Psychopharmacology of Substance Use Disorders 2017

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Disclosures

• Merrill Norton, PharmD, DPh, ICCDP-D, declares no conflicts of interest, real or apparent, and no financial interests in any company, product, or service mentioned in this program, including grants, employment, gifts, stock holdings, and honoraria.

How many of you know someone who is addicted?
Do you know what happened to cause the addiction?

So What is Addiction?

The Neuroscience and Pharmacology of Addiction 2017
The Brain’s Addiction Network

- The Reward System
- The Anti-Reward System
- The Brain Stress System
- The BDNF System
- The Neurotransmitters
- The Receptors
- The Drugs
- The Genetics
- The Addiction Process
- The Mental Component
- The Cravings
- The Relapse Process

“Let’s just go in and see what happens.”
Addiction is a Complex Illness

...with biological, sociological and psychological components

Addiction is Treatable!

BRAIN RECOVERY WITH PROLONGED ABSTINENCE

Normal Brain  1 month of abstinence  14 months of abstinence

Psychoactive Drug Use

- Usually a single episode
- May have consequences depending on amount of drug taken:
  - 1. Physical - allergic reactions to the drug, similar to a penicillin like reaction;
  - 2. Emotional – may cause depression or over-excitation depending on the drug classification;
  - 3. Social/Legal: violence, fights or DUIs
Drug Abuse
Drug abuse (includes alcohol) is a patterned use of a substance (drug) in which the user consumes the substance in amounts or with methods neither approved nor supervised by medical professionals. Substance abuse/drug abuse is not limited to mood-altering or psycho-active drugs. If an activity is performed using the objects against the rules and policies of the matter (as in steroids for performance enhancement in sports), it is also called drug abuse. Therefore, mood-altering and psychoactive substances are not the only types of drugs abused.
- [ ] There is a wanting to use the drug again;
- [ ] A physical withdrawal syndrome may occur;
- [ ] May have consequences similar to drug use depending on amount of drug taken.

Drug Addiction
An authoritative definition of drug addiction is that propounded by the World Health Organization:
"Drug addiction is a state of periodic and chronic intoxication detrimental to the individual and to society, produced by the repeated consumption of a drug (natural or synthetic). Its characteristics include: (1) An overpowering desire or need (compulsion) to continue taking the drug and to obtain it by any means; (2) A tendency to increase the dose; (3) A psychic (psychological) and sometimes a physical dependence on the effects of the drug."

Desire Corresponds with Drug Use
- Liking
  - Non-problematic Use
- Wanting
  - Abuse
- Craving
  - Addiction
Desire Corresponds with Drug Use

50% of US population DOES NOT USE any alcohol/drugs

- Liking
  - Non-problematic Use 50%
- Wanting
  - Use 89%
- Craving
  - Addiction 11%

The Addicted Brain - 2017

Neurobiology of Addiction 2017

- Addiction is increasingly understood as a neurobiological illness where repetitive substance abuse corrupts the normal circuitry of rewarding and adaptive behaviors causing drug-induced neurotransmitter changes.
- The addictive process can be examined by looking at the biological basis of substance initiation to the progression of substance abuse to dependence to the enduring risk of relapse.
- Critical neurotransmitters and neurocircuits underlie the pathological changes at each of these stages.
- Enhance dopaminergic transmission in the nucleus accumbens is part of the common pathway for both drug reward and for initiation of the addiction process.
- γ-Aminobutyric acid, opioid peptides, serotonin, acetylcholine, the endocannabinoids, and glutamate systems also play a role in the initial addictive process.
- Dopamine also plays a key role in conditioned responses to drugs of abuse, and addiction is now recognized as a disease of pathological learning and memory.
- In the path from substance abuse to addiction, the neurochemistry shifts from a dopamine-based behavioral system to a predominantly glutamate-based one characterized by dysregulated glutamate transmission from the prefrontal cortex to the nucleus accumbens in relation to drug versus biologically oriented stimuli. This has been called the anti-reward brain.
- This is a core part of the executive dysfunction now understood as one of the hallmark features of addiction that also includes impaired decision making and impulse control.
- Understanding the neurobiology of the addictive process allows for a theoretical psychopharmacological approach to treating addictive disorders, one that takes into account biological interventions aimed at particular stages of the illness.
Dopamine
Primary chemical in the brain responsible for activating the reward pathway
During the preoccupation phase of addiction, dopamine is being released stimulating desire for a drug
During the intoxication phase, all the dopamine in the brain is released giving the user a euphoric feeling
During the withdrawal phase, the brain has run out of dopamine and can not function properly until more is made

DSM IV TR Definitions
addiction
2 Abuse
Midbrain
physical and psychological dependence

Dopamine/Endorphins
Receptors

1 USE Cortex

Physical Dependence
Natural Rewards Elevate Dopamine Levels

FOOD

SEX

% of Basal DA Output

DA Concentrations (% Baseline)

Di Chiara et al., Neuroscience, 1999.

FOOD

Mounts

Intromissions

Ejaculations


Natural Rewards Elevate Dopamine Levels

Effects of Drugs on Dopamine Release

AMPHETAMINE

COCAINEN

NICOTINE

MORPHINE

Increased cAMP produced in post-synaptic cell
Definitions

• cAMP - Cyclic adenosine monophosphate used for intracellular signal transduction (power source - electrical)
• BDNF - Brain-derived neurotrophic factor - encourage the growth and differentiation of new neurons and synapses (chemical).
• CREB - (CAMP Response Element Binding) - neuronal plasticity and long-term memory formation in the brain (transformer - converts electrical messages to chemical messages).

BDNF and Moderation

• Growth factors, long studied for their involvement in neuronal development and plasticity, also regulate responses to drugs of abuse, including alcohol. This review details the intricate interaction between the Brain-Derived Neurotrophic Factor (BDNF) and alcohol, and provides evidence to suggest that corticostriatal BDNF signaling acts to keep alcohol drinking in moderation. Specifically, we describe studies in rodent models suggesting that moderate consumption of alcohol increases BDNF levels in the dorsal striatum, which in turn act to suppress alcohol intake by activating a Mitogen-Activated Protein Kinase (MAPK)-dependent genomic mechanism.


Dynorphin, Dysphoria, and Dependence: the Stress of Addiction

Charles Chavkin and George F Koob

The hypothesis that the dynorphin-kappa opioid receptor system may be a key component of the neuroplasticity associated with stress-induced mood disorders and the 'dark side' of addiction (withdrawal-negative affect stage) continues to gain preclinical and clinical experimental support. The endogenous kappa opioid peptides derived from prodynorphin encode the dysphoric, anxiogenic, and cognitive disrupting responses to behavioral stress exposure (Bruchas et al, 2010; Carroll and Carlezon, 2013)

Neuropsychopharmacology 41, 373-374 (January 2016) doi:10.1038/npp.2015.258.

Addiction is Greater Than a Mother’s Love (Dynorphin)

The reason for the that addicts can not stop using is once the dopaminergic system is deactivated (depleted) due to multiple neurobiological reasons the reinforcing effects of the drug becomes more powerful than a mother’s love for her children. In 2016, the potencies of most street drugs (marijuana/heroin) have increased. This increased potency creates the increased reinforcing effects of dopamine thus increasing the addiction liability of the drug on the brain.

Brain Region Overview

Prefrontal (choices/good/bad) → nucleus accumbens (reward pathways) → Ventral Tegmental Area (memory)
Prefrontal Cortex  Decision Maker

Used in planning, decision making, and alignment of actions with goals.

Normal brain: Contributes to social behavior and planning for enjoyment.
Addicted brain: Drugs become the primary motivator at the expense of the aspects of normal life activities.

Nucleus Accumbens: Type of Euphoria  
Sweet Thang you make me feel soo..goood....

Main part of the reward pathway of the brain.
Normal brain: Processes the rewarding aspect of experiences such as food, water, sex, and exercise.
Addicted brain: Dopamine production from some drugs causes a depletion of natural dopamine production so reward is only stimulated through drugs.

Ventral Tegmental Area
(Memory Systems of Our Greatest Pleasures)

Involved in dopamine production, memory, mood, and strong emotions. It sends these signals to the prefrontal cortex and nucleus accumbens.
Normal brain: Sends the reward signal when stimuli is presented that cause the brain to remember strong emotions such as love.
Addicted brain: Dopamine produced from drug use causes the lack of ability to respond to other stimuli because of a dopamine deficit.
### Opioid Receptors (Euphoria Receptors)

- **µ (mu):**
  - Activated by morphine: analgesia
  - Primary action site of all opioids
  - Distribution: primarily in CNS and also GI
  - Linked to substance use disorders

- **δ (delta):** for endogenous peptides - Nerve Conduction - slows pain signal between the peripheral nervous system and the central nervous system (brain, hypothalamus, spinal cord)

- **κ (kappa):** analgesia, endocrine changes and dysphoria (brain-amygdala, spinal cord) Stress Reduction

### Substance Use Disorders Change the following:

Opioid Receptors (mu, kappa, delta)-euphoria;

The Endogenous Opioid Peptide System (Endorphins/Dynorphins);

Cellular Membrane Action - down-regulation of GTP to GDP (release of beta-arrestins (2 & 3) that is responsible for opioid tolerance);

Dopamine Pathways - decreased production, storage, and transport;

Brain Derived Neurotropic Factors changes that may cause psychiatric mood dysregulation.

### Opioid Receptors (I)

- Five classes of opioid receptor
  - Mu(µ), Delta(δ), Kappa(κ) Nociceptin Subtypes (σ, ε receptors)
- Subtype of µ, δ, κ receptor
- Structural characteristics** (The more characteristics - the higher addiction liability)
  - Typical G-protein-coupled receptor
  - Seven hydrophobic region
  - Three intracellular loops
  - Three extracellular loops
  - Intracellular carboxy-terminal tail
  - Extracellular amino-terminal tail
Opioid Receptors (II)

The Basic Pharmacology of the Endogenous Opioids

Dopamine Neural Pathways

1. Behaviors-Pleasure
2. Euphoria-Addiction
3. Movement-Parkinson's Disease-EPS
4. Perception-Psycosis
Thinking Brain

Judgment Brain

Instinctual Brain

Pleasure Brain

“i want a beer”

“It makes me feel gooood”

“Miller Lite”

**Slide used with permission from DVD series “From DisGrace To Grace: The Hijacking of the Brain” By Dr. Merrill Norton, Pharm.D., D.Ph., ICCDP-D, University of Georgia College of Pharmacy, Athens**

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**MESOLIMBIC DOPAMINE SYSTEM**

- **Circuit #1 Occasional Use -**
  - Relief/Like
  - Occasional Use -
    - Dopamine
    - Mesocorticolimbic

- **Circuit #2 Pattern of Use -**
  - Endorphins
  - Repeat/Want
  - Basolateral n. of amygdala

- **Circuit #3 Addiction -**
  - Dynorphins
  - Need/Craving
  - Periaqueductal gray of brain stem

**Stimulation of the periaqueductal gray matter of the midbrain activates enkephalin - releasing neurons that project to the raphe nuclei in the brainstem. Enkephalin (endogenous opioid neurotransmitter), binds to mu opioid receptors.**

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**DSM 5 DEFINITION AND CRITERIA FOR SUBSTANCE USE DISORDER (RELEASED SPRING 2013) (ICD-10 CODES EFFECTIVE 10-1-2015)**

Substance Use Disorder - A maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by 2 (or more) of the following, occurring within a 12-month period:

1. Recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home (e.g., repeated absences or poor work performance related to substance use; substance-related absences, suspensions, or expulsions from school; neglect of children or household)

2. Recurrent use in situations in which it is physically hazardous (e.g., driving an automobile or operating a machine when impaired by substance use)
DSM 5 Substance Use Disorder Criteria

3. continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance (e.g., arguments with spouse about consequences of intoxication, physical fights)

4. tolerance, as defined by either of the following:
   a. need for markedly increased amounts of the substance to achieve intoxication or desired effect
   b. markedly diminished effect with continued use of the same amount of the substance (Note: Tolerance is not counted for those taking medications under medical supervision such as analgesics, antidepressants, anti-anxiety medications or beta-blockers.)

5. Withdrawal is manifested by either of the following:
   a. The characteristic withdrawal syndrome for substance used;
   b. Medication or closely related is taken to relieve or avoid withdrawal symptoms;

6. There is a persistent desire or unsuccessful efforts to cut down or control use;

7. Substance taken in larger amounts or over a longer period than intended;

8. Spend lots of time obtaining the substance, using the substance, or recovering from its effects;

9. Important social, occupational, or recreational activities are given up or reduced because of substance use;

10. The substance use is continued despite knowing you have a serious physical or psychological problem that is likely to have been caused or made worse by the substance;

11. Craving or a strong desire or urge to use a specific substance.
Moving To A Dependent State - Craving Is New in the Diagnosis

Cravings
- Craving: memory of the rewarding aspects of drug use superimposed on a negative emotional state
- Compels drug-seeking in dependent individuals

3 Types of Cravings
- Withdrawal induced
- Drug-induced
- Cue-induced
Reward Craving-Type 1

- Craving-induced by stimuli that have been paired with drug self-administration such as environmental cues
- An animal model of craving-type 1 is cue-induced reinstatement where a cue previously paired with access to drug reinstates responding for a lever that has been extinguished.
- Neurobiological substrates include glutamatergic projections from medial prefrontal cortex and basolateral amygdala to nucleus accumbens

Role of Glutamate and Dopamine Neurotransmission in Relapse to Drug-Seeking Behavior


Relief Craving-Type 2

- State of protracted abstinence in subjects with addiction or alcoholism weeks after acute withdrawal.
- Conceptualized as a state change characterized by anxiety and dysphoria or a residual negative emotional state that combines with Craving-Type 1 situations to produce relapse to excessive drug taking
- Animal models of Craving-Type 2 include stress-induced reinstatement and increased drug taking in animals during protracted abstinence
- Neurobiological substrates include residual activation of brain stress systems including corticotropin releasing factor and norepinephrine in the extended amygdala
Positive and Negative Reinforcement - Definitions

**Positive Reinforcement** — defined as the process by which presentation of a stimulus (drug) increases the probability of a response (non dependent drug taking paradigms).

**Negative Reinforcement** — defined as a process by which removal of an aversive stimulus (negative emotional state of drug withdrawal) increases the probability of a response (dependence-induced drug taking).

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**Drug-induced Craving**

![Graph showing craving levels](image)

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**DSM 5 Addiction Severity Levels**

- **Mild**: 2-3 criteria
- **Moderate**: 4-5 criteria
- **Severe**: 6 or more
So what happens ....... In the beginning.....how does a person become addicted?

It starts with occasional use of alcohol or any other drug like marijuana or prescription medications and with the development of the brain............

The average age of first use in the United States is 14 years old. At that age, the brain is NOT mature biologically with the age of complete maturity of the brain being 24-28 years old. This immaturity creates a risk factor for addiction.
Factors Contributing to Vulnerability to Develop a Specific Addiction

use of the drug of abuse essential (100%)

Genetic (25-50%)
- DNA
- SNPs
- other polymorphisms

Environmental (very high)
- prenatal
- postnatal
- contemporary
- cues
- comorbidity

Drug-Induced Effects (very high)
- mRNA levels
- peptides
- proteomics
- neurochemistry
- behaviors

Kreek et al., 2000

Initially, a person takes a drug hoping to change his or her mood, perception, or emotional state

Translation...
...hoping to change their brains.

"I want a beer"
"It makes me feel gooooood"
"Miller Lite"

Slide used with permission from DVD series "From DisGrace To Grace: The Hijacking of the Brain."
By Dr. Merrill Norton, Pharm.D., D.Ph., ICCDP-D
University of Georgia, College of Pharmacy
Athens, Georgia

Georgia Prescription Drug Abuse Prevention Initiative Training
We know that despite their many differences, most abused substances enhance the dopamine and serotonin pathways.

Then you add the changes to the chemicals responsible for “feeling good” - Dopamine and its family members- that comes with regular use of alcohol and other drugs.

“The Necessary Nine”
- stimulant, anger, fear, anxiety, fight, flight
- depressant, sleep, calm, pleasure
- relaxant, stress reduction, seizure threshold
- pain relief, pleasure
- involuntary actions, memory, motivation
- Anandamide-memory, new learning, calmness
- organization of brain signaling, memory, pain
- perception, movement, pleasure
- Dynorphins- loving of one’s self, others, GOD
The Neurobiology of Reward

- The neurobiology of reward has been well understood for decades, whereas the neurobiology of addiction is still being explored.
- Most scientists have learned of reward pathways including projections from the ventral tegmental area (VTA - memory of greatest pleasures) of the brain, through the median forebrain bundle (MFB - pleasure pathway), and terminating in the nucleus accumbens (Nuc Acc - type of pleasure experienced), in which dopamine neurons are prominent.
Current neuroscience recognizes that the neurocircuitry of reward also involves a rich bidirectional circuitry connecting the nucleus accumbens and the basal forebrain. This means that the brain has several different pleasure pathways, thus the brain may experience different types of pleasure from the various drugs of abuse.

It is the reward circuitry where reward is registered, and where the most fundamental rewards such as food, hydration, sex, and nurturing exert a strong and life-sustaining influence.

**A (very) Brief Overview of the Neurobiology of Addiction**

<table>
<thead>
<tr>
<th>Dopamine</th>
<th>- Like Occasional Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endorphins</td>
<td>- Want: Pattern of Use</td>
</tr>
<tr>
<td>Dynorphins</td>
<td>- Craving: Addiction</td>
</tr>
</tbody>
</table>

**Brain Reward Pathways**
Use Changes Reward Patterns

- Normal Reward Brain Pathways
  - Dopamine Release (Happiness & Joy)
  - Eventually, the sources (Endorphins, Dynorphins) are depleted
  - Anti-reward brain

- Anti-Reward Brain in Addiction
  - Brain systems in place to limit reward
  - Triggered by excessive activity in the reward system
  - Glutamate/GABA Release (Pain/Depression/Anxiety)

Activation of the reward pathway by addictive drugs

Dopamine Pathways

The Changing of the Brain’s Communication Highway

1.) Alcohol, Marijuana, Rx medications alter the receptors and neurotransmitters with any use; it happens like this:
2.) The person experiences euphoria from the release of dopamine (excessive amounts) when they drink or use a drug;
3.) The brain records this pleasurable experience in short term memory—“this was a good time”;
4.) If the person begins to repeat the pleasurable experience, the dopamine becomes depleted, the brain attempts to stabilize the chemistry by using another set of chemicals, the endorphins, to reset the brain back to normal; but this attempt just creates a need for more of the drug—tolerance and withdrawal;
5.) If the person continues to use (thinking that they can get back to normal), the brain activates a third set of chemicals, the dynorphins, to keep the brain’s communication highway open.
The Changing of the Brain's Communication Highway

6.) The dynorphins are responsible for many things in the brain, one of the most important is stress reduction created by intimate relationships (family, friends, church, etc.) A long term memory system is activated.

7. As the person continues to use the drug, the dynorphins are depleted over time, making normal relationships less important.

8. As the depletion of the dynorphins continues, the brain will begin to substitute the drug of abuse for the brain's natural dynorphin.

9.) The brain becomes "hijacked" using the drug of abuse as the primary relationship of importance, instead of the normal relationships in the person's life. This is addiction.

10.) Once the hijacking occurs it is irreversible—addiction is a chronic disease process.

MESOLIMBIC DOPAMINE SYSTEM

Circuit #1 Occasional Use—Dopamine
- Relief/Like
- Dopamine neurotransmission
- Mesocaudatal

Circuit #2 Pattern of Use—Endorphins
- Repair/Want
- Endorphins and enkephalins
- Basolateral n. of amygdala

Circuit #3 Addiction—Dynorphins
- Need/Craving
- Dynorphins are depleted
- Pathologic desire & demand circuit
- Periaqueducal gray of brain stem

Stimulation of the periaqueductal gray matter of the midbrain activates enkephalin—releasing neurons that project to the raphe nuclei in the brainstem. Enkephalin (endogenous opioid neurotransmitter) binds to mu opioid receptors.

Thinking Brain
Judgment Brain
Instinctual Brain

"I want a beer"
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Addicted Brain

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Addicted Brain

Slide used with permission from DVD series "From DisGrace to Grace: The Hijacking of the Brain" by Dr. Merrill Norton, Pharm.D, D.PH, ICCDP-D, University of Georgia College of Pharmacy, Athens, Georgia.
How Long Does the Brain Remember the drug of choice?

Front of Brain
Amygdala not lit up

Back of Brain
Nature Video
Cocaine Video

Three Stages of Addiction

- Binge/intoxication
  - Reward Brain
- Withdrawal/negative affect
  - Anti-reward Brain
- Preoccupation/ anticipation/ craving
  - Addiction- Craving Brain

The Anti-Reward Brain

- 1. A key element of addiction is the development of a negative emotional state during drug discontinuation.
- 2. The neurobiological basis of the negative emotional state derives from two sources: decreased reward circuitry function and increased anti-reward circuitry function.
- 3. The anti-reward circuitry function recruited during the addiction process can be localized to connections of the extended amygdala in the basal forebrain.
- 4. Neurochemical elements in the anti-reward system of the extended amygdala have as a focal point the extrahypothalamic corticotropin-releasing factor system.
- 5. Other neurotransmitter systems implicated in the anti-reward response include noradrenaline, dynorphin, neuropeptide Y, and nociceptin.
- 6. Vulnerability to addiction involves multiple targets in both the reward and anti-reward system, but a common element is sensitization of brain stress systems.
- 7. Dysregulation of the brain reward system and recruitment of the brain anti-reward system are hypothesized to produce an allostatic emotional change that can lead to pathology.
- 8. Nondrug addictions may be hypothesized to activate similar allostatic mechanisms.
Preadolescent and adolescent exposure to alcohol, tobacco, or drugs of abuse significantly increases the propensity for dependence in adulthood.

Adolescents first intoxicated with alcohol at age 16 or younger are 2–3 times more likely to develop dependence (similar to tobacco).

Early onset of drug use is a predictor of subsequent drug problems.

A concept based on the hypothesis that there are brain systems in place to limit rewards that are triggered by excessive activity in the reward system.
Sensitivity to Anti–Reward Neuroadaptations

- Psychodynamic self–medication hypothesis
  - Focuses on underlying developmental difficulties, emotional disturbances, structural factors, building of self, and personality organization
  - Individuals hypothesized to take drugs as a means to cope with painful and threatening emotions

- Comorbid Psychiatric disorders
  - Some of the strongest associations are found with mood disorders, antisocial personality disorders, and conduct disorders
Addiction is Treatable!

Thank You For Your Time

Any Questions?

References

- "Brain Reward Pathways." Icahn School of Medicine, Nestler Laboratory. Retrieved September 02, 2015.
References