



## Exploring Current Theories on the Neurobiology of Addictions

Fritz Jean-Noel, M.D.

September 9<sup>th</sup>, 2011

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### Objectives

- Pathophysiology
- Genetics
- Medications
- Other forms of treatment



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### Addiction

“She goes from one addiction to another. All are ways for her to not feel her feelings”

Ellen Burstyn



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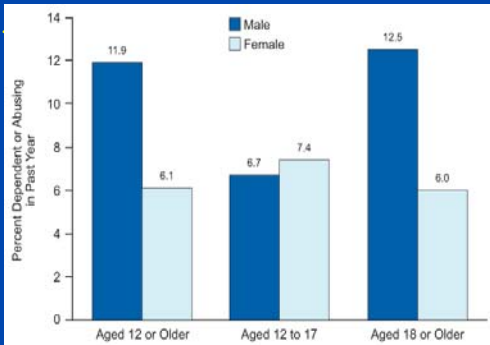
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Substance Dependence or Abuse in the Past Year, by Age and Gender: 2009 (NIDA)




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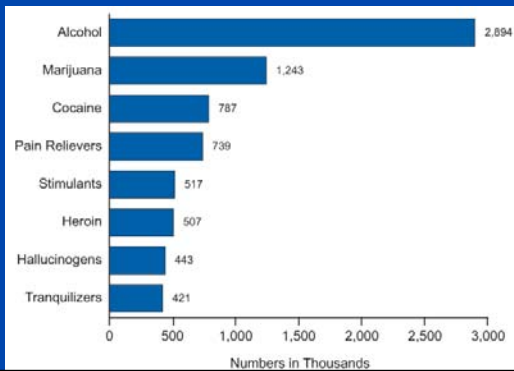
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Substances for Which Most Recent Treatment Was Received in the Past Year among Persons Aged 12 or Older: 2009 (NIDA)




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**Case 1**

- 18 year old male, single, new father of 2 month year old. Did not complete high school.
- Multiple legal charges: accidentally shot girlfriend (mother of his child) while intoxicated
- Drug of choice: "I don't know. Everything?"
- Substance use history: cannabis, alcohol, cocaine, amphetamines, opiates

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## DSM V

- Substance Use Disorder
  - Moderate
  - Severe (there is no Mild)
  - No more Abuse vs. Dependence!
- Criteria for Substance Use Disorder
  - Abuse, Dependence, + craving, - legal
  - Cannabis withdrawal will also be coming
  - Pathological Gambling will be added to the section entitled "Addiction and related disorders"
  - Caffeine use disorder is being debated



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## CONDITIONING

### REINFORCEMENT:

INCREASE a behavior or response



### PUNISHMENT:

DECREASE a behavior or response



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## CONDITIONING

REINFORCEMENT: INCREASE a behavior

**Positive reinforcement:** the *adding of pleasure*

- (give dog cookie for a trick)
- ↑ cookie → ↑ tricks

**Negative reinforcement:** the *removal of non-pleasure*

- (loud noise without seatbelt)
- ↓ noise → ↑ seatbelt



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## CONDITIONING

- **PUNISHMENT: DECREASE a behavior or response**
- **Positive punishment:** the adding of *non-pleasure*  
(mother yell at child to not run into street)
- ↑ Yelling → ↓ running
- **Negative punishment (omission training):** remove a *pleasure*  
(removing a toy in order to stop crying )
- ↓ Toy → ↓ crying



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## Early Theories

- Drugs initially consumed to produce pleasure (reward) and dependence was repeated drive for pleasure. (Wise, 1980) (Zur 1988)
- Seen as Positive Reinforcement.
- ↑ DRUG → ↑ PLEASURE



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## Early Theories

- Positive Reinforcement doesn't explain
- Multiple Use the Pleasure goes away
- Need Higher Doses, More Frequency to get Pleasure



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## Early Theories

Soon enough:

- No Drug → Withdrawal, Adverse Effects
- Negative Reinforcement (Carr and Fenn, 2003)
- Take Drug to Avoid Withdrawal (Adverse Effects)



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## Get Trapped in a Cycle

- Positive Reinforcement:
- Take Drug → Pleasure → Withdrawal
- Negative Reinforcement:
- Withdrawal → Take Drug → Normal
- Cycles:
- Normal → Take Drug → Pleasure



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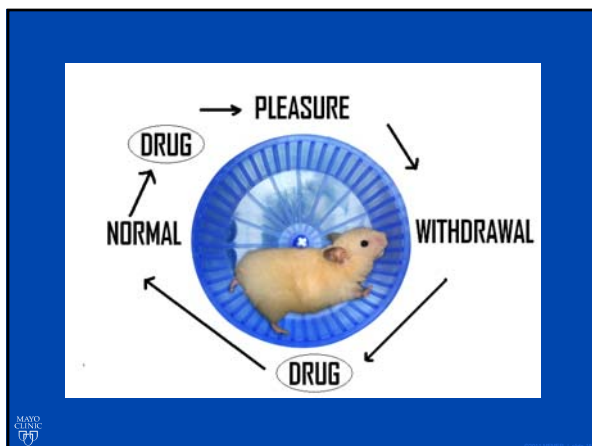
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## Neuro-adaptation

- Repeated use leads to adaption in pathways

### Myriad of theories:

- Hedonic set point (Koob, 1997)
- Incentive sensitization (Robinson and Berridge, 1993, 1995)
- Hypersensitivity theory (Clark and Overton, 1998)
- Aberrant Stimulus Response (Wise 2002)
- Prefrontal alterations (Jentsch and Taylor, 1999)

Each theory builds of another and sometimes overlap



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- “Quitting smoking is easy. I’ve quit hundreds of times.”

- Mark Twain



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## Case #2

- 50 year old married mother of three
- Liver Cirrhosis (Alcohol) (Hepatitis C)
- Cachetic, Jaundice
- Continued drinking despite transplant possibility



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## Drugs of Abuse

- Alcohol: GABA
- Cocaine and Amphetamines: NE, Dopamine
- Cannabis: Cannabinoids
- Narcotics: Opiate receptors
- Nicotine: nAch receptors



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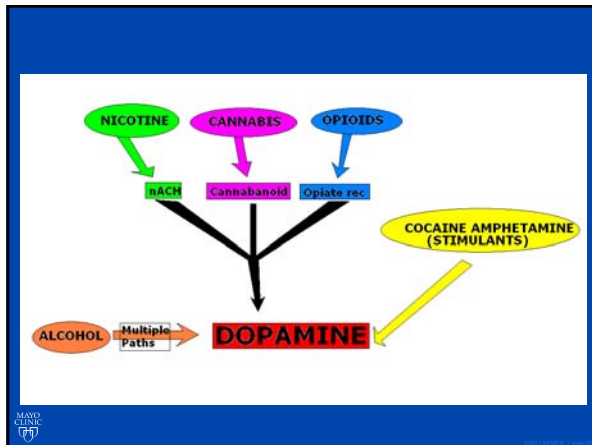
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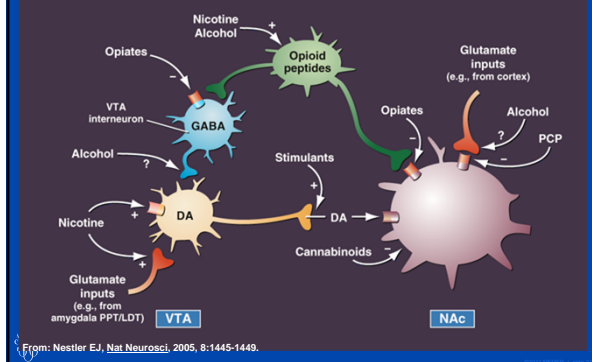
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## Converging Acute Actions of Drugs of Abuse on the Ventral Tegmental Area and Nucleus Accumbens



From: Nestler EJ, *Nat Neurosci*, 2005, 8:1445-1449.

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## Common Pathway

Despite the myriad of effects:

- Mesocorticolimbic Pathway



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## Mesocorticolimbic

- Meso (Middle)
- Cortico (Cortex)
- Limbic (Edge)



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## MesoCorticoLimbic Pathway

### Dopamine:

Catecholamine

Multiple functions (movement, hormonal, cognition)

### Glutamate:

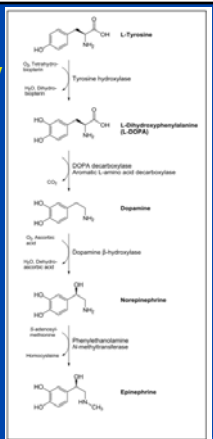
Excitatory neurotransmitter

Associated with neuroplasticity

### GABA

Inhibitory neurotransmitter

Also multiple function



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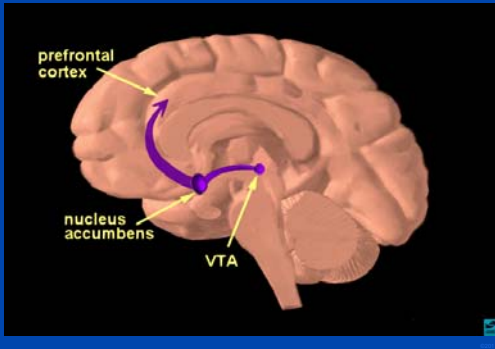
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### Mesocorticolimbic Pathway



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### MesoCorticoLimbic Pathway

- Ventral Tegmental Area (VTA): dopamine
- Nucleus Accumbens (NA): reward
- Prefrontal Cortex (PFC): motivation, emotion

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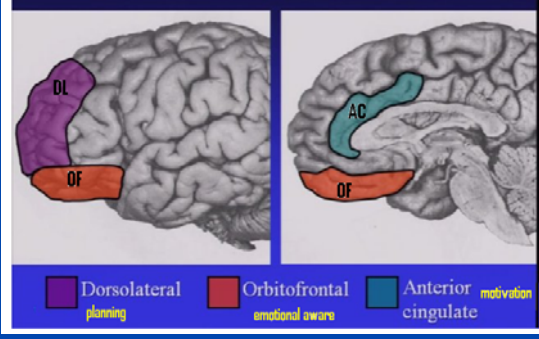
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### Neurobehavioral Prefrontal Circuits



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## Mesocorticolimbic System

- “Reward System”: Food, Sex
- VTA → Limbic Structures

Limbic (emotions, long term memory)

- Amygdala: fear and anxiety
- Ventral Pallidum: motivation
- Hippocampus: memory
- Nucleus Accumbens: reward center



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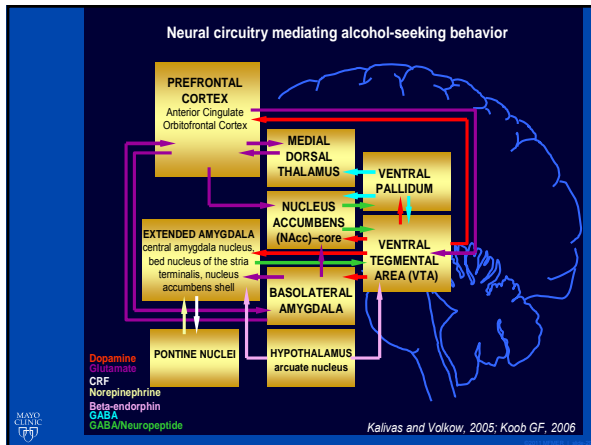
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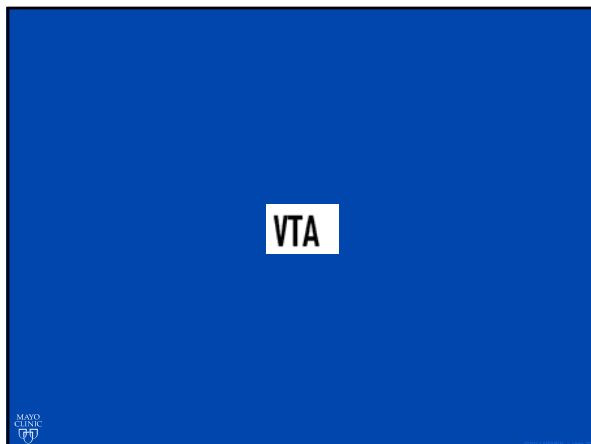
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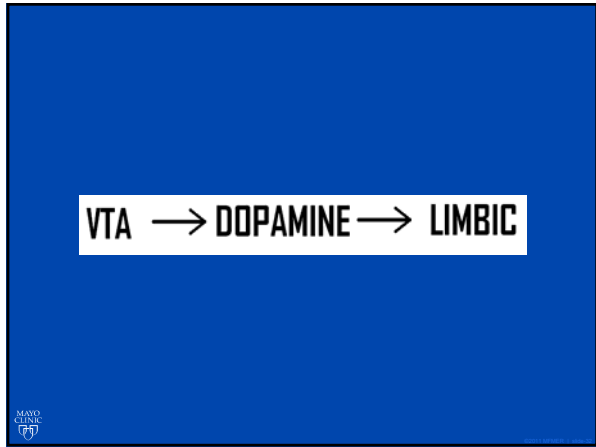
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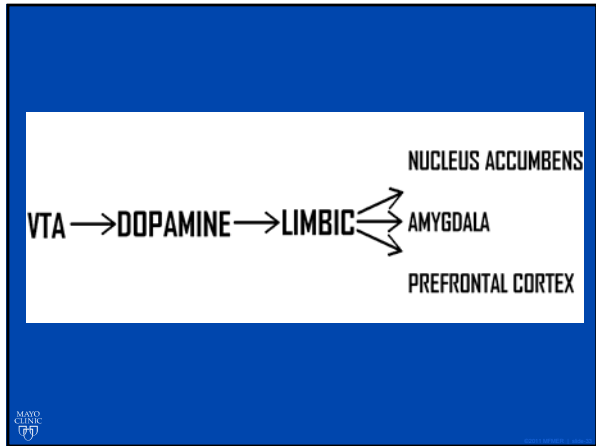
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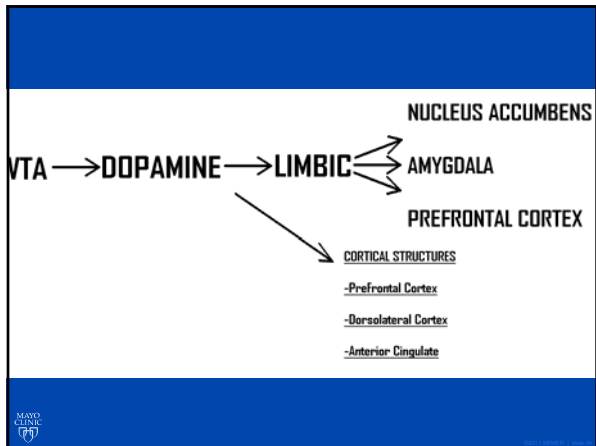
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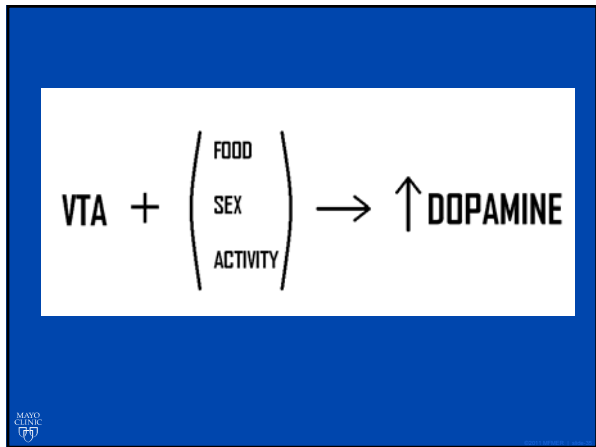
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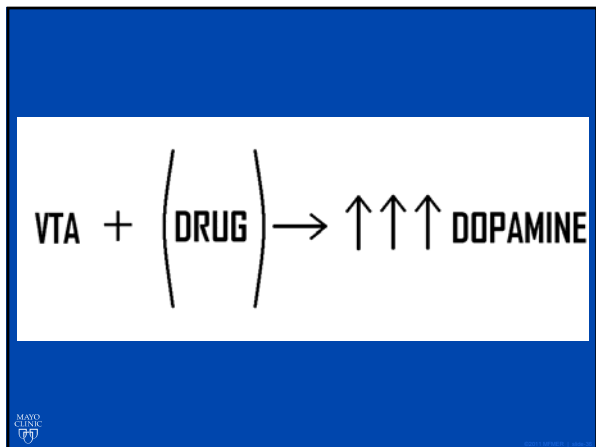
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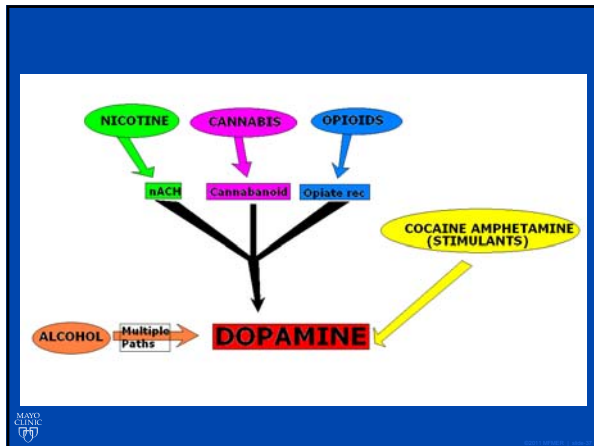
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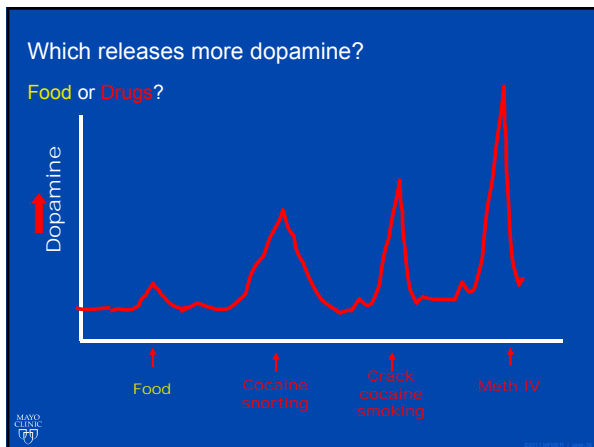
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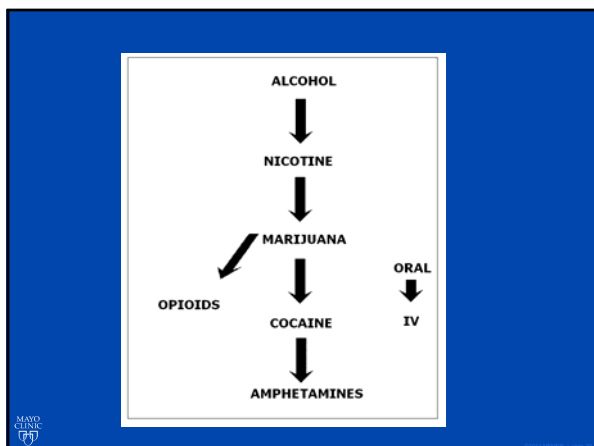
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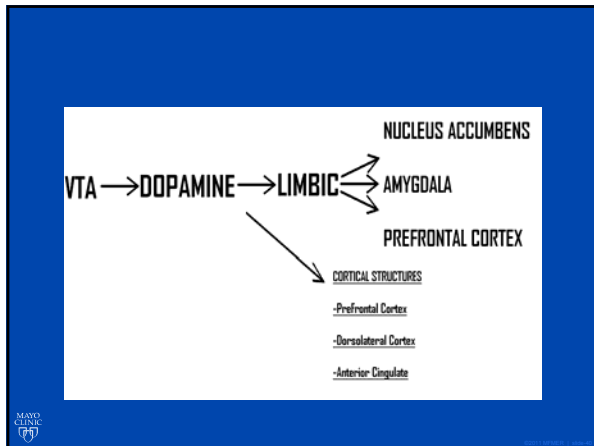
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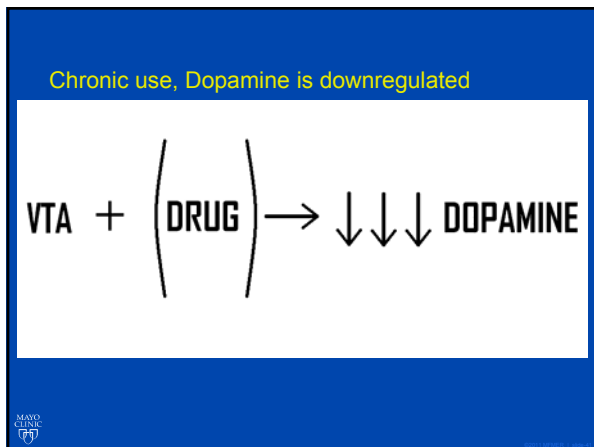
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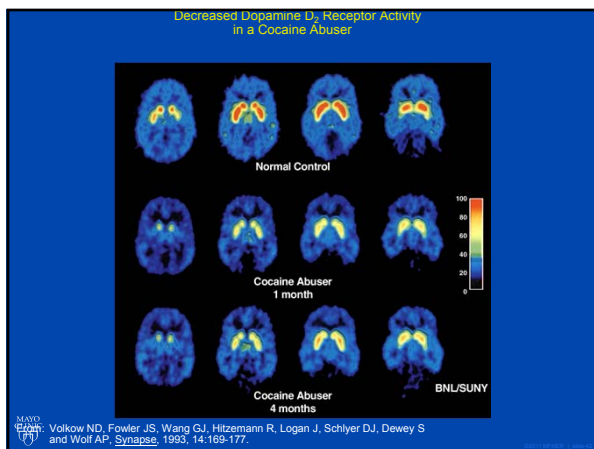
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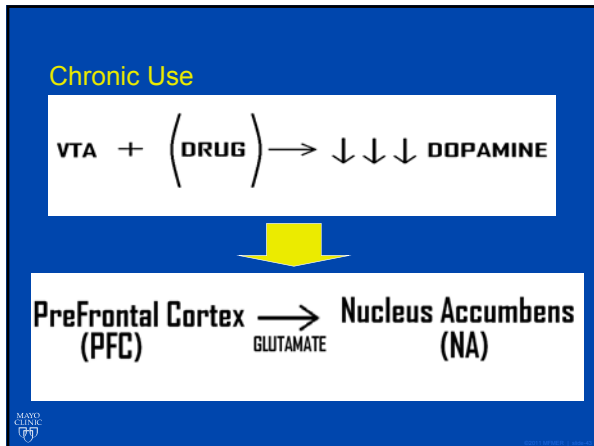
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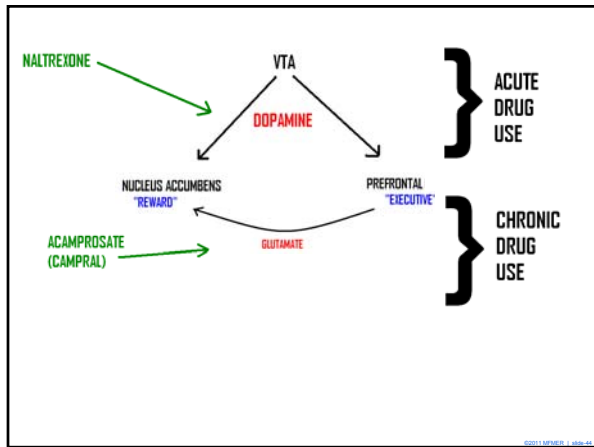
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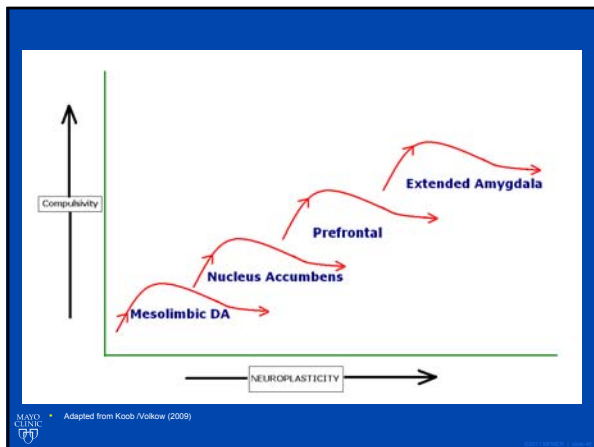
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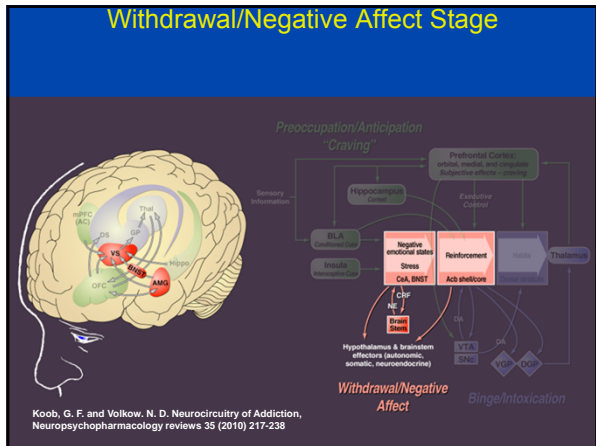
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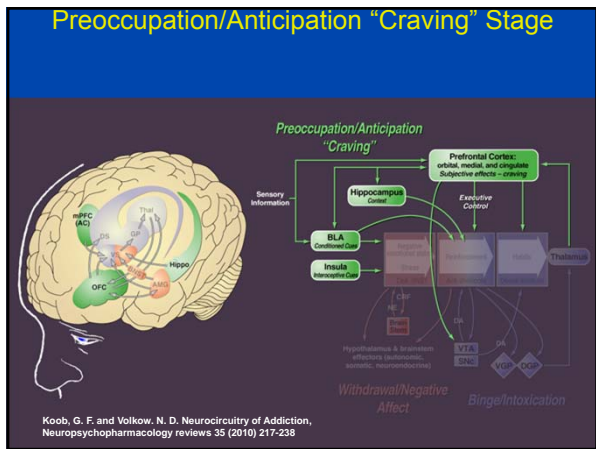
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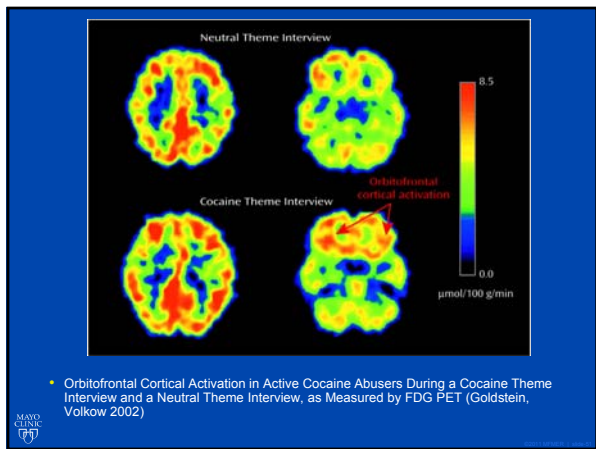
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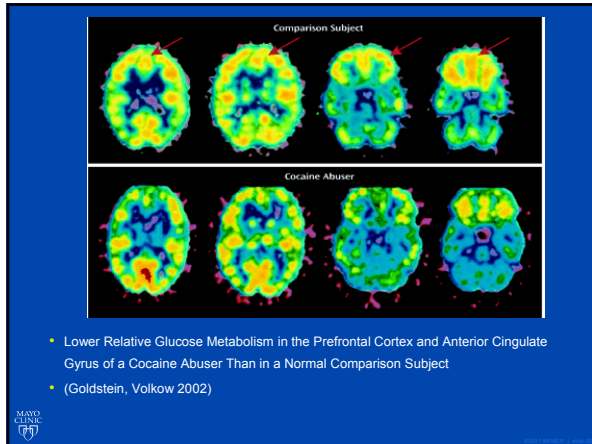
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### Memory

- The first "high" is recorded in the memory
- Repeated use "reinforces" memories
- HIPPOCAMPUS (LONG TERM MEMORY)
- -sights, sounds, smells, touch

MAYO CLINIC

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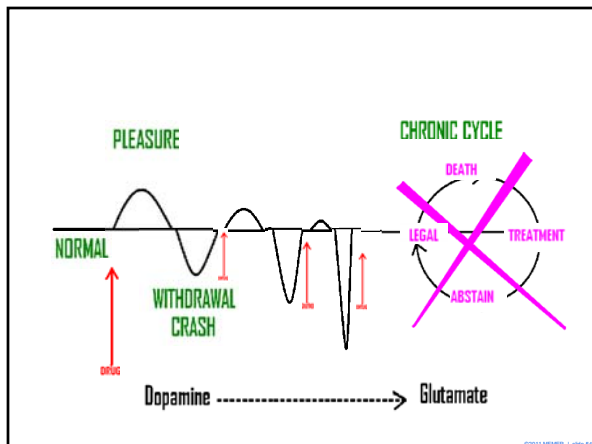
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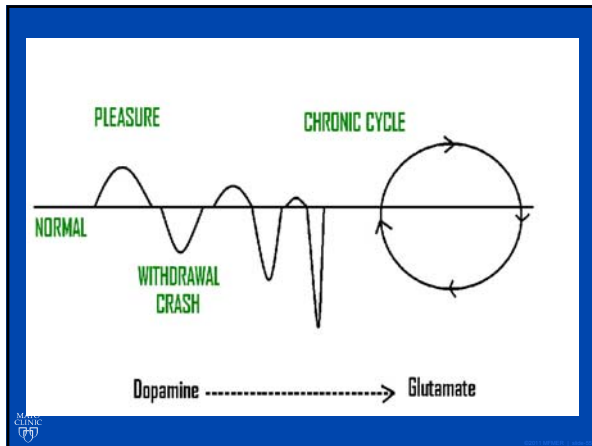
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**Case #4**

- 22 year old female, single, working
- Quit job abruptly because of hangover
- Multiple legal issues: DUIs, jail, lost license, probation
- Drinking very high amounts (10 drinks per day)
- Nicotine
- No other substances

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**Treatment**

- “People who drink to drown their sorrow should be told that sorrow knows how to swim.”
- Ann Landers

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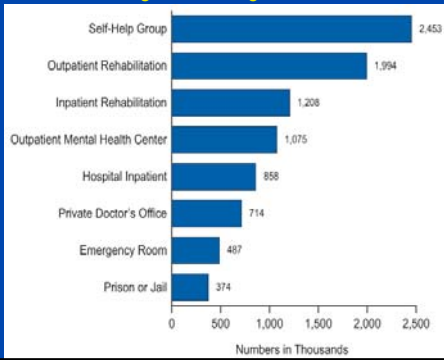
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Locations Where Past Year Substance Use Treatment Was Received among Persons Aged 12 or Older: 2009




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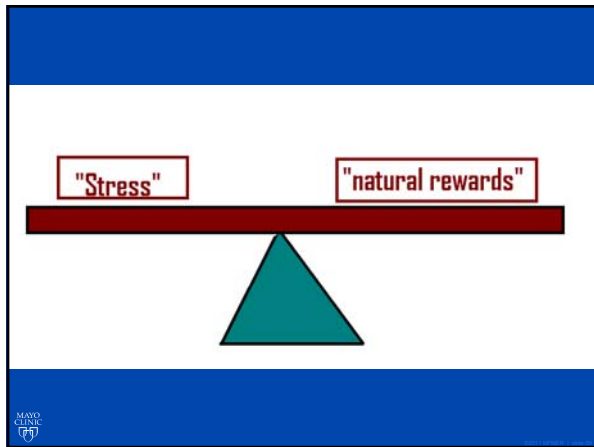
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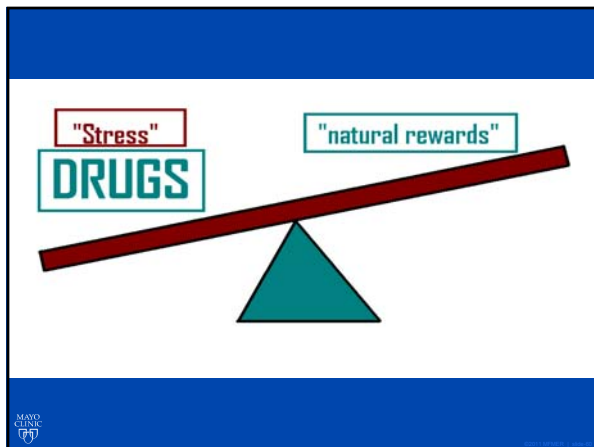
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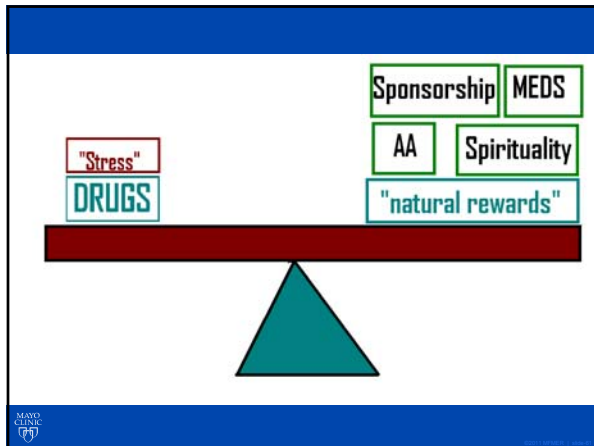
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- Medications**
- **Naltrexone**
  - Acamprosate (Campral)
  - Disulfiram (Antabuse)

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- Naltrexone**
- Stimulates opiate receptors to target "cravings"
  - Used in alcohol and opiate dependence
  - Different from naloxone

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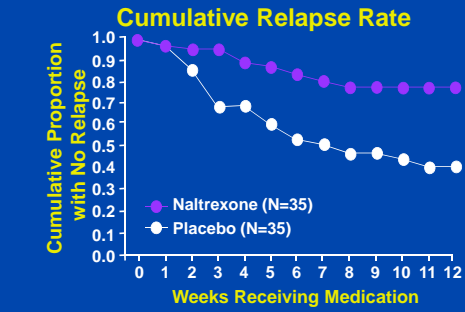
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## Naltrexone in the Treatment of Alcohol Dependence



Volpicelli et al., Arch Gen Psychiatry, 1992

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## Medications

- Naltrexone
- *Acamprosate (Campral)*
- Disulfiram (Anatabuse)

MAYO CLINIC

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## Acamprosate

- FDA approved in 2004, available in Europe since 1989
- Exact mechanism unknown
- Applies its effects on glutamate

MAYO CLINIC

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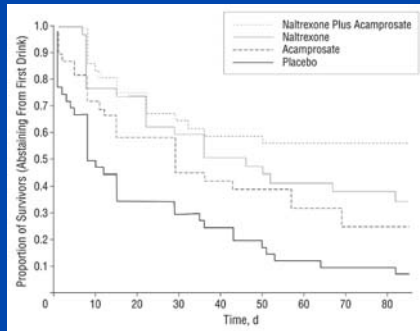
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### Combination (Naltrexone and Acamprosate)



### Endophenotype *Endorphin Dependent Alcoholism*

- Alcohol → Endogenous Opioids
- Euphoria/Stimulation from beta endorphin [BE]
- Family History with genetic polymorphism
- Sensitive  $\mu$  Receptors & low beta endorphin
- Specific therapy with Naltrexone to raise BE
- Alcohol stimulation and Craving from BE surge blocked by Naltrexone



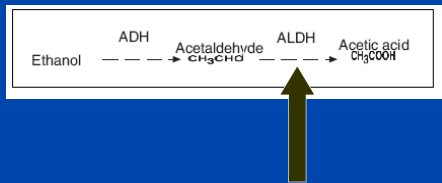
### Medications

- Naltrexone
- Acamprosate (Campral)
- Disulfiram (Anatabuse)



## Disulfiram (Antabuse)

- Acetaldehyde Dehydrogenase Inhibitor



www.mayoclinic.org

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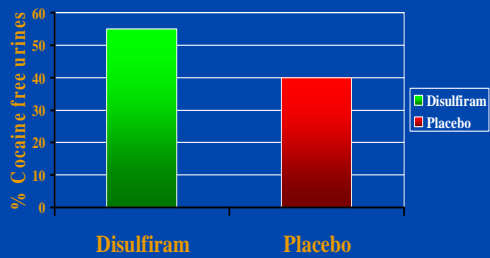
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## Disulfiram increases Cocaine-Free Urines in over 600 Outpatients (7 Studies - P<0.001)



Thomas Kosten, M.D.  
Baylor College of Medicine

www.mayoclinic.org

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## Cases

- 18 yom polysubstance abuser
- 50 yof cirrhosis and hep c
- 50 yof years of heavy alcohol use
- 22 yof few months of heavy alcohol use



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## Genetics

- Epigenetics : changes to gene expression without changing UNDERLYING DNA code
- mRNA drug induced changes in VTA and nAC long after abstinence (Freeman, 2001) (Kreek 2005) (McClung 2005) (yao 2004)



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## Genetics

- Liability to addictions is widespread, but individuals with addicted first-degree relatives are at greater risk. (GOLDMAN ET AL.)
- 1990: Dopamine receptor (DRD2 gene) A1 variation (lower dopamine): higher risk of abuse



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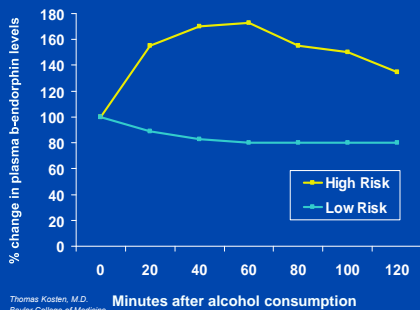
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Change in beta- Endorphin Levels after Alcohol Consumption by Family History Risk



Thomas Kosten, M.D.  
Baylor College of Medicine

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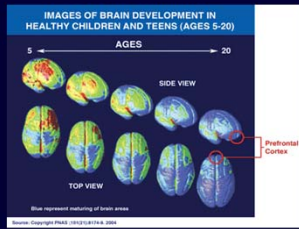
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The brain continues to develop into adulthood and undergoes dramatic changes during adolescence.



MAYO CLINIC

NIDA

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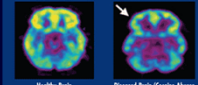
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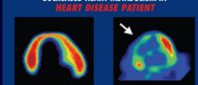
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DECREASED BRAIN METABOLISM IN DRUG ABUSER



Healthy Brain / Diseased Brain / Cocaine Abuser



Healthy Heart / Diseased Heart

Addiction is similar to other diseases, such as heart disease. Both disrupt the normal, healthy functioning of the underlying organ, have serious harmful consequences, are preventable, treatable, and if left untreated, can last a lifetime.

Source: From the laboratories of Drs. N. Volkow and H. Scheibert



MAYO CLINIC

NIDA

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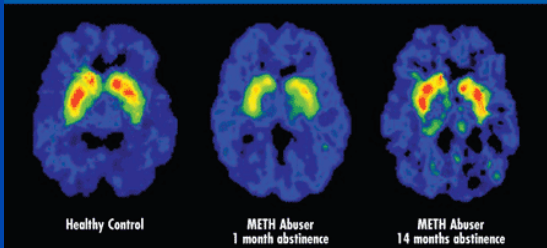
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RECOVERY OF BRAIN FUNCTION WITH PROLONGED ABSTINENCE



Healthy Control / METH Abuser 1 month abstinence / METH Abuser 14 months abstinence

These images of the dopamine transporter show the brain's remarkable potential to recover, at least partially, after a long abstinence from drugs - in this case, methamphetamine.



NIDA

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Questions & Discussion

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