alpha_2$-adrenergic receptor agonist, is effective at reducing nervous system hyperactivity associated with acute opiate withdrawal.

Noradrenergic neuron in the locus coeruleus

Modified from C. Chavkin University of Washington
# Effects of Opioids

<table>
<thead>
<tr>
<th>Acute effects</th>
<th>Acute toxic dose</th>
<th>Chronic use</th>
<th>Withdrawal</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Euphoria</td>
<td>Pinpoint-size pupil</td>
<td>Risk of overdose</td>
<td>Irritability</td>
<td>Methadone</td>
</tr>
<tr>
<td>Well-being</td>
<td>Slow respiration</td>
<td>Malnutrition</td>
<td>Dysphoria</td>
<td>Naltrexone</td>
</tr>
<tr>
<td>Near stuporous state</td>
<td>Death</td>
<td>Reduced immunity</td>
<td>Nausea and vomiting</td>
<td>Naloxone</td>
</tr>
<tr>
<td>Sweating</td>
<td>Risks due to IV injections</td>
<td>Muscles aches</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea-vomiting</td>
<td>Reduced pain</td>
<td>Runny nose</td>
<td>Dilated pupils</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Diarrhea</td>
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<td></td>
<td></td>
<td></td>
<td>Yawning</td>
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</tr>
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<td></td>
<td></td>
<td></td>
<td>Fever</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Insomnia</td>
<td></td>
</tr>
</tbody>
</table>
Opiate Tolerance

receptor desensitization compensatory adaptations in neuronal circuit learning mechanisms

**Physical Dependence**
compensatory adaptations in neuronal circuit

**Drug Withdrawal**
removal of opiate unmasks compensatory adaptations

**Drug Addiction**
(rare during treatment of pain)
Opioid withdrawal/abstinence syndrome

Severity depends on dose used and rate of elimination.

Rhinorrhea
Lacrimation
Chills
Goose flesh
*Muscle aches
*Diarrhea
Yawning
*Anxiety
Hostility

Precipitated withdrawal by a partial agonist or antagonist administration
Opioid Antagonists

• Naloxone (Narcan®)
  - *Naloxone is specifically used to counteract life-threatening depression of the central nervous system and respiratory system*

• Naltrexone
  - *Naltrexone hydrochloride is a pure opioid antagonist, markedly attenuates or completely blocks the subjective effects of intravenously administered opioids.*
  - *When co-administered with morphine, on a chronic basis, Naltrexone hydrochloride blocks the physical dependence to morphine, heroin and other opioids.*

<table>
<thead>
<tr>
<th>Heroin/opiate addiction</th>
<th>FDA approved</th>
<th>Naltrexone</th>
<th>Methadone</th>
<th>Buprenorphine</th>
<th>Mu opioid receptor (antagonist)</th>
<th>Mu opioid receptor (substitution with different pharmacokinetics)</th>
<th>Mu opioid receptor (substitution)</th>
</tr>
</thead>
</table>

Psychostimulants

Large class of diverse compounds

- Stimulate alertness, arousal ("psycho-")
- Stimulate motor activity ("-motor")

Major Psychostimulants:
- Amphetamines and related compounds
- Cocaine
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Dopamine transporter (DAT)  
(amphetamine reverses DAT and VMAT direction; cocaine blocks DAT)
Amphetamine (racemic)
- mixture of d- and l- isomers
- Benzedrine®
- “speed”

d-Amphetamine
- dextroamphetamine
- Dexedrine®
Amphetamine related drugs

Methylphenidate
- Ritalin®
- attention deficit disorder

Fenfluramine
- Redux®
- anorectic

Phenmetrazine
- Preludin®
- anorectic
## Amphetamine

<table>
<thead>
<tr>
<th>Acute dose</th>
<th>Acute toxic dose</th>
<th>Chronic use</th>
<th>Withdrawal</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Euphoria</td>
<td>Chest Pain</td>
<td>Cardiac damage</td>
<td>Depression</td>
<td>Treat aspects of withdrawal</td>
</tr>
<tr>
<td>Increased self-esteem</td>
<td>Unconsciousness</td>
<td>Liver Damage</td>
<td>Decreased energy</td>
<td></td>
</tr>
<tr>
<td>Increased self-confidence</td>
<td>Psychotic reaction</td>
<td>Weight loss</td>
<td>Increased appetite</td>
<td></td>
</tr>
<tr>
<td>Hyperactivity</td>
<td></td>
<td>Paranoid states</td>
<td>Low self-esteem</td>
<td></td>
</tr>
<tr>
<td>Immunity to fatigue</td>
<td></td>
<td>Amphetamine psychosis</td>
<td>Decreased libido</td>
<td></td>
</tr>
<tr>
<td>Sterotyped behavior</td>
<td></td>
<td>Depression</td>
<td>Paranoia</td>
<td></td>
</tr>
<tr>
<td>Chills</td>
<td></td>
<td>IV related illnesses</td>
<td>Paranoid schizophrenia</td>
<td></td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Cocaine

Naturally-occurring alkaloid in leaves of shrub *Erythroxylon coca*

**Raw leaves**
- chew
- alkaloid content low (0.6 - 1.8 %)
- not stable

**Coca paste**
- initial extraction
- smoked
- around 80% cocaine
Forms of cocaine

Cocaine HCl
- purified and converted to HCl salt
- crystalline form, water soluble
- pure if not diluted
- snorted or i.v.

Cocaine free base: crack
- extract
- smoked
<table>
<thead>
<tr>
<th>Cocaine</th>
<th>Acute mild dose</th>
<th>Acute high dose</th>
<th>Acute toxic dose</th>
<th>Chronic use</th>
<th>Withdrawal</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Euphoria</td>
<td>Stereotyped behavior</td>
<td>Restlessness</td>
<td>Weight loss</td>
<td>The crash</td>
<td></td>
<td></td>
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<tr>
<td>Increased self-esteem</td>
<td>Impaired judgement</td>
<td>Agitation</td>
<td>Sleep disorders</td>
<td>Withdrawal</td>
<td></td>
<td>treat aspects of withdrawal</td>
</tr>
<tr>
<td>Increased self-confidence</td>
<td>Chills</td>
<td>Intense anxiety</td>
<td>Memory impairment</td>
<td>Extinction</td>
<td></td>
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</tr>
<tr>
<td>Improved mental performance</td>
<td>Nausea and vomiting</td>
<td>Tremors</td>
<td>Attention deficit</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immunity to fatigue</td>
<td>Chest pains</td>
<td>Muscular twitching</td>
<td>Irritability and mood swings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improved sexual performance</td>
<td>Cardiac arrhythmias</td>
<td>Delirium and hallucination</td>
<td>Social isolation</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Increased heart rate</td>
<td>Death</td>
<td>Paranoia</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Elevated BP</td>
<td>Loss of interest in pleasure</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Dilated pupils</td>
<td>Diminished libido</td>
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<tr>
<td></td>
<td></td>
<td>Constriction of blood vessels</td>
<td>Depression</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Increased respiration</td>
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<tr>
<td></td>
<td></td>
<td>Decreased appetite</td>
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<tr>
<td></td>
<td></td>
<td>Increased metabolic rate</td>
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</tbody>
</table>
## Cocaine addiction-pharmacotherapy

### Clinical target

<table>
<thead>
<tr>
<th>Alcoholism</th>
<th>Medication</th>
<th>Biological target</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA approved</td>
<td>Disulfiram (Antabuse; Wyeth-Ayerst)</td>
<td>Aldehyde dehydrogenase (triggers aversive response)</td>
</tr>
<tr>
<td>Under investigation</td>
<td>Naltrexone</td>
<td>Mu opioid receptor (antagonist; interferes with reinforcement)</td>
</tr>
<tr>
<td></td>
<td>Acamprosate</td>
<td>Glutamate related</td>
</tr>
<tr>
<td></td>
<td>Topiramate</td>
<td>GABA/glutamate</td>
</tr>
<tr>
<td></td>
<td>Valproate</td>
<td>GABA/glutamate</td>
</tr>
<tr>
<td></td>
<td>Citalopram</td>
<td>5-HT receptor</td>
</tr>
<tr>
<td></td>
<td>Namfene</td>
<td>Mu opioid receptor (antagonist)</td>
</tr>
<tr>
<td></td>
<td>Baclofen</td>
<td>GABAb receptor (agonist)</td>
</tr>
<tr>
<td></td>
<td>Pyrolopyrimidine compound</td>
<td>CRF1 receptor (inhibits stress-triggered responses)</td>
</tr>
<tr>
<td></td>
<td>Rimonaabant (Acomplia; Sanofi-Synthelabo)</td>
<td>CB1 receptor (antagonist)</td>
</tr>
</tbody>
</table>

### Nicotine addiction

| FDA approved | Nicotine replacement | Nicotinic receptor (substitution with different pharmacokinetics) |
| Under investigation | Bupropion | DA transporter blocker (amplifies DA signals) |
| | Deprenyl | MAO-B inhibitor (inhibits metabolism of DA) |
| | Rimonaabant (Acomplia; Sanofi-Synthelabo) | CB1-receptor antagonist |
| | Methoxsalen | CYP2A6 (inhibits nicotine metabolism) |
| | Nicotine conjugate vaccine | Blocks entry into brain |

### Heroin/opiate addiction

| FDA approved | Naltrexone | Mu opioid receptor (antagonist) |
| Under investigation | Methadone | Mu opioid receptor (substitution with different pharmacokinetics) |
| | Buprenorphine | Mu opioid receptor (substitution) |

### Cocaine addiction

| Under investigation | Topiramate | GABA (agonist) |
| | γ-VPyl GABA (GVG) | GABA transaminase (inhibits GABA metabolism) |
| | Gabapentin | GABA/glutamate (synthesis) |
| | Tagrobine | GABA transporter (inhibitor) |
| | Baclofen | GABAa receptor (agonist) |
| | Methadon | Glutamate |
| | Disulfiram | Unknown for cocaine |
| | Cocaine vaccine | Blocks entry into brain |

**Volkow & Li, Nature Reviews**
Delta FosB: a sustained molecular switch for addiction?

- Increase rewarding properties of cocaine
- Increase in behavioral sensitization
- Increase in self administration of cocaine

ΔFosB is known to directly regulate:
- Cholecystokinin (CCK)
- AMPA Glutamate subunits - GluR2
- Cry2
- Ca$^{2+}$/calmodulin-dependent protein kinases II (CaMKII)
- Sirtuin 1 (Sirt1)
Epigenetic Regulation of Gene Expression Governs Long-Term Changes