

From Impulsivity to Altruism:  
*What psychopharmacology can learn from  
12 Step Recovery*

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# Wizard of Oz

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# Why do people start taking drugs? <sup>1</sup>

<sup>1</sup> This is not a trick question

# Why do people start taking drugs?


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- **Intense pleasure**
- To feel better – alleviate negative affects
- Enhance performance
- Curiosity

In the Wizard of Oz, Dorothy is carried to Oz by a tornado

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Why do people keep  
taking drugs?

# Why do people keep taking drugs?

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- Pleasure
- **Alleviate negative affects**
  - Craving
- Block withdrawal
- Social reinforcement

# How might addiction treatments work?

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- Block pleasure – Naltrexone, Buprenorphine, Methadone
- Decrease craving – Naltrexone, Varenicline
- Interfere with social reinforcement - Methadone
- Decrease abstinence syndrome – Acamprosate, Varenicline



In the Wizard of Oz, Dorothy is carried to Oz by a tornado

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# Treatments To Block Reward

*'I get no kick from champagne'*

# NATURAL REWARDS

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■ Food

■ Water

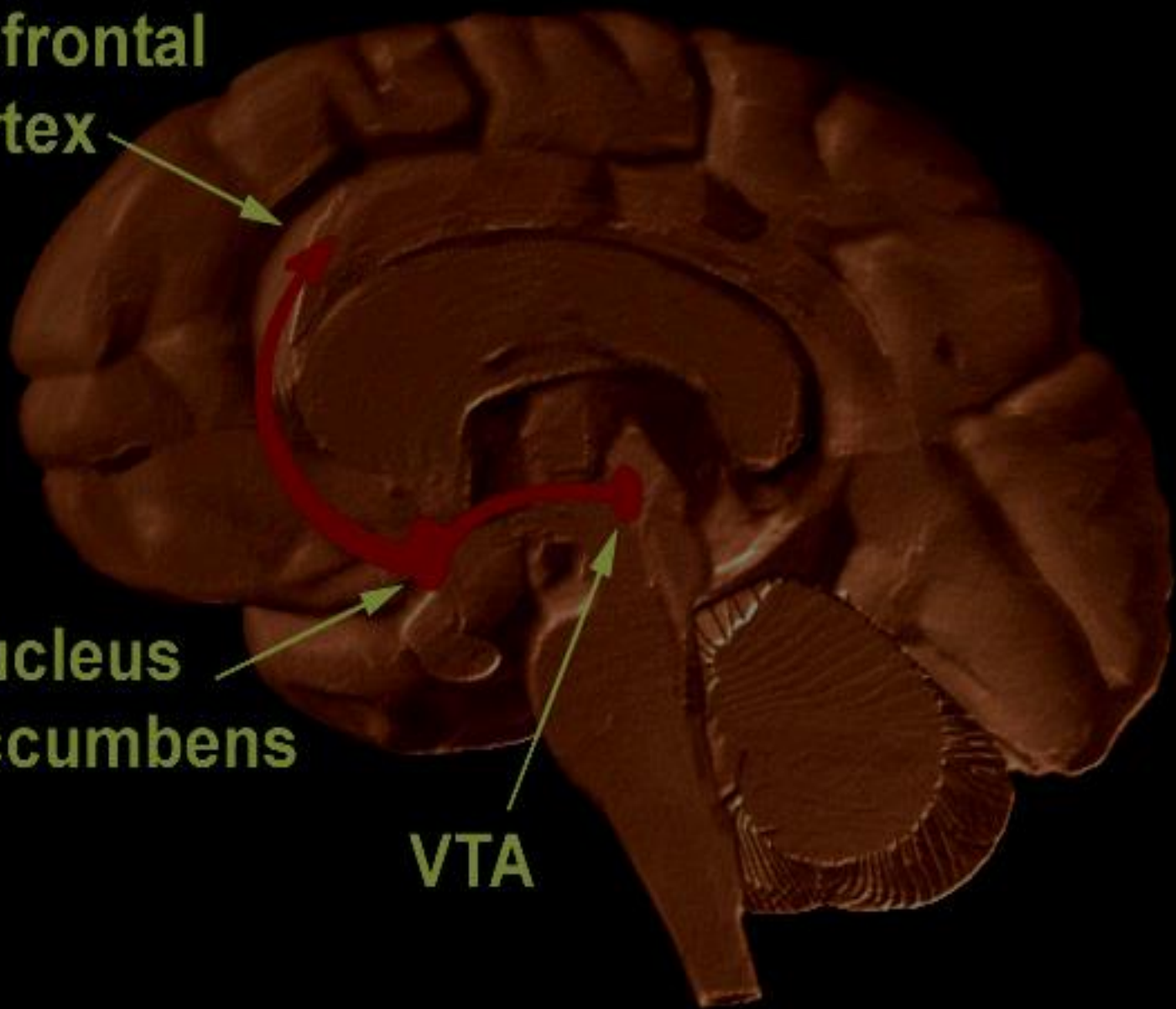
■ Sex

■ Nurture

**prefrontal cortex**

**nucleus accumbens**

**VTA**



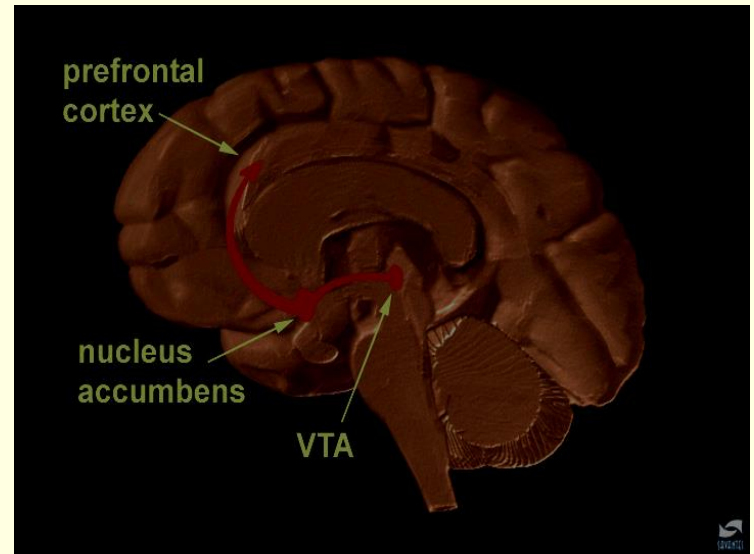
# VENTRAL TEGMENTUM AREA

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- Dopamine cell bodies of the mesocorticolimbic dopamine system
- Drug and natural reward circuitry of the brain
- Important in cognition, motivation, drug addiction, intense emotions relating to love

# NUCLEUS ACCUMBENS

- Reward & pleasure
- Laughter
- Addiction
- Aggression
- Fear

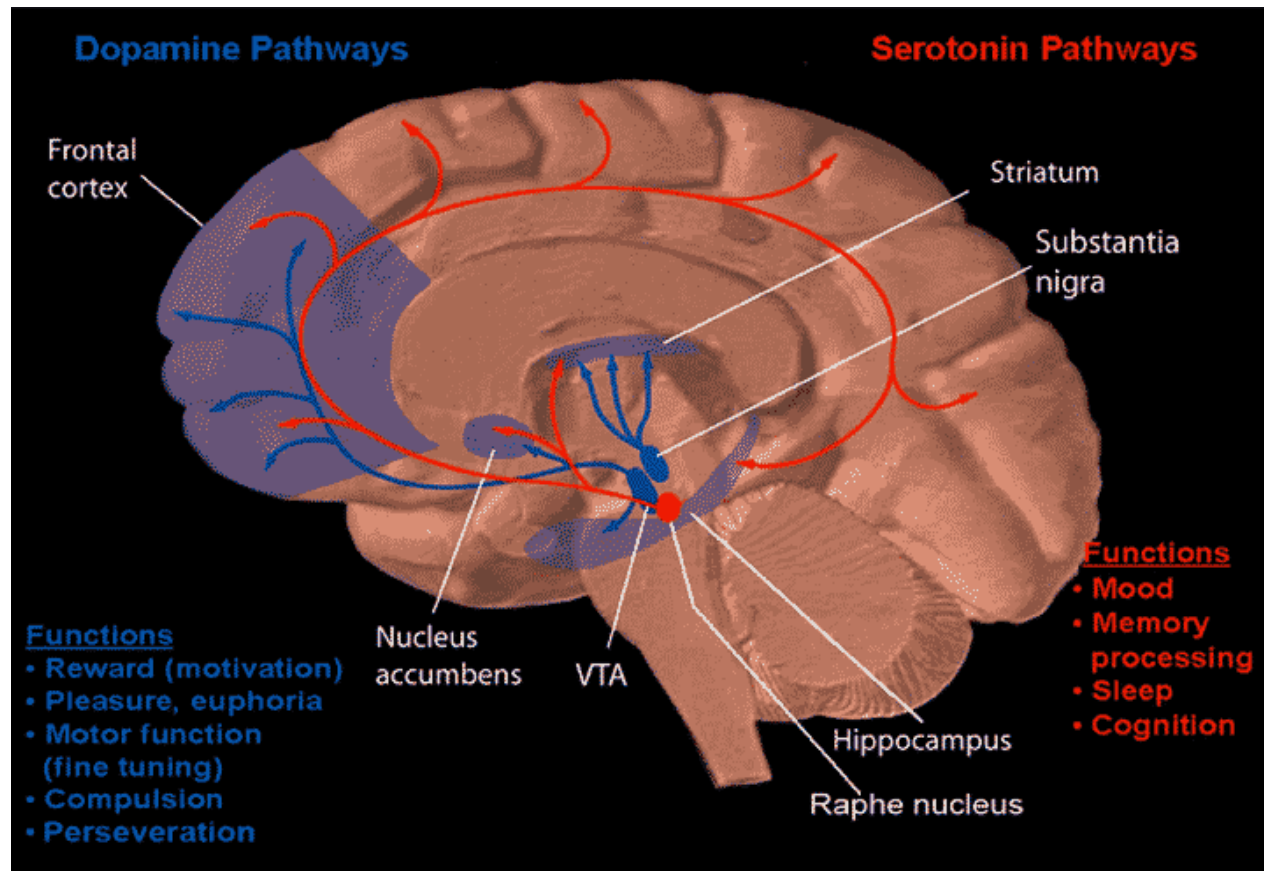


# PREFRONTAL CORTEX

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- Inhibits immediate reaction –
- “Metacognition”
- Executive function - determine good and bad, better and best, same and different, future consequences of current activities, working toward a defined goal

# The Reward System





# Dopamine (DA) and the Reward System

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- DA containing cells in the Ventral Tegmental Area (VTA) project to the Nucleus Accumbens (NAc)
- NAc processes motivated behavior
- NAc DA is essential for reward related learning
- DA mediates non-drug rewards (food, sex) and drug rewards

# Dopamine Hypothesis of Addiction

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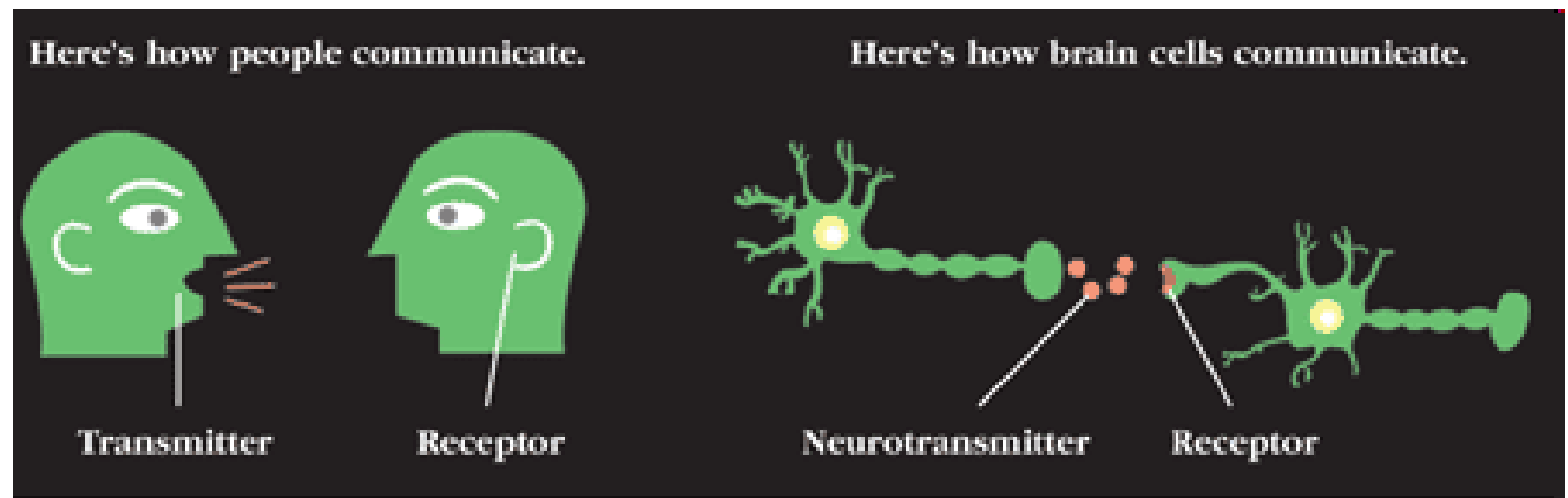
- Activation of the mesocorticolimbic dopamine system is key to mediating the reinforcing effects of drugs of abuse
- DA mediates the euphoria elicited by drugs
- Blocking DA receptors attenuates euphoria/reward of drugs
- Other areas of the brain – amygdala, hippocampus and hypothalamus are associated with emotional memories and drug addiction

# Pharmacological Treatment of Cocaine Dependency

A case study in the DA hypothesis as it  
relates to treatment

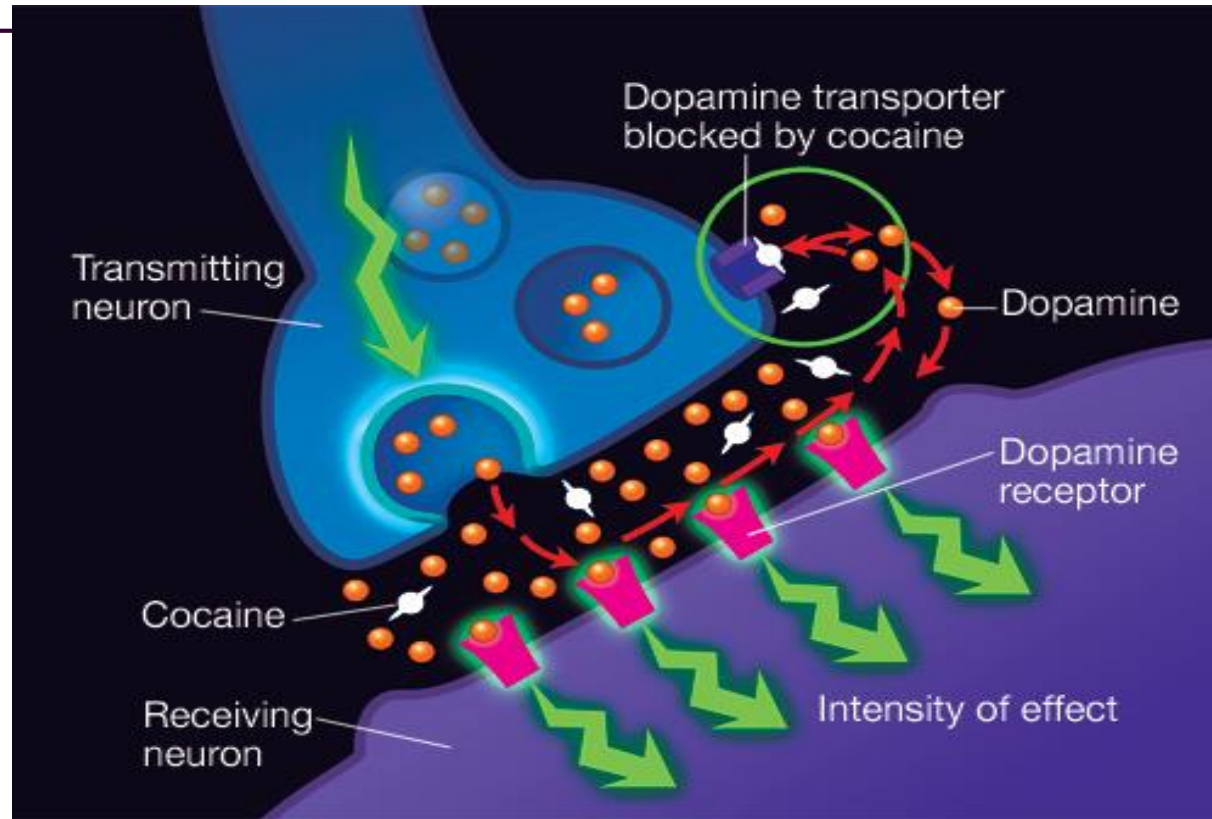
# Neurotransmitters – Chemical Signal from One Nerve Cell to the Next

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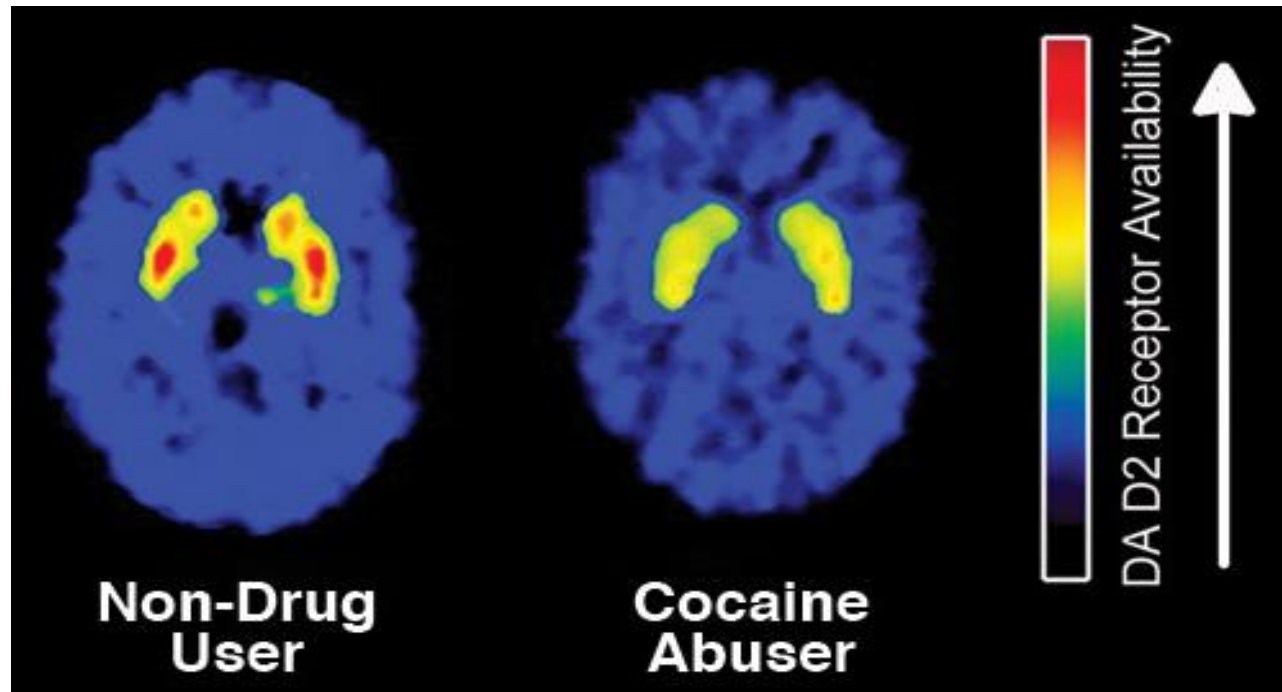
*Concept courtesy: B.K. Madras*

# How Cocaine Affects Dopamine



- Cocaine blocks the DA transporter
- Markedly increases DA in synapse

# The Consequence of Chronic Cocaine



- Decreases DA (D2) receptors in the brain, depletes DA
- Impairs motivation, natural rewards less effective

# Cocaine: A test case for dopaminergic treatments

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- Cocaine most directly and selectively affects the DA system
- Causes intense euphoria and craving
- Brain DA production is reduced and D2 receptors decreased

*Is enhancing DA function in cocaine dependency effective?*

# Enhancing DA activity

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- Agonists – drugs that mimic DA
- Indirect agonists – drugs that cause DA to be released
- Increase DA synthesis
- Drugs that block the breakdown of DA
- Outcome measures
  - Retention in treatment
  - U/A for cocaine metabolites



# Drugs that Raise Dopamine Levels

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- Enhance synthesis
  - L-dopa/cabidopa (Sinemet)
- 3 failed trials (no difference from placebo)
- Inhibit breakdown
  - MAO inhibitor
    - Selegiline – no benefit
  - COMTI
    - Withdrawn hepatotoxicity
  - DBH inhibitor
    - Disulfiram (Antabuse)
    - Only effective in patients with comorbid alcohol dependency

# Agonists

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- Amantadine (Symmetrel)
  - Indirect agonist
  - Did not improve retention
  - Did not improve abstinence
  - Did not decrease number of positive urines
- Desipramine (Norpramin)
  - NE transporter inhibitor, also inhibits DA re-uptake in frontal cortex
  - No increase in retention
  - No increase in Abstinence

# Agonists (cont.)

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- Bromocriptine
  - Direct D2 agonist
  - Did not decrease positive urines
- Bupropriion (Welbutrin)

# Promoting DA has failed.

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- Agonists failed
- Precursors failed
- Blocking breakdown failed



# Opiates and Reward

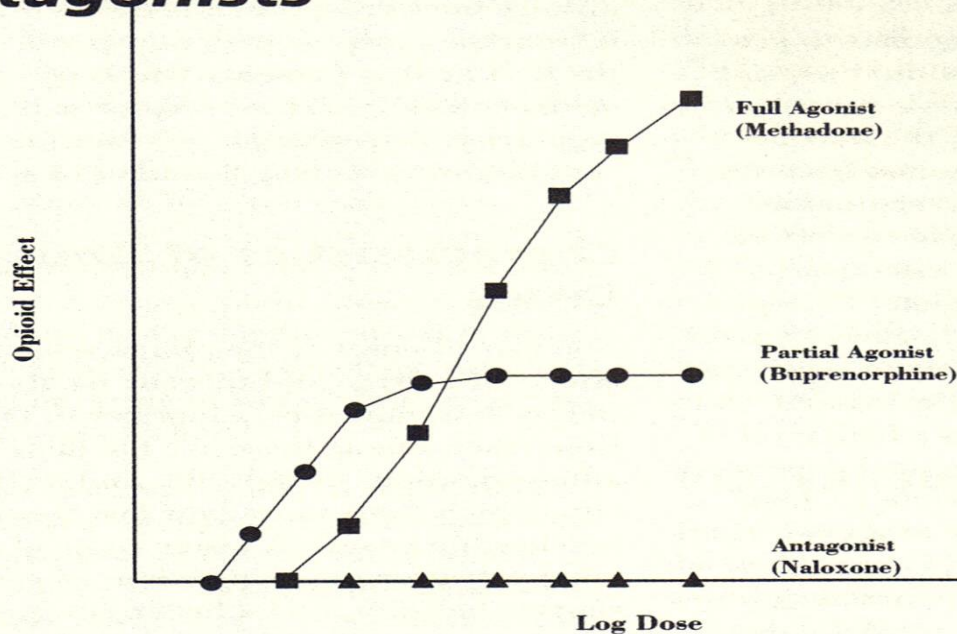
# Approved Treatments For Opiate Dependency

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- Methadone
  - Full  $\mu$  receptor agonist
  - Binds tightly and activates receptor
- Naltrexone
  - Full antagonist
  - Binds tightly to receptor and blocks activation
- Buprenorphine (Subutex, Suboxone)
  - Partial agonist
  - At low concentrations binds to receptor and activates it
  - At high concentrations blocks the receptor

# Relative Effects on Opiate Receptor

## Conceptual Representation of Opioid Effect Versus Log Dose for Opioid Full Agonists, Partial Agonists, and Antagonists\*



\*Conceptual representation only, not to be used for dosing purposes.

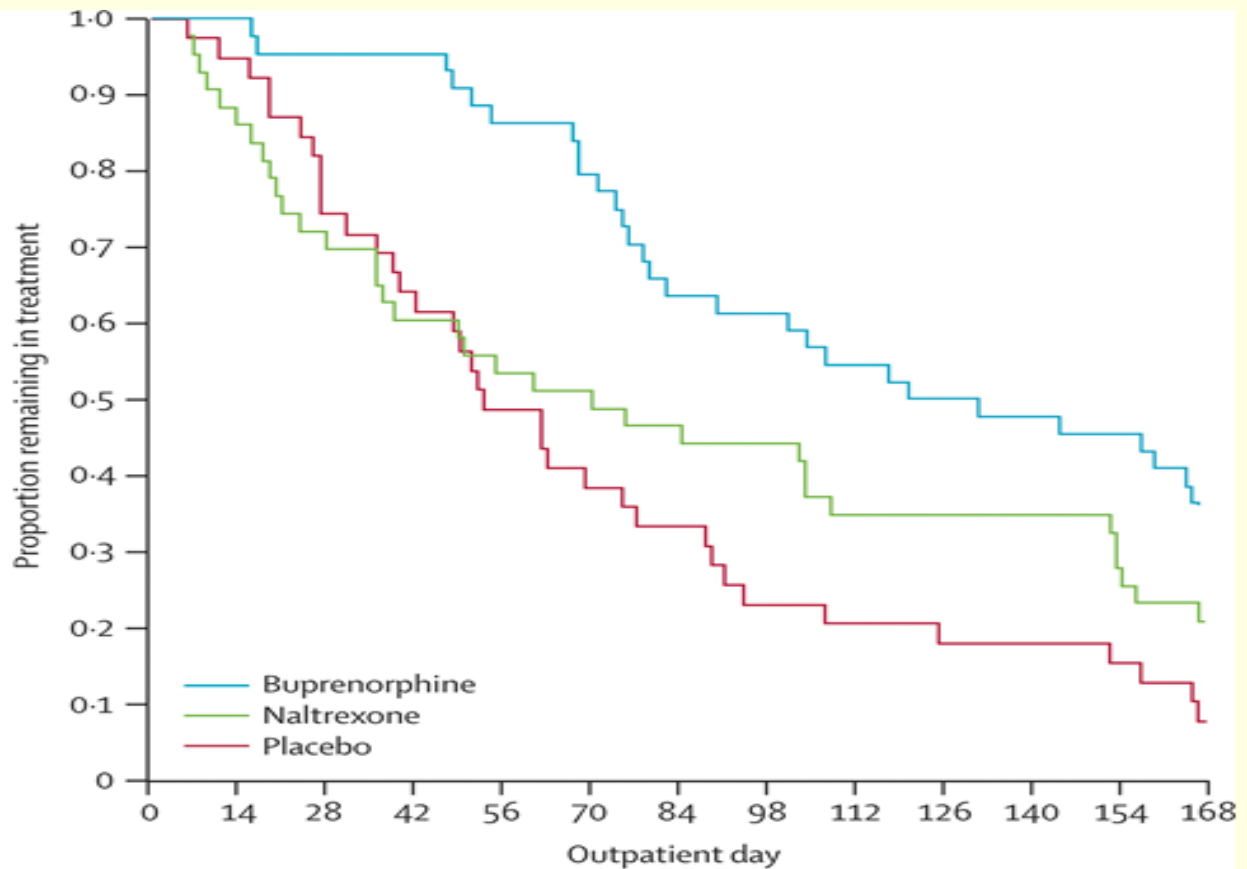
# ...Itself and Its Opposite

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- Methadone and naltrexone have similar results when it comes to blocking the reward from the opiate receptor by opposite means
- Methadone causes massive tolerance, meaning insensitivity of the receptor
- Naltrexone sits on the receptor so no opiate agonists can bind to it



# Limits of Success



**Number remaining in treatment**

Buprenorphine	44	42	38	28	24	21	18
Naltrexone	43	30	23	19	15	15	9
Placebo	39	29	19	13	8	7	5

# Why Don't Reward Treatments Work Better?

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- Hedonic/Reward responses are critical to drug initiation but not maintenance
- Changes in learning and memory are only partially related to changes in Dopamine
- Maintenance of drug dependency is caused by complex behavioral differences in addicts that precede drug use and are worsened by drug use

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The way into forest....

Is not necessarily the  
way out of the forest!

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What are we treating and why are we treating it?

# What is addiction?

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- A disorder of the brain's reward system
- A spiritual malady of self-centeredness
- Genetic disease of impulsivity
- An expression of poor nurturance, abuse, neglect
- An attempt to cope with intra-psychic distress

# New Path – Stay Close to Treatments

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- 12 Step Recovery
  - Increases long term abstinence
  - Results in meaningful social and behavioral change
  - Active processes of 12 step recovery are understudied
    - Number and duration of participation
    - Do you have a sponsor

# Why is AA Understudied?

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- AA does not consider itself a treatment program
- It exists to carry the message to those who still suffer with the disease
- Very limited infrastructure by design
- Remain forever non-professional
- Investigators have limited understanding of recovery
- Secular humanists distrust spirituality
- Limited access to the process (closed meetings etc.)
- Focus has been on the number of meetings and whether one has a sponsor

# Can 12 Step Programs Tell Us Where To Look?

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- Sharing/Learning
- Caring/Empathy
- Service/Altruism



# WHAT IS IMPULSIVITY?

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A predisposition toward rapid, unplanned reactions to internal and external stimuli without regard to the negative consequences of those reactions to oneself or others.

Non-planning impulsiveness

▣ Response inhibition

▣ Delayed discounting



# NON-PLANNING

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- Do things on the spur of the moment
- Without thinking about the future
- ‘heat of the moment’
- Buying a car, even when it means you won’t have the rent

# RESPONSE INHIBITION

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- Ability to suppress a previously learned response
- When the rules change we have to be able to change
- Go-No Go tasks used to measure it

# DELAYED DISCOUNTING

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- Universal human trait to value any reward that is immediately available over any reward that is delayed
- Think about 2 TVs: one costs \$1500 now, the other cost 1600 now, but comes with a \$200 rebate. Which would you choose?
- Delay discounting is a measure how much one values a delayed reward

# IMPULSIVITY PRECEDES ADDICTION

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- Children of drug addicts score high on impulsivity questionnaires
- Do worse on response inhibition tasks
- Discount future rewards more
- Young adults with steeper discounting drink more
- Genetics accounts for about 40% of differences in delayed discounting

# DRUGS MAKE PEOPLE MORE IMPULSIVE

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- Whether its cocaine, opiates, alcohol or tobacco – drug addicts discount future rewards more
- Delayed discounting caused by drugs improves but very slowly, many months
- Contributes to relapse

# TWO BRAIN SYSTEMS INVOLVED

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- Delayed discounting involves reward pathways
  - Striatum (NAc), prefrontal cortex
  
- Response inhibition involves executive controls systems
  - Anterior cingulate cortex and related areas
  
- Impulsive individuals (as measured by DD) show LESS activation in the medial PFC and striatum (reward pathways) when presented with a future reward



# HOW DOES IMPULSIVITY CONTRIBUTE?

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- More impulsive youth take their first drink/cigarette/mj at a younger age
- Impulsivity is linked with other psychological problems that are associated with drug abuse
  - Conduct disorder
  - Attention deficits
  - Aggressiveness



# Treating Impulsivity

# AA AND Impulsivity

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- One day at a time
- Slow and easy
- Sharing in meetings

# TWO WAYS TO BECOME LESS IMPULSIVE

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- Improve memory
- Prospection

# IMPROVE MEMORY

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- Valuing a future reward requires that you remember what it's worth
- In both animal and humans impaired memory causes increased impulsivity
- Memory training decreases impulsivity in newly abstinent amphetamine addicts
- AA improves memory through repetitions, steps and practice

# MEMORY TRAINING AS TREATMENT

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- Frequent memory training exercises improve working memory
- Decrease impulsivity on a DD task
- Not yet known whether it will improve clinical outcomes but it should!
- We are piloting computer based memory training in some programs to improve outcome

# PROSPECTION

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- Ability to project yourself into the future
- Mental time traveling
- Thinking about what will happen in the future
- Sharing at meetings is about prospection – wanting what the guy has

# Treatments For Impulsivity

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- Dopamine stabilizers that will decrease the 'push' toward relapse
- Memory enhancers that improve our ability to value what we have and what we want



# Empathy, Altruism and Substance Abuse

*We Care*

# What is Empathy

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- Involves insights into the thoughts/feelings of others
- “to project yourself into what you observe”
- The way in which we perceive what others feel

*“Empathy is central to what it means to be fully human. It allows us to tune into how someone else is feeling.”*

# The Social Role of Empathy

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- Associated with morality, altruism, pro-social behavior and cooperation
- Critical to moral development

# Empathy is Impaired in SA/ETOH

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- Callous-unemotional children are at greater risk for conduct disorders, antisocial personality and substance abuse
- Alexithymia, the inability to identify and describe feelings occurs in 40% of Alcoholics compared with 5-7% of population
- Empathy in detoxified alcoholics is significantly lower than controls

# Loss of Empathy: State or Trait

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- Diagnosis of alcohol dependence (and by extension other SUDs) is intrinsically characterized by impaired capacity for empathy
- Drugs create a pseudo-empathic experience among users related to the synchronous emotional experience induced by the high/intoxication
- Empathy for others diminishes as craving and withdrawal dominate the addict's emotional state
- Alexithymia is a stable trait among substance misusers related to impaired empathy

*Loss of empathy precedes drug use and is made worse by drug use*

# AA: A Behavioral Plan That Restores Empathy

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- *A spiritual malady of self-centeredness*
- Step 4. A fearless moral inventory of ourselves
- Step 5. Admitted to God, ourselves and another human being the exact nature of our wrongs
- Step 8. Make a list of persons we have harmed and become willing to make amends to them
- Step 9. Make direct amends wherever possible

# Biological Basis of Empathy

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- Oxytocin (OT) is the most abundant neuropeptide in the hypothalamus
- Peripheral effects include uterine contractions, milk ejection in lactation
- OT is released locally in amygdala and septum, areas associated with emotional memory
- OT receptors are found in many sites related to drug seeking
  - Nucleus accumbens, ventral tegmental area, amygdala, hippocampus

# Behaviors Regulated by Oxytocin

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- Sexual arousal and orgasm
- Monogamous pair bonds
- Maternal Behavior
- Peer-to-peer social interaction
- Promotes attachment, trust and reciprocity among strangers
- Social memory and anxiety reduction



# OT in Humans

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- Can be administered intranasally
- Increases trust
- Decreases amygdala response to fear stimuli
- Increases the recognition of social cues
- Critical to the development of maternal-infant attachment
- Increases ability to infer mental states
- Less likely to show decreased trust after breaches of trust

# Generosity in Humans

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- Definitions:
  - Altruism is helping another at a cost to oneself
  - Generosity is offering more to another than he or she expects or needs
- Evolutionary theories of giving include kin selection, direct and indirect reciprocity, group selection and strong reciprocity
  - But most charitable giving is not reciprocal
- Empathy believed to prompt altruistic acts

# Does OT Affect Generosity in Humans

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## ■ Ultimatum Game

- Decision Maker 1 gets \$10 endowment and told to offer a split to Decision Maker 2 who has no endowment
- If Decision Maker 2 accepts the offer the money is paid out to both
- UG measures **generosity**

# Does OT Affect Generosity?

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- OT increased generous behavior in the Ultimatum Game (offers exceeded the average)
- Generosity was 80% greater in the OT group

# Does Service Improve Outcomes?

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- How do you measure Service/Altruism
  
- In the past week:
  - How often have you been patient with others when others were irritating in their words/actions?
  - How often have you met the needs of friends or relatives?
  - How often did you think about the problems of others?

# Results

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- More time spent helping corresponds with higher abstinence rates at 6 and 12 months (Zemore SE 2006)
- Helping behaviors predicted remission at 3 years (Hazard ratio = 2.59,  $p = .01$ ) (Pagano ME 2006)
- Increased helping behaviors, resulted in greater AA/NA involvement at 6 months (Zemore SE 2004)

# Do brain chemicals mediate the benefits of service?

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- Experimental construct for Service is Altruism
- Empathy triggers the release of Oxytocin

AND AT THE SAME TIME

- Increases generosity by 50%

# Empathy and Altruism: Pharmacological Targets for Drug Treatment

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- Defects in empathy are common in addiction
- 12 step recovery targets moral behavior and increases empathy
- Research demonstrates a connection between service (altruism) and long term outcome
- Oxytocin promotes generosity, empathy and pro-social behaviors





# A Memory Disorder

# Why do you drink?

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I drink to forget.

*What do you  
want to forget?*

My problems.

*What are your  
problems?*

I can't remember.

*Why don't you  
remember?*

Because I drink to much.

# Alcohol and Learning

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- Alcohol causes cognitive deficits in 50-80% of alcoholics
- Memory deficits develop **after** prolonged drinking ceases and is worse in abstinent alcoholics
- Repeated periods of Alcohol followed by withdrawal impairs memory
- Alcohol impairs prospective memory/working memory
- Impairs the ability to learn complex novel information
- Caused by changes in grey matter microstructure and decreases in hippocampus volume

# 12 Steps and Memory

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- Sharing
  - Deficits in avoidance/negative reinforcement
- One day at a time
  - Deficits in short term and long term logical memory, executive function
- Steps
  - Deficits in working memory

# Why is Sharing important?

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- Alcohol impairs contextual learning
- When Tones are Paired with foot shock, rodents learning to fear the tone AND the environment associated with the shocks
- With ETOH animals fear the box but NOT the tone
- Binge drinkers failed to learn associations in aversive conditioning tests

*Looked at another way, Alcohol interferes with your ability to remember threatening situations.*

# Alcohol and State Dependent Learning

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- Learning under drugged conditions shows little or no transfer to non-drugged states
- Learning that occurs during a drugged state transfers to a similar drug state

*Things learned while 'high' are recalled poorly when sober.*

# Memory and Alcohol Dependency

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- If memory deficits are caused by alcohol...
- If impaired memory contributes to relapse...
- If AA exerts some of its benefits by compensating for the deficits in executive memory, prospective memory and avoidance memory.....

*Would Pharmacological Treatments That Prevent Alcohol Related Memory Deficits Treat Alcoholism?*

# Nimodipine (Nimotop)

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- Dihydropyridine approved for hypertension
- Binding sites on calcium channels that regulate glutamate and are associated with excitability after prolonged alcohol exposure
- Blocks withdrawal related hyperexcitability
- Reduces dopamine depletion after alcohol withdrawal
- Memory deficits are associated with effects of withdrawal



# Nimodipine and ETOH memory deficits

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- Rats were fed alcohol for 8 months
- Memory was tested 1 month after ETOH d/c
- 2 tasks
  - Object Recognition
  - T-Maze
- Nimodipine twice daily for two weeks during the last two weeks of alcohol exposure
- Nimodipine in a single dose immediately prior to alcohol withdrawal

# What the tests measure

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- Object recognition
  - Rats attracted to novel objects, and once they 'learn' an object they spend less time with it
- T-maze: prospective memory test
  - 'unlearning test' – non-matching to place
  - Placed in maze with one arm blocked and food in the other arm
  - Retested with blocking door removed
  - Count the number of times they return to the previously UNBLOCKED arm (errors)

# Results

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- One month after withdrawal, alcohol treated animals showed marked memory deficits on both tasks
- On the T-maze they make approximately twice as many 'bad' choices (perseverative errors)
- Nimopidine either for two weeks or as a single dose completely prevented memory loss due to alcohol

# Conclusions

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- Deficits in learning, empathy and altruism predispose to substance abuse and are worsened as a result of chronic substance abuse
- The benefits of 12 step recovery are related to the program's ameliorative effects on alcohol/drug related deficits in three key processes: learning, empathy, altruism
- We predict that pharmacological interventions that support normalization in these functions rather than reward regulation, will prove effective for treating drug dependency

# Wizard of Oz

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In the Wizard of Oz, Dorothy is carried to Oz by a tornado

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But with the help of friends whose apply their brain, heart and courage to her problem

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She is returned home .... through the recognition of the emotional bonds she has to the people there.

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