Pharmacotherapy for Substance Use Disorders

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What is addiction?

Addiction can be defined as compulsive drug use despite negative consequences

What is addiction?

Physiologic dependence and withdrawal avoidance do not explain addiction

Neurobiology of addiction attempts to explain the mechanisms by which drug seeking behaviors are consolidated into compulsive use:

-long persistence of relapse risk

-drug-associated cues control behavior

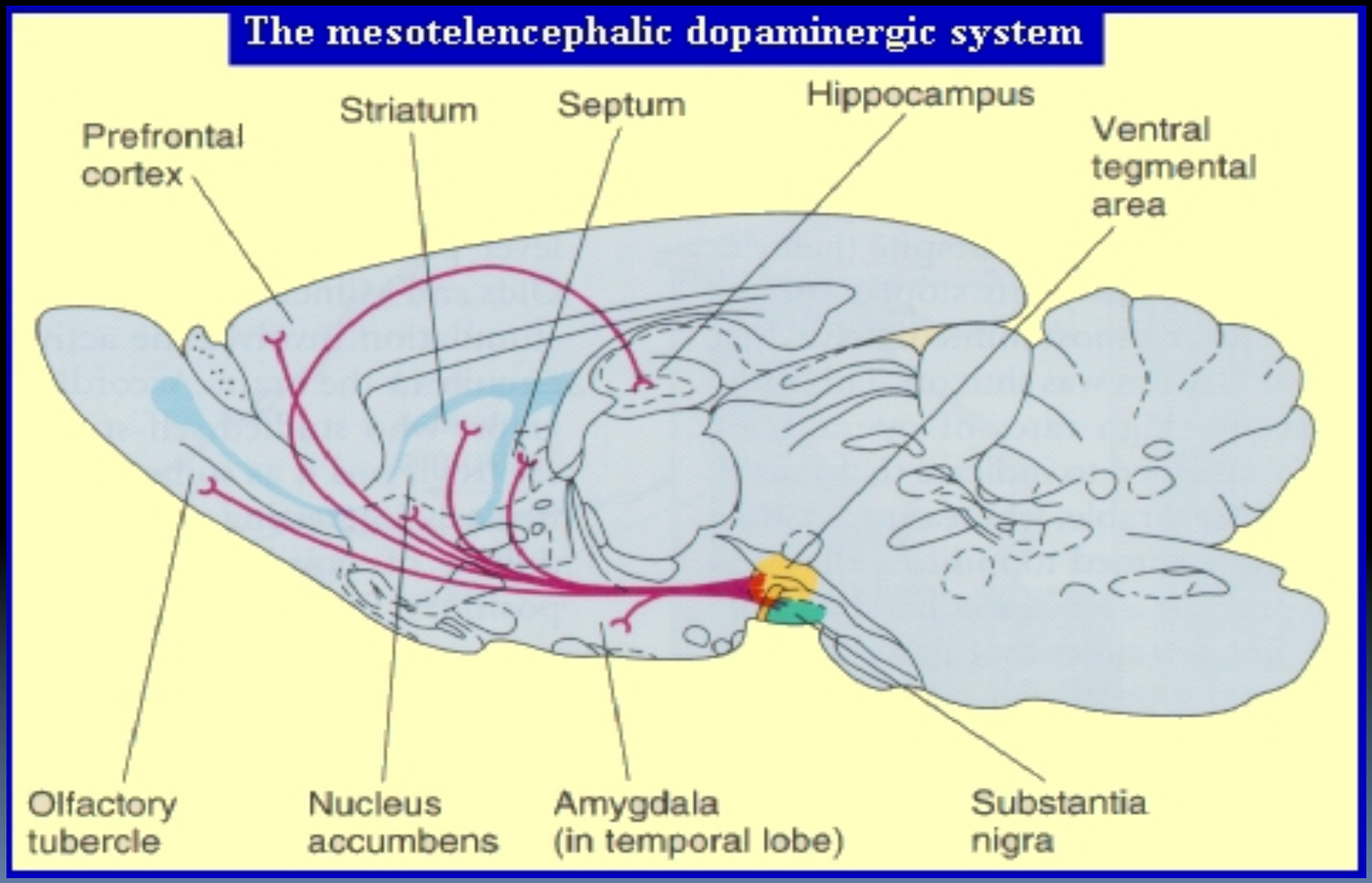
Although addictive drugs are pharmacologically diverse…

- Stimulants (act as a serotonin-norepinephrine-dopamine reuptake inhibitors)
  - Cocaine, amphetamines, MDMA
- Opioids (agonist action)
  - Heroin, morphine, oxycodone, fentanyl
- GABAergic agonists/modulators
  - Alcohol, benzodiazepines, barbiturates
- Cannabis (binds cannabinoid receptors)

…they all lead to a common pathway

- All addictive drugs pharmacologically release dopamine in the nucleus accumbens

The dopamine system



The Dopamine Reward Pathway

How Dopamine Leads to behavior change

- Dopamine required for natural stimuli (food, opportunity for mating, etc) to be rewarding and drive behavior
- Natural rewards and addictive drugs both cause dopmine release in the Nucleus Acumbens
- Addictive drugs mimic effects of natural rewards and thus *shape behavior*

The Dopamine Reward Pathway
How Dopamine Leads to behavior change

- Survival demands that organisms find and obtain needed resources (food, shelter) and opportunity for mating despite risks -survival relevant goals
- These goals have natural "rewards" (eating, safety, sex)
- Behaviors with rewarding goals persist to a conclusion and increase over time as they are positively reinforcing

The Dopamine Reward Pathway
How Dopamine Leads to behavior change

- Internal states (hunger) increase value of goal-related cues and increase pleasure of consumption
- likelihood that complex behavioral sequence (hunting) will be brought to successful conclusion

The Dopamine Reward Pathway
How Dopamine Leads to behavior change

- Behavioral sequences involved in obtaining reward (steps required to hunt) become overlearned/automatized
- Automatized behavioral repertoires can be activated by cues predictive of reward

Prediction Error Hypothesis

- Exposure to an unexpected reward causes transient firing of dopamine neurons which signals brain to learn a cue.
- Once cue is learned, burst of firing occurs at cue, *not at reward.*
- If the reward does not arrive, dopamine firing will decrease below baseline levels → serves as an error signal about reward predictions
- If reward comes at unexpected time, dopamine firing will increase → positive predictive error signal: "better than expected!"

Dopamine Gating Hypothesis

- Because drugs cause dopamine release (due to pharmacological actions), dopamine firing upon use does not decay over time → brain repeatedly gets positive predictive error signal: "better than expected!"
- Drug cues become ubiquitous (drug cues difficult to extinguish)
- Cues that predict drug availability take on enormous incentive salience (consolidates drug seeking behavior)
- Drug cues will become powerfully overweighted compared to other choices (contributes to loss of control over drug use)

Cue Learning

- Glutamate is another excitatory neurotransmitter involved in cue learning:
  - Specific information about cues
  - Evaluation of cue significance
  - Learned motor responses
- Enhances dopamine dependant learning

Source: Am J Psychiatry 2005;162:1414-1422

Clinical Implications

- Addictive behaviors are a important and normal part of human behavior
- Addictive drugs pharmacologically modify functioning of reward circuits to overvalue drug rewards and reduce the comparative value of other rewards
- Intention to stop use is not enough to stably quit substance use.

4 FDA approved medications for Alcohol Dependence

- Naltrexone oral (Revia)
- Naltrexone injection (Vivetrol)
- Acamprosate (Camprel)
- Disulfiram (Antabuse)

Naltrexone (Revia)

- opiate antagonist
- Prevents dopamine release normally produced by alcohol consumption
- All other effects of alcohol still occur
- Reduces reward associated with alcohol use, leading to extinction of alcohol seeking behaviors
- Less binge drinking, craving is reduced

Naltrexone (Revia)

- 50-100 mg QD
- Side effects: nausea, vomiting, headaches, dizziness, fatigue, insomnia, somnolence, anxiety
- Caution/avoid: opioid agonists, acute hepatitis, liver failure

Naltrexone (Vivetrol)

- Same profile as oral
- Risk of injection site reaction
- Caution/avoid if: thrombocytopenia, coagulation disorder, inadequate muscle mass
- 380 mg IM q month

Acamprosate (Campral)

- Pharmacologically “messy”
- Has effects on glutamatergic and GABAergic systems
- Seems to reduce cravings via an undetermined mechanism
- Works best in abstinent patients to prevent relapse

Acamprosate (Campral)

- Side effects: diarrhea (common), anxiety, weakness, insomnia, depression, suicidality
- Requires kidney function monitoring if renal impairment or elderly
- Caution/avoid if: renal impairment
- 666 mg TID

Disulfiram (Antabuse)

- Aversive agent
- Inhibits enzyme that that breaks down acetaldehyde (alcohol byproduct that causes flushing, nausea, and palpitations)
- To avoid feeling sick, people will avoid drinking
- Only works if you take it, works best if dosing can be observed

Disulfiram (Antabuse)

- Must be abstinent for 24 hours to start
- 250 mg QD
- Side effects: hepatoxicity, perpheral neuropathy, psychosis, delirium, disulfriam/ alcohol reaction
- Monitor liver function
- Caution/avoid: severe liver/cardiac/ respiratory disease, severe psychiatric disorder, metronidizole

Opiate Replacement Therapy

- Methadone
- Buprenorphine

All most effective when combined with counseling and monitored treatment

Methadone

- Opioid substitution therapy
- Long acting synthetic mu opiod
- Slow onset
- Interacts with many medications
- Risk of prolonged QT interval
- Must be admitted to an opioid treatment program

Methadone

- Side effects: dizziness, sedation, nausea, vomiting, sweating, constipation, swelling, sexual dysfunction, respiratory depression, EKG changes
- Get baseline EKG
- Caution/avoid: patient enrolled at another OTP, liver failure, use of opioid antagonists, benzodiazepine use, cardiac arrythmias

Buprenorphine

- Partial opioid agonist

  -less reinforcing than full agonist, milder effects

  -easier withdrawal

  -safety- overdose ceiling effect
- High affinity to the opiate receptor
- Long duration of action
- Suboxone = buprenorphine coated with nalaoxone (Narcan)

Buprenorphine

- Side effects: dizziness, sedation, nausea, vomiting, sweating, constipation, liver disease, sexual dysfunction, respiratory depression, precipitated withdrawal
- Hepatic metabolism- monitor LFT's
- Caution/avoid: patient on full agonist opiods, benzodiazepines, naltrexone, respiratory/ liver/renal impairment
- Store out of reach of children

Methadone vs. Buprenorphine

-clinic only
-requires daily visits
-high level monitoring
-observed dosing
-treats severe pain
-many drug interactions
-can be sedating
-can be euphorigenic
-safety concerns
-blocks opiate use

-office based
-can see MD every 30 days
-limited monitoring
-self dosing
-treats for mild-mod pain
-minimal drug interactions
-minimally sedating
-minimally euphorigenic
-safety: ceiling effect
-blocks opiate use

Behavioral Treatments for Substance Use Disorders

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- Motivational Interviewing
  - Focuses on exploring and resolving ambivalence and centers on motivational processes within individual that facilitate change
  - Supports change in a manner congruent with a persons own values and concerns

Behavioral Treatments for Substance Use Disorders

- Behavioral Couples Counseling
  - Focuses on reduced alcohol or drug use in patient and improving overall relationship satisfaction
  - Series of behavioral assignments to increase positive feelings, shared activities, constructive communication
  - May include sobriety contract: urine drug screens, session attendance, 12-step participation

Behavioral Treatments for Substance Use Disorders

- Community Reinforcement Approach (CRA)
  - Comprehensive cognitive behavioral intervention that focuses on environmental contingencies that impact and influence behavior
  - Build motivation, initiate sobriety, analyze use pattern, increase positive reinforcement, learn new coping skills, occupational rehab, involve significant other

Behavioral Treatments for Substance Use Disorders

- Contingency Management
  - Non-monetary or monetary rewards made contingent on objective evidence
  - “pay people for clean urines”

Behavioral Treatments for Substance Use Disorders

- Twelve Step Facilitation
  - brief, structured, and manual-driven approach to facilitating early recovery from alcohol abuse, alcoholism, and other drug abuse and addiction problems
  - implemented over 12 to 15 sessions.
  - based on the behavioral, spiritual, and cognitive principles of 12-step fellowships such as Alcoholics Anonymous (AA) and Narcotics Anonymous (NA)

References/Resources/Recommended Reading

- Addiction: A Disease of Learning and Memory. Am J Psychiatry 2005;162:1414-1422
- Health Services for VA Patients with Substance Use Disorders: Comparison of Utilization in Fiscal Years 2011, 2010, and 2002 (draft)
- Confrontation in Addiction Treatment, William R. Miller, PhD and William White, MA (http://www.cafety.org/miscellaneous/755-confrontation-in-addiction-treatment)
- VA/DoD Clinical Practice Guideline: Management of Substance Use Disorders (www.healthquality.**va**.gov/sud/sud_full_601f.pdf)
- National Survey on Drug Use and Health (NSDUH) https://nsduhweb.rti.org/
- Substance Abuse & Mental Health Services Administration http://www.samhsa.gov/