Substance Abuse

Eric D Peselow M.D.
Research Professor of Psychiatry
NY Medical College

Major Teaching Points

- Addiction is both a chronic relapsing disorder & a treatable condition, comparable to adult onset diabetes & hypertension
- There is no one treatment for addiction – some individuals recover with behavioral interventions & 12-step programs, while others require medications on an acute or chronic basis
- The most effective medications currently are for treatment of alcohol or opioid dependence. There are no approved medications for stimulant or marijuana dependence
- Comorbid conditions such as mood and anxiety disorders require treatment even in the face of active substance usage

Outline
Substance Abuse

I. Epidemiology
a. Social problems and their cost
b. Magnitude of problem
c. Substance related health effects

II. Substance Related Drug Problems
a. Problems by drug category
b. Diagnosis of substance abuse/dependence
c. Definitions of tolerance and withdrawal

III. Comorbidity - Extent and by Substance

IV. Drugs & Adolescence
V. Making an Addict
a. Addicting drug
b. Susceptible person
c. Mechanism to bring them together

VI. Diagnostic Issues
VII. Pharmacological Treatment – Acute & Chronic
a. Alcohol
b. Opioids
c. Stimulants
d. Nicotine

VIII. Ethical Issues

Pre-Lecture Exam Question 1

1. **Which of the following statements is false:**

A. Physical dependence is synonymous with addiction.

B. One can be addicted without being physically dependent.

C. Once a patient has met criteria for Substance Dependence, they should not be diagnosed in the future with Substance Abuse.

D. A critical feature of addiction is compulsive use in spite of harm.

Question 2

2. Which of the following statements is false:

A. Psychiatric disorders can cause substance abuse.

B. Substance abuse can cause psychiatric disorders.

C. If both substance abuse and a psychiatric disorder are present, treating the psychiatric disorder is usually not necessary.

D. Treating an underlying psychiatric disorder usually does not adequately treat the substance abuse.

Question 3

3. **The most common comorbid psychiatric diagnosis in patients with substance abuse is:**

A. Schizophrenia
B. Antisocial Personality Disorder
C. Anxiety Disorder
D. Major Depression

Question 4

4. Which one of the following is false:

A. Cocaine decreases negative symptoms in schizophrenics.

B. When cocaine free, schizophrenics have more negative symptoms.

C. Chronic cocaine use increases depression in schizophrenics.

D. Chronic cocaine decreases positive symptoms of schizophrenia.

Question 5

5. **Which of the following are considered "Gateway Drugs"?**

A. Alcohol

B. Marijuana

C. Nicotine

D. A & C only

E. A, B, & C

Question 6

6. **Adolescent substance abuse is associated with:**

A. Increased school dropout

B. Increased depression and suicidality

C. Premature involvement in sexuality

D. All of the above

Question 7

7. **The proportion of users who ever became dependent is as follows (from high to low):**

A. Nicotine, alcohol, heroin, cocaine, marijuana.

B. Alcohol, nicotine, cocaine, heroin, marijuana.

C. Nicotine, heroin, cocaine, alcohol, marijuana.

D. Nicotine, alcohol, marijuana, cocaine, heroin.

Question 8

8. Which of the following is not used as a maintenance agent in heroin addiction:

A. Methadone

B. Clonidine

C. Naltrexone

D. Buprenorphine

Question 9

9. Which category of medications is <u>not</u> yet available for treatment of heroin addiction:

A. Agonists
B. Antagonists
C. Partial agonists
D. Anti-craving agents
E. Anti-withdrawal agents

Question 10

10. Which of the following statements are true:

A. Naltrexone blocks the effects of alcohol.

B. Drinking while on naltrexone can make one very ill.

C. Benzodiazepines are the usual agents used for alcohol withdrawal.

D. All of the above

Categories of Drugs

- Depressants
- Stimulants
- Opiates
- Cannabinoids
- Hallucinogens
- Phencyclidine (PCP)
- Inhalants/solvents
- Others

*Magnitude of Problem (USA)

- Nicotine - over 50 million dependent
- Alcohol - 12 - 18 million alcoholics and problem drinkers
- Marijuana - over 3 million dependent
- Cocaine - 2-3.5 million dependent
- Heroin - 800,000 - 1 million dependent
- Prescription opioids – 2-4x heroin number

Health Effects of Drugs

(1) Infections
  - Hepatitis (heroin, cocaine, alcohol)
  - AIDS (heroin, cocaine, inhalants)

(2) Gastrointestinal Pain and Bleeding
  - Ulcers (alcohol)

(3) Brain and Peripheral Neuron Damage
  - Dementia (alcohol, stimulants, inhalants)

(4) Cardiovascular
  - Stroke and heart attack (stimulants)

*Continuum of Drug Use

- Initiation/intoxication
- Harmful use/abuse
- Dependence/withdrawal
- Relapse and craving
- Recovery and persisting deficits

Definitions

- Psychological dependence/addiction
- Physical dependence/addiction
- Tolerance
- Dependence syndrome

Substance Intoxication

- Reversible syndrome
- Maladaptive behavior (anger, depression, cognitive impairment)
- Not due to medical condition

Substance Abuse (DSM-IV)

....made only in the absence of dependence or history of dependence

One or more of the below:

- Failure to fulfill major role obligations
- Use in hazardous situations
- Legal problems
- Use despite problems

*Substance Dependence

- Maladaptive pattern of use including 3 or more of the below in the same 12 month period:
  - With tolerance or withdrawal
  - More use than intended
  - Unsuccessful attempts to cut down
  - Reduce other activities
  - Great deal of time spent on drug use
  - Continued use despite adverse consequences

Tolerance

- Occurs after prolonged (usually weeks), regular (daily), heavy use
- Increased amounts for desired effect
- Diminished effects

Withdrawal

- Requires regular (at least daily) use for prolonged period
- Specific physiological syndromes by drug
- Substance taken to avoid syndrome
- Not due to general medical condition

*Possible Relation Between Substance Use and Psychiatric Disorder

- Psychiatric disorder causes substance abuse
- Substance abuse causes psychiatric disorder
- Both caused by common underlying disorder
- Both occur independent of the other

Categories of Drugs Most Likely to Produce Psychopathology

- Stimulants
  - all forms of amphetamines and all forms of cocaine
- Depressants
  - alcohol
  - benzodiazepines
  - barbiturates
  - carbonates
    - (i.e. meprobamate)

*Substance-Induced Disorders

- Development of a substance-specific syndrome which is usually reversible.
- Symptoms are:
  - not due to general medical condition
  - not better accounted for by another mental disorder
- There is evidence obtained from:
  - history
  - physical exam
  - toxicologic analysis of body fluids

*Drugs of Abuse are Known to Exacerbate Prior Psychiatric Disorders

by increasing:

- Mood swings
- Anxiety
- Paranoia
- Hallucinations
- Confusion

*Psychostimulants and Negative Symptoms of Schizophrenia

- Negative symptoms reduced in laboratory studies using amphetamines (0.25mg/Kg/day)
- Fewer negative symptoms in ER presentations of cocaine abusing schizophrenics
- At four-week cocaine free follow-up, more negative symptoms in cocaine abusing schizophrenics
- Chronic cocaine increases anxious, agitated depression in schizophrenics

*Psychostimulants and Positive Symptoms of Schizophrenia (I)

- More paranoia
- Hallucinations specifically intensified
- Global psychotic symptoms may be lower in stimulant abusing schizophrenics, when abstinent

*Psychostimulants and Positive Symptoms of Schizophrenia (II)

- Stimulant abusing schizophrenics hyposensitive to amphetamine effects (Kornetsky 1976)
- Psychotomimetic cocaine effects last hours to days; may relate to sleep deprivation
- Regular stimulant use for over 6 years associated with psychosis induction (McLellan 1979)

*Gateway Drugs and Later Dependence

- Alcohol, nicotine, marijuana
- Use before age 15
- Earlier use more likely to result in dependent young adults
- Risk of dependence varies by drug used

*Normal Growth and Development and Substance Abuse

- Hormonal control: growth hormone, testosterone
- Drugs disrupt hormone release/effects
- Adolescent struggle for independence
- Pseudoindividuation of drug abuse
- Experimentation vs. dependence on drugs

*Drug Abuse and Adolescent Development

- Drug use as integral to growing up
- Premature involvement in work and sexuality
- Deviant behavior and crime
- Poor social integration and education
- Cognitive processes disrupted

*Adolescent Social Disruption With Drug Abuse

- Early family formation and divorce
- Increased stealing
- Reduced job stability
- Increased high school dropout
- Increased depression and suicidality

Adolescent Social Forces in Hard Drug Use

- Not peer pressure
- Distress and alienation
- Vary by type of drug (alcohol vs. cocaine)

*It takes 3 things to make an addict

- Addicting drug
- Susceptible person
- Mechanism to bring them together

*Susceptible Person

- Genetic issues
- Psychological issues
- Psychosocial issues

*Mechanism to Bring Drug/person Together

- Availability - physical, economic, psychological, legal status
- Role of poverty

Effective Identification of Substance Use Disorders

- Recognize prevalence problem
- Drop stereotypes
- Always screen for disorders
- Corroborate results

M.A.S.T.
Michigan Alcoholism Screening Test

- 25 item self-administered questionnaire
- Self-report of alcohol (and perhaps drug) problems
- Paper and pencil test
- Helpful, but not diagnostic

CAGE - AID

- Have you felt you ought to Cut down on your drinking or drug use?
- Have people Annoyed you by criticizing your drinking or drug use?
- Have you ever felt bad or Guilty about your drinking or drug use?
- Have you ever had a drink or used drugs first thing in the morning to steady your nerves or to get rid of a hangover (Eye-opener)?

(Brown, R.L., & Rounds, L.A. (1995). Conjoint screening questionnaires for alcohol and other drug abuse: Criterion validity in a primary care practice. Wisconsin Medical Journal, 94, 135-140)

Sharing the Diagnosis (Confrontation or Intervention)

- Give specific findings
- Remember patient is responsible
- Watch for signs of denial
- Repeat as needed

Stimulant Intoxication (I)

- Euphoria
- Agitation/retardation
- Weakness, respiratory depression
- Chest pain, cardiac arrhythmia
- Confusion, seizures, coma
- Dystonias, dyskinesia

Stimulant Intoxication (II)

- Tachycardia
- Pupillary dilation
- Elevated blood pressure
- Perspiration/chills
- Nausea/vomiting
- Weight loss

Opioid Intoxication

- Pupillary constriction
- Drowsiness
- Slurred speech
- Impaired attention

Sedative and Alcohol Intoxication

- Maladaptive behavior (aggression/depression)
- Slurred speech/incoordination
- Nystagmus/unsteady gait
- Impaired attention (stupor)

Hallucinogen Intoxication

- Perceptual changes (intensified, depersonalization)
- Maladaptive behavior (paranoia, anxiety, ideas of reference)
- Pupillary dilation, blurred vision
- Tachycardia, sweating, tremors
- Incoordination

Optimize Levels of Physical Functioning

- Careful physical examination
- Appropriate detoxification procedures when needed
- Efforts to reverse physical pathology

Detoxification
for Depressants, Stimulants, and Opiates

- Physical exam
- Educate, reassure
- Vitamins, etc.
- Meds?

Medications for Detoxification

- Alcohol Withdrawal
  - Benzodiazepines, e.g., chlordiazepoxide or oxazepam
- Cocaine Withdrawal
  - Medications generally not needed
- Opioid Withdrawal
  - Methadone
  - Buprenorphine
  - Clonidine and sleep meds as adjuncts
- Cannabis Withdrawal
  - Experimental use of dronabinol (Marinol^{R}), a Schedule III THC

Rehabilitation for Substance-Use Disorders

- Use best data
- Establish realistic goals
- Change is the patient's responsibility
- Use all resources
- Agree on goals
- Addiction erodes but does not erase addict's ability to control behavior

Maximize Motivation for Abstinence

- Lectures
- Discussion groups with patients
- Discussion groups with family members
- Using counselors in recovery
- Self-help groups
- Motivational Enhancement Therapy (MET)

Rebuild a Life Without Substances

Substances have been a very important part of life and are very difficult to give up.

Lectures and discussion groups to talk about issues.

- Appropriate use of free time
- Interaction with relatives and friends now that you are sober
- Appropriate interaction with or avoidance of substance-using friends
- Saying no to substances when offered (refusal skills)

Relapse Prevention

- Avoid high risk situations
- Anticipate minor relapses
- Recovering from relapses
- Identify triggers

Aftercare

- Lessons learned can be reinforced
- Provides opportunity to apply knowledge to everyday situations

Recovery from Dependence

- Early remission - no symptoms for one to 12 months
- Full remission - no symptoms for one year
- On agonist therapy (e.g., methadone)
- In controlled environment (e.g., T.C.)
- Relapse vs. slip
- Protracted withdrawal symptoms after opioid dependence can last as long as 9 months and are a frequent cause of relapse

Pharmacology of Nicotine Addiction

Nicotine Replacement Therapies (NRTs)

•Currently available treatment for NUDs includes first-line therapies, nicotine replacement therapy (NRT), bupropion, varenicline, and second-line treatments (nortriptyline, clonidine).

•There are 5 NRT formulations FDA approved for use in the US: transdermal patch, gum, lozenge, nasal spray, and vapor inhaler.

•The transdermal patch is the one long-acting NRT and provides continuous release of nicotine for 16-24 hours, while the inhaler, nasal spray, gum and lozenge constitute the short-acting NRTs (SANRTs).

•NRTs works via the mechanism of agonist substitution reducing the reinforcing properties of nicotine delivery by tobacco and also reducing the severity of cravings and withdrawal symptoms.

•A meta-analysis comparing the efficacy of various forms of NRT demonstrated that all NRTs double the chance of long-term (≥ 6 months) abstinence from tobacco products & reduce craving with no appreciable differences between the patch & the SANRTs

•Although administering NRT agents has theoretical risks of addiction itself, NRTs have low addictive liability, especially relative to inhaled nicotine from tobacco and they are not associated with withdrawal symptoms upon discontinuation

Pharmacology of Nicotine Addiction

Nicotine Replacement Therapies (NRTs)

Bupropion

•Bupropion was the first non-nicotine agent to get FDA approval for smoking cessation and is a first-line agent used.

•Bupropion acts as a DA and to a lesser extent a NE reuptake inhibitor as well as having some NAR antagonism properties.

•From a replacement point of view, increasing DA and NE levels mimics some of the effects of nicotine.

•From an antagonist point of view, the partial antagonistic properties at the NAR receptor may explain some of its anti-addictive properties.

•Also, as mentioned above, the fact that it increases DA levels may be helpful to counteract DA hypofunctioning in the NA and thus increase the salience value of biologically relevant and novel rewards.

•A meta-analysis of 19 trials with bupropion demonstrated that similar to NRTs, bupropion approximately doubles the odds of smoking cessation (≥ 6 months) and diminishes craving and the severity of withdrawal, compared to placebo.

Pharmacology of Nicotine Addiction

Nicotine Replacement Therapies (NRTs)

Bupropion

•Initially, it was hypothesized that bupropion exerted its anti-addictive properties in tobacco dependent patients as an indirect result of its anti-depressant properties.

•However, it has been found equally efficacious in tobacco dependent individuals with or without co-morbid depression.

•Of course, if a patient with tobacco dependence presented with co-morbid major depression, using bupropion would be preferable over NRT or varenicline to address symptoms of both disorders.

Pharmacology of Nicotine Addiction

Nicotine Replacement Therapies (NRTs)

Varenicline

•Varenicline, the most recent FDA approved (May 2006) medication for smoking cessation, is a long-acting (24 hours), partial agonist at the $\alpha_4\beta_2$ NAR.

•In animal models, varenicline's effect on DA turnover in the NA was between 35-60% of the response by nicotine injections.

•By being a partial agonist, varenicline acts as both agonist replacement therapy and as an antagonist. As a partial agonist, it stimulates release of enough DA to reduce craving and withdrawal; however, in the presence of inhaled nicotine from tobacco it acts partially as an antagonist by blocking the full reinforcing effects of smoked tobacco.

•In 2 large phase III trials in the US with approximately 1,000 subjects in each trial, varenicline (1mg po bid) was compared to both bupropion SR (150mg po bid) and placebo.

• In these trials, after 12 weeks of treatment, varenicline approximately increased the odds of abstinence by a factor of 4 compared to placebo and by a factor of 2 compared to bupropion and after 1 year the quit rate was approximately 2.5 times better than placebo and approximately 1.7 times better than bupropion

Pharmacology of Nicotine Addiction

Nicotine Replacement Therapies (NRTs)

Varenicline

- **Varenicline's most common side effects include nausea, insomnia, and headache.**

- **Of significance, in the 4th quarter of 2007, varenicline was associated with 988 serious adverse events in the US reported to the FDA, more than any other drug in that time period and included the following types of adverse events: accidents and injuries, vision disturbance, arrhythmias, seizures and abnormal muscle spasms or movements, moderate and severe skin reactions (including Stevens-Johnson), diabetes and neurpsychiatric symptoms.**

- **The neuropsychiatric symptoms included 'changes in behavior, agitation, suicidal ideation, attempted and completed suicide,' and prompted the FDA to issue a Public health Advisory**

Pharmacology of Nicotine Addiction

Pharmacologic Treatment of Nicotine Use Disorders (NUDs): Second-line agents

Nortriptyline

•Nortriptyline is a tricyclic antidepressant that acts as a NE reuptake inhibitor as well as a NAR antagonist.

•Meta-analysis of the 6 randomized trials of nortriptyline indicate that like NRT and bupropion, it approximately doubles the rate of smoking cessation (≥ 6 months) compared to placebo.

•Like bupropion, its anti-addictive properties with nicotine appear to be independent from its anti-depressant properties.

•Nortriptyline is a second-line agent, however, because of its adverse effects profile including: anti-cholinergic effects (i.e. dry mouth, constipation, sedation, delirium), potentially fatal cardiac arrhythmogenic properties and potential for dangerous drug-drug interactions, especially with monoamine oxidase inhibitors.

Pharmacology of Nicotine Addiction

Pharmacologic Treatment of Nicotine Use Disorders (NUDs): Second-line agents

Clonidine

•Clonidine is an alpha$_2$ adrenergic agonist that diminishes noradrenergic release and thus decreases sympathetic activation.

•It's mechanism of action for smoking cessation is not completely understood but it is thought to counteract CNS manifestations of nicotine withdrawal as hyperadrenergic states are a common feature across a spectrum of withdrawal syndromes including alcohol and opioids and also likely represent activation of the brain stress systems.

•Meta-analysis of the 6 trials of clonidine use for smoking cessation demonstrated an approximate doubling of abstinence rates (≥ 3 months) compared with placebo.

Pharmacology of Nicotine Addiction

Pharmacologic Treatment of Nicotine Use Disorders (NUDs): Second-line agents

Combination Therapy

- **Combination therapy involves adding an SANRT to a longer-acting agent such as nicotine patch, bupropion or varenicline and is used after monotherapy has failed**

- **It has been shown that smoking cessation rates are significantly enhanced with a greater number of agents attempted and treatment duration.**

- **A meta-analysis of the use of SANRT in combination with the nicotine patch showed a significant although not pronounced effect on improving abstinence rates relative to monotherapy (OR 1.42; 95% CI, 1.14-1.76).**

Pharmacology of Nicotine Addiction

Pharmacologic Treatment of Nicotine Use Disorders (NUDs--Future Options

Rimonabant

•The endogenous cannabinoid system has been implicated in the reinforcing properties of certain drugs of abuse such as alcohol and nicotine.

• Rimonabant is a CB1 receptor antagonist that has been shown in pre-clinical studies to diminish nicotine self-administration as well as to decrease conditioned cue relapse.

•In a US trial of approximately 800 smokers, rimonabant doubled the rate of abstinence at 14 weeks compared to placebo.[34]

•However, in 2006 the FDA rejected approval of rimonabant for smoking cessation and in 2007, the manufacturer withdraw its application for an obesity indication because of increased concerns over its side effect profile such as increased reports of depression, anxiety, insomnia and suicidal ideation.

Pharmacology of Nicotine Addiction

Pharmacologic Treatment of Nicotine Use Disorders (NUDs--Future Options

•Vaccine therapy represents a new immunologic type of pharmacotherapy to treat addictive disorders and has been studied for cocaine, methamphetamine, and nicotine addiction.

•The goal of antibody therapy, either active or passive immunization, is to reduce substances of abuse from penetrating into the CNS via pharmacokinetic antagonism.

•Pre-clinical studies in rats have demonstrated that nicotine vaccinations reduce nicotine distribution to the brain by 40-60%, decrease nicotine induced DA release in the NA, decreased nicotine self-administration, and decreased nicotine-seeking in drug re-instatement paradigms.

•Three nicotine vaccines are in development and have been tested in humans in phase I and II trials.

•So far, the vaccines have been reported to be safe and well tolerated. In clinical trials, the 3 vaccines have demonstrated abstinence rates of approximately 2-5x greater than placebo up to year follow-up.

•It has been shown that a sufficient and elevated level of antibody production is necessary for a clinical effect necessitating multiple injections over a 1-2 month period

Pharmacology of Alcohol Addiction

Pharmacologic Treatment of Alcohol Use Disorders: FDA Approved medications

Aversive Conditioning: Disulfiram

Disulfiram, the first FDA approved medication for alcoholism, works by inhibiting aldehyde dehydrogenase, the enzyme that converts acetaldehyde to acetate in the catabolism of alcohol.

Build-up of acetaldehyde causes the disulfiram-ethanol reaction (DER) that can include: sweating, headache, facial flushing, nausea, vomiting, tachycardia, hyperventilation, dyspnea, and hypotension.

The DER is an aversive state that serves to extinguish addictive behavior through punishment, negative reinforcement and behavioral counter-conditioning.

In severe reactions, respiratory depression, cardiovascular collapse, arrhythmias, myocardial infarction, acute congestive heart failure, seizures, unconsciousness and death can occur

Pharmacology of Alcohol Addiction

Pharmacologic Treatment of Alcohol Use Disorders: FDA Approved medications

Aversive Conditioning: Disulfiram

•Side effects of disulfiram include headache, fatigue, allergic dermatitis, impotence, peripheral neuropathy, garlic-like after-taste, and in some cases acute hepatitis.

•Disulfiram is contra-indicated in patients with significantly abnormal liver function, cardiovascular and cerebrovascular illnesses, significant cognitive impairment, the elderly, and pregnant women.

•At the recommended average maintenance dose of 250mg daily (range of 125mg-500mg/day), disulfiram is considered a safe and well-tolerated medication used as an adjunctive pharmacotherapy in an abstinence oriented treatment model to prevent alcohol use and relapse.

Pharmacology of Alcohol Addiction

Pharmacologic Treatment of Alcohol Use Disorders: FDA Approved medications

Aversive Conditioning: Disulfiram

•The efficacy data on disulfiram has been mixed. Much of the research with disulfiram in alcoholism from the late 1940s through the late 1990s failed to show a benefit over placebo; however, much of this research was plagued by poor design methodology such as non-randomization, lack of blinding, no measurement of medication compliance, and lack of adequate follow-up.

•A large multisite, randomized, placebo-controlled trial of disulfiram conducted in a veterans administration population found no difference between disfulfiram and placebo in terms of abstinence rates and time to first drink.[51]

Pharmacology of Alcohol Addiction

Pharmacologic Treatment of Alcohol Use Disorders: FDA Approved medications

Aversive Conditioning: Disulfiram

•However, in this study only 20% of the subjects were medication compliant which likely contributed to the negative findings.

•It is now understood that medication adherence is key to the successful use of disulfiram in patients with alcoholism.

•Treatments used to enhance disulfiram compliance such as directly observed treatment, contingency management, and community reinforcement have been associated with improved outcomes such as decrease in overall drinking and increased abstinence rates compared to placebo.

• In general, the following patient characteristics have been associated with improved outcomes with disulfiram: high motivation for sobriety, AA attendance, longer drinking histories, socially stable, and being cognitively intact

Pharmacology of Alcohol Addiction

Pharmacologic Treatment of Alcohol Use Disorders: FDA *Non-Selective Opiate Antagonist Therapies*

Naltrexone

•Naltrexone is an opiate antagonist that has been used to treat alcoholism since gaining FDA approval in 1994.

•Naltrexone's average dose is 50mg daily and the most common side effects include sedation, nausea, vomiting, dizziness, and abdominal pain.

•Hepatocellular injury as been associated with high dose naltrexone (i.e. 300mg) administration and its use is contraindicated in patients with acute liver illness or liver enzymes greater than 3 times above normal as well as patients currently being treated with opiates due to the risk of precipitated withdrawal.

Pharmacology of Alcohol Addiction

Pharmacologic Treatment of Alcohol Use Disorders: FDA *Non-Selective Opiate Antagonist Therapies*

Naltrexone

•The initial FDA approval was based on 2 small clinical trials that demonstrated a reduction in frequency of drinking, craving, and relapse to heavy drinking compared to placebo

•Several reviews and meta-analyses of naltrexone use in alcoholism have shown that compared to placebo, naltrexone has only a modest but significant effect on drinking outcome measures such as drinking frequency and relapse to heavy drinking but not necessarily on absolute abstinence rates

•This has led some to hypothesize that naltrexone is useful as a relapse prevention agent to diminish the 'high' or positive reinforcement ('reward' craving) causing a reduction in heavy drinking or overall drinking in a use reduction model as opposed to maintaining total abstinence.

• In other words, it may reduce the 'priming' effects of alcohol and diminish the likelihood that a 'slip' will turn into a complete reinstatement of previous heavy drinking behavior.

•It is still unclear why some respond to naltrexone and others do not but the following subgroups appear to respond better to naltrexone: positive family history of alcoholism, subjective report of enhanced craving for alcohol, enhanced opioid activity in response to alcohol ingestion and those with a specific genetic polymorphism (most notably A118G) in the mu-opioid receptor.

Pharmacology of Alcohol Addiction

Pharmacologic Treatment of Alcohol Use Disorders: FDA *Non-Selective Opiate Antagonist Therapies*

Naltrexone

•In 2006, the FDA approved a monthly depot injection formulation of naltrexone (Vivitrol) for the treatment of alcohol dependence.

•Poor adherence is common with oral medications used to treat alcoholism and the lack of compliance is strongly correlated with higher relapse rates.

•Evidence of vivitrol's efficacy in reducing heavy drinking comes from a national, multisite study where 380mg IM monthly injections over a 6-month period significantly reduced median heavy drinking days per month (from pre-treatment level of 19/month to 3/month) compared to placebo by 25%; however, there was a strong placebo response with a reduction from 19/month to 6/month).

Pharmacology of Alcohol Addiction

Pharmacologic Treatment of Alcohol Use Disorders: FDA *Non-Selective Opiate Antagonist Therapies*

Nalmefene

•Nalmefene, similar to naltrexone, is a non-selective opiate antagonist but one with advantages over naltrexone such as: longer half-life and lower prevalence of side effects, particularly hepatotoxicity.

• Nalmefene reduces voluntary alcohol consumption in animals and human clinical trials so far have shown positive results with regard to reductions in the relapse rates to heavy drinking, similar to naltrexone

Pharmacology of Alcohol Addiction

Pharmacologic Treatment of Alcohol Use Disorders: Glutamate-based interventions: Acamprosate

•Acamprosate was approved in 2004 by the FDA as a relapse prevention medication used to treat alcohol dependent patients at a dose of approximately 2g per day taken in doses of 333mg, 2 tablets three times daily.

• It is a safe and well-tolerated medication with diarrhea being the most common side effect.

•It has no pharmacokinetic interaction with alcohol, disfulfiram or benzodiazepines, does not appreciably induce or inhibit the cytochrome P450 system, is not associated with any withdrawal syndrome, has no effect on cognitive function, has no addictive liability, is not metabolized by the liver and is excreted unchanged in the urine.

•As such, it can be given to patients with liver disease but is contraindicated in patients with severe renal disease

Pharmacology of Alcohol Addiction

Pharmacologic Treatment of Alcohol Use Disorders: FDA approved Glutamate-based interventions: Acamprosate

•Acamprosate's clinical efficacy data was well established in over a dozen studies in Europe where it consistently was superior to placebo in rates of total abstinence, cumulative abstinence duration, and time to first drink when given to patients who, in general, were recently detoxified.

•In contrast, 2 US trials failed to provide any benefit of acamprosate compared to placebo.

•However, since the US trials included only a small minority of patients (less than 8%) who required detoxification prior to treatment (in contrast to the European studies where greater than 90% received detoxification prior to treatment) and the primary outcome variables related more to reduction in heavy drinking than in maintenance of abstinence (in contrast to the European studies where abstinence was the primary outcome variable), it has been argued that patients who benefit from acamprosate are those with: greater severity of illness, higher baseline levels of motivation, and those where the medication is given in the protracted withdrawal period

Pharmacology of Alcohol Addiction

Pharmacologic Treatment of Alcohol Use Disorders: *GABA-ergic interventions:*

Baclofen

•In addition to being useful to treat alcohol withdrawal, GABAergic agents are now being looked at regarding potential efficacy in reducing alcohol use or prevention of relapse.

•Baclofen, a selective metabotropic $GABA_B$ receptor agonist, has shown some promise.

•In addition to preclinical animal studies where baclofen was able to inhibit the acquisition of alcohol intake, suppress acquired alcohol self-administration and reduce alcohol reinstatement behaviors.

•Preliminary human studies with baclofen in 2 open-label and a double-blind controlled study suggested a postive effect in relapse prevention, abstinence maintenance, and craving in patients recently detoxified from alcohol.

• Baclofen seems to work by selectively activating $GABA_B$ receptors on VTA DA neurons leading to a reduction in DA release in the NA.

Pharmacology of Alcohol Addiction

Pharmacologic Treatment of Alcohol Use Disorders: FDA *GABA-ergic interventions:*

GABA-ergic interventions:

Topiramate

•A promising agent with potential to treat alcoholism is topiramate.

•Given that topiramate enhances $GABA_A$ activity and diminishes glutamatergic transmission by antagonism at the AMPA and kainite glutamate receptors, one could predict that it could be useful as a relapse prevention agent to treat alcoholics.

•In 2 double-blind placebo controlled trials, topiramate at a dose of 300mg was better than placebo in reducing heavy drinking and increasing the percentage of abstinent days.

•Further research is needed, especially in community settings to determine which sub-population of alcoholics would optimally benefit from topiramate.

Pharmacology of Alcohol Addiction

Pharmacologic Treatment of Alcohol Use Disorders: *Serotonergic Agents*

Despite animal models suggesting a potential anti-dipsotropic effect and despite data suggesting a reduced desire to drink in non-alcoholic humans, SSRIs have failed to show a clear effect as an anti-addictive agent in alcoholic humans except via indirectly diminishing depressive symptoms in those alcoholic patients with co-morbid major depression.

However, ondansetron, a 5HT-3 antagonist, has been associated with improved drinking outcomes in 2 placebo-controlled trials of alcoholic patients, suggesting a role of the 5HT3 receptor in some of the reinforcing effects of alcohol.

It appears that alcohol enhances activity of 5HT3 receptors, likely located on VTA DA neurons, leading to release of DA in the NA and partially accounting for some of the indirect DA increases and positive reinforcement associated with alcohol ingestion.

Pharmacology of Alcohol Addiction

Pharmacologic Treatment of Alcohol Use Disorders: *Endocannabinoid Agents*

•It appears that some of alcohol's reinforcing properties are mediated by activating the CB1 receptor which is believed through an unknown mechanism to increase DA transmission in the mesolimbic circuit.

•Evidence for this comes from animal studies where CB1 antagonists were shown to reduce alcohol intake as well as disrupting conditioned relapse to alcohol-seeking behaviors.

•Further research in human trials would be warranted to determine if CB1 antagonists/inverse agonists can be useful anti-addictive agents in the treatment of alcohol use disorders.

Pharmacology of Alcohol Addiction

Pharmacologic Treatment of Alcohol Use Disorders: *Combination Therapy*

Given the non-specific pharmacodynamic properties of alcohol and its acute and chronic effects involving multiple neurotransmitter systems, it would seem that combination pharmacotherapy to target the various receptors involved in the reinforcing properties of alcohol might be necessary for optimal outcomes. It would also seem important to use agents for a particular stage of illness that takes into account the efficacy or lack thereof of the agent for the specific stage. Moreover, within a particular stage, medications could theoretically be combined to target various processes driving the addictive process such as relapse prevention agents that diminish positive reinforcement (i.e. naltrexone) and those diminishing negative reinforcement (i.e. acamprosate).

Regarding disulfiram combination therapy, there is some preliminary data to suggest that disuliram-naltrexone may be more effective in improving drinking outcomes compared to disulfiram alone[87] (Landabaso 1999) and that disfulfiram-acamprosate may provide for a higher degree of cumulative abstinence duration compared to either agent alone

Pharmacology of Alcohol Addiction

Pharmacologic Treatment of Alcohol Use Disorders:

•Given that naltrexone and acamprosate may target different aspects of the relapse process, it made sense to test whether both agents in combination would be superior to either alone to prevent relapse.

•However, the data has been mixed. Project COMBINE, sponsored by NIAAA, was a multicenter, randomized, controlled trial involving approximately 1,400 subjects to investigate whether combination therapy with naltrexone and acamprosate was superior to either agent alone or to placebo with primary outcome measures being time to first drink and percentage of days abstinent.

•All groups (including placebo) showed a substantial reduction in drinking by up to 80%; however, only naltrexone was better than placebo and acamprosate (either alone or in combination with naltrexone) showed no advantage over placebo.

•However, this study included a less severely dependent alcoholic population with only about 2% of the patients requiring detoxification prior to initiation of pharmacotherapy and the primary outcome variables focusing on reduction of heavy use—all factors that would favor naltrexone over acamprosate. In contrast, a recent study in Germany demonstrated that the combination of acamprosate and naltrexone was better than acamprosate and placebo alone, but not naltrexone alone and a study in Australia that matched subjects for severity of illness and previous detoxification, acamprosate and naltrexone were more effective than either medication alone.

•Future studies are needed to determine which combination therapies might confer additive advantages and in particular sub-populations of alcoholic patients& at what optimal stage of illness.

Pharmacology of Opiate Addiction

Pharmacologic Treatment of Opiate Use Disorders:Opioids

Agonist Substitution (Blockade)
Methadone Maintenance

•Developed in the 1940s as an analgesic medication and introduced by Dole and Nyswander in New York City in the 1960s to combat a heroin epidemic, methadone is the most widely used agent in medically managed opiate maintenance programs.

•Given the high relapse rates with opiate addiction, in particular heroin, and all of the extensive morbidity and mortality associated with prolonged use, a harm reduction replacement therapy model is used with opiate dependence with methadone being the first type of opiate replacement therapy.

•Unlike a short acting opiate (i.e. heroin, half-life approximately 1 hour, that needs to be dosed several times daily), methadone has a half-life of 24-36 hours (range 13-50 hours) and can be dosed once daily.

•The most common side effects of methadone are sweating, constipation, urinary retention, and orgasm dysfunction in men.

•Long-term methadone use has not been associated with end organ damage to the lungs, liver, kidneys or heart and there is some evidence it may have cardioprotective properties by reducing atheroslerotic plaque formation

Pharmacology of Opiate Addiction

Pharmacologic Treatment of Opiate Use Disorders:Opioids

Agonist Substitution (Blockade)

Methadone Maintenance

•Methadone can be fatal in overdose with the risk enhanced by active liver disease, concomitant use of alcohol, sedative-hypnotics (i.e. benzodiazepines, barbiturates, GHB), and medications that inhibit the cytochrome CYP3A4 system (as methadone is primarily metabolized through this system).

•Given that methadone accumulates erratically during the induction phase and can take over a week to reach steady state, it is recommended that an initial induction dose not exceed 30mg and that the total dose for the first 24 hours not exceed 40mg to avoid overdose fatalities.

•Moreover, at doses above 120mg/day, methadone has been associated with possible cardiac conduction problems (i.e. QT prolongation and the risk of Torsade de Pointes) prompting a black box warning in 2006 from the FDA

Pharmacology of Opiate Addiction

Pharmacologic Treatment of Opiate Use Disorders:Opioids

Agonist Substitution (Blockade)

Methadone Maintenance

- **Methadone maintenance is the only treatment for opiate dependence that has clearly been shown in clinical trials to diminish illicit opiate use more than detoxification, placebo, no treatment or drug free treatment and in a recent cochrane review comparing methadone maintenance to no opiate replacement therapy, methadone was more effective in terms of treatment retention and decreased illicit opiate use.**

- **Other studies have shown other benefits such as decreased morbidity and mortality, decreased transmissibility of viral infections (i.e. HIV and Hepatitits C), and reduced criminal behavior, especially when combined with enhanced psychosocial services.**

- **Regarding optimal dosing, although 30-40mg of methadone suppresses most craving and withdrawal symptoms, it is not sufficient through cross-tolerance to block the reinforcing properties of high doses of illicit opiates.**

- **A meta-analysis of studies from 1966 to 1999 demonstrated that high doses of methadone ($\geq$ 50mg/day) was better than lower dose of methadone ($\leq$ 50mg/day) in reducing illicit opiate use and that the optimal dose range for most methadone maintenance programs is between 80-120mg**

Pharmacology of Opiate Addiction

Pharmacologic Treatment of Opiate Use Disorders:Opioids

Agonist Substitution (Blockade)

Methadone Maintenance

Pharmacology of Opiate Addiction

Pharmacologic Treatment of Opiate Use Disorders:Opioids

- **A major limitation of methadone relates to the regulatory restrictions governing its use where it can only be dispensed for opiate addiction at certified federal and state programs and patients have to come daily for their dose with only some restrictions lifted over time based on positive outcomes such as abstinence rates.**

Pharmacology of Opiate Addiction

Pharmacologic Treatment of Opiate Use Disorders:Opioids

Buprenorphine Maintenance

•In accordance with the Drug Abuse Treatment Act (DATA) of 2000, in October 2002, the FDA approved the use of buprenorphine as a schedule III agent to treat opiate dependence in outpatient office-based practices by physicians who received 8 hours of specialized training and attained a waiver from the Department of Health and Human services.

• Although the limit on the number of patients per provider is 100 after one year of having the waiver, buprenorphine has increased the options of pharmacotherapy for patients with opiate addiction by diminishing the regulatory hurdles that prescribe its use as opposed to methadone.

Pharmacology of OpiateAddiction

Pharmacologic Treatment of Opiate Use Disorders:Opioids

Buprenorphine Maintenance

•To mitigate the potential for parenteral abuse and diversion, buprenorhine was developed in a combination form with naloxone, suboxone, in addition to the mono-form of buprenorphine alone, subutex.

•When suboxone is taken in its sublingual form, the naloxone is poorly bioavailable and mostly inactive but when liquefied and taken parenterally the naloxone becomes active and can induce opiate withdrawal.

•Buprenorphine is a long-acting (up to 48 hours), high affinity partial mu-opioid agonist, and kappa antagonist in which its high affinity for the mu opioid receptor causes it to act as a functional antagonist blocking the effects of pure mu agonists, except at very high agonist doses where the blockage can be overridden.

•Because buprenorhine is a partial agonist, unlike a pure mu agonist like methadone, it is safer in overdose as it has a ceiling on respiratory suppression; however, there have been deaths reported when buprenorphine was injected along with benzodiazepines

Pharmacology of Opiate Addiction

Pharmacologic Treatment of Opiate Use Disorders:Opioids

Buprenorphine Maintenance

•Buprenorphine induction done in the outpatient setting can occur either in a closely monitored clinic setting or less restrictively over the telephone.

•Since buprenorphine is a partial mu agonist it can precipitate withdrawal in patients who are on full mu agonists.

•As such, one begins induction only when the patient is in the beginning of active opiate withdrawal with the time-frame predicated on whether the individual is dependent on short (minimum of 12-16 hours after last dose) or long-acting opiates (minimum of 36 hours after last dose).

•To transfer an individual from a long-acting full mu agonist (i.e. methadone, oxycontin) to buprenorphine, it is key that the dose is first reduced to an equivalent of 30-40mg of methadone given the mu opioid ceiling effects with buprenorphine.

•Induction is done over a 4-day period with a typical initial dose of 4mg sublingual given once the patient is in active opiate withdrawal. After the initial dose on day 1 of induction, one to two hours later, if the patient is still in opiate withdrawal, a second 4mg dose is given and if necessary a 3rd dose given several hours later if needed with a maximum of 12mg on the first day.

•On subsequent days, additional doses of 4mg every 2 hours can be given with a usual maximum of an additional 8mg per day. However, the field of practice is evolving and some practitioners will induce patients in one day. The typical maintenance dose is 16-24mg with the ceiling effect at approximately 32mg per day

Pharmacology of Opiate Addiction

Pharmacologic Treatment of Opiate Use Disorders:Opioids

Buprenorphine Maintenance

•Buprenorphine's FDA approval was based on several studies in patients with opiate dependence—one where 8mg buprenorphine sublingual demonstrated better treatment retention and lower opiate use compared to an active control group receiving 20mg of methadone and another study where buprenorphine 8mg SL had better retention and less opiate use than an active control group with 1-mg buprenorphine.

•Given buprenorhine's favorable safety profile and relaxed regulatory restrictions compared to methadone, some have worried that buprenorphine might supplant the use of methadone for opiate addiction.

•However, a recent Cochrane review that analyzed 24 studies that either compared buprenorphine maintenance to placebo or methadone maintenance demonstrated the following: buprenorphine at medium and high doses was superior to placebo in terms of diminished illicit opiate use and treatment retention; buprenorphine given in flexible doses was less effective than methadone in retaining patients; low dose methadone was more likely to retain patients than low dose buprenorphine; medium dose buprenorphine did not retain patients more than low dose methadone but may better diminish opiate abuse; and medium dose methadone was better than medium dose buprenorphine in terms of opiate use but equal in terms of treatment retention.

Pharmacology of Opiate Addiction

Pharmacologic Treatment of Opiate Use Disorders:Opioids

Buprenorphine Maintenance

•These results make sense when taking into account that buprenorphine is a partial mu agonist with a maximal dose approximately equal to 70mg of methadone and as mentioned above the optimal methadone maintenance dose is between 80-120mg.

•Methadone may be more suited especially for those patients that have a ‘large habit’ of a full mu agonist.

•In addition, other advantages of methadone over buprenorphine include: markedly reduced cost, established safety in pregnancy although recent studies have demonstrated good safety with buprenorphine in pregnancy comparable to methadone and the utility of daily contact (as mandated by methadone regulatory guidelines) in terms of enhanced opportunity for patient engagement and the provision of psychosocial treatments and services.

•Depot buprenorphine as a subcutaneous delivery formulation is actively being studied to treat opiate addiction

Pharmacology of Opiate Addiction

Pharmacologic Treatment of Opiate Use Disorders:Opioids

Antagonist Blockade

Naltrexone Maintenance

•As an alternative to opiate replacement therapy for opiate addiction, naltrexone is used as a relapse prevention tool in an abstinence oriented treatment model and one that takes advantage of naltrexone's long-acting, high affinity mu-opioid receptor antagonist properties.

•Naltrexone has benefits over opiate replacement therapies including a more favorable safety profile (i.e. no risk of overdose), no addictive liability, and diminished stigma where many believe that opiate replacement is simply giving one addictive substance for another, despite the well established efficacy data of methadone and buprenorphine as described above.

•However, despite some trials demonstrating improved outcomes in oral naltrexone compared to placebo, several trials have shown no benefit over placebo and a recent Cochrane review failed to unequivocally support the efficacy (i.e. treatment retention rates, relapse prevention) of oral naltrexone in the treatment of opiate addiction compared to placebo.

•Patient preference for opiate maintenance therapies over naltrexone likely contribute to high dropout rates early in treatment, with treatment retention strengthened in more highly motivated patients or those where external incentives are provided such as contingency) or through the use of coercion such as the criminal justice system or state licensing boards for addicted physicians

Pharmacology of Opiate Addiction

Pharmacologic Treatment of Opiate Use Disorders:Opioids

Antagonist Blockade

Naltrexone Maintenance

•As part of efforts to improve treatment compliance and outcomes in using naltrexone for relapse prevention in opiate addicts, sustained-release preparations such as a 1-month acting depot preparation (i.e. vivitrol) make sense to apply clinically.

•Current efforts are underway in multiple academic medical centers to formally evaluate the efficacy of sustained release naltrexone in an opiate dependent population as the data currently does not provide sufficient evidence to formally evaluate the efficacy

Pharmacology of Opiate Addiction

Pharmacologic Treatment of Opiate Use Disorders:Opioids

Future Options
CRF antagonists

•The stress system is increasingly recognized as playing an important role in the addictive process, in particular in drug reinstatement.

•Pre-clinically, CRF antagonists have been shown to attenuate opiate withdrawal, block conditioned aversion responses and diminish stress induced relapse, holding out promise as a potential relapse prevention agent in humans.

Pharmacology of Opiate Addiction

Pharmacologic Treatment of Opiate Use Disorders:Opioids

Future Options

Iboga Alkaloids

•Ibogaine is a psychoactive hallucinogenic indole alkaloid that is the most abundant alkaloid found in the root bark of the Apocynaceous shrub Tabernathe iboga in West Central Africa.

•In addition to demonstrating that ibogaine is not a drug of abuse, animal studies have revealed ibogaine's attenuation of heroin, morphine, cocaine, nicotine and alcohol-seeking behaviors as well as its dramatic ability to treat opiate withdrawal with just one dose.

•In addition, ibogaine has also been shown to inhibit operant alcohol self-administration in rats and to reduce alcohol intake in a reinstatement paradigm.

•Human anectodal reports and several case series studies have indicated that ibogaine diminishes or eliminates withdrawal symptoms and drug craving for multiple drugs of abuse including opiates, cocaine, and amphetamines, with the most promising and widely used indication being opiate withdrawal.

Pharmacology of Opiate Addiction

Pharmacologic Treatment of Opiate Use Disorders:Opioids

Iboga Alkaloids

- **In addition to treating opiate withdrawal, iboga alkaloids could be useful for relapse prevention.**

- **However, the use of ibogaine remains unavailable for use in the United States because of concerns regarding its safety, specifically neurotoxic and cardiotoxic issues.**

- **The neurotoxicity of greatest concern relates to possible cerebellar damage, observed in rats but not in mice or primates.**

- **The cardiac toxicity includes bradycardia and possible other forms of arrhythmia, including QT prolongation.**

- **There have been deaths reported within 72 hours of ibogaine use since 1990.**

Pharmacology of Opiate Addiction

Pharmacologic Treatment of Opiate Use Disorders:Opioids

Iboga Alkaloids

•Ibogaine has a complicated set of receptor interactions including: serotonin (pre-synaptic release, inhibition of the serotonin re-uptake transporter (SAT), 5HT2a agonism [hallucinogenic mediated effects], 5HT3 agonist); glutamate (NMDA antagonism); opioid (mu agonist, kappa agonist); acethylcholine (muscarinic agonist; nicotinic antagonist).

•However, its exact anti-addictive mechanism remains elusive and further research into ibogaine's potential use with addictive disorders should continue with the goal of translating the anecdotal and preclinical findings into the supervised clinical setting as well as further characterizing its anti-craving mechanisms.

•Moreover, it would be important to use iboga alkaloid compounds that confer the therapeutic effects while minimizing or eliminating the toxic side effects.

•One such potential agent to consider is 18-methoxycoronaridine (18-MC), a synthetic ibogaine congener designed specifically for this purpose

Pharmacology of Cocaine Addiction

Pharmacologic Treatment of Cocaine Use Disorders
Cocaine

Dopamine based treatments: Replacement therapy, Antagonism, and Aversive Conditioning
Replacement Therapy & Antagonism

Pharmacotherapy Efficacy Evidence base

•Despite numerous controlled studies of over 60 medications—including dopamine receptor agonists (i.e. bromocriptine, amphetamine), D1 agonists, dopamine partial receptor agonists (i.e. terguride), dopamine reuptake inhibitors (i.e. amantadine, vanoxerine, methylphenidate and various TCAs and SSRIs), dopamine metabolism inhibitors (i.e. disulfiram, selegiline), dopamine antagonists (i.e. haloperidol, risperidone), GABA-ergic agents (i.e. gabapentin, baclofen, tiagabine, vigabatrin, lamotrigine, valproate), Beta-adrenergic antagonists (i.e. propanolol), compounds targeting the opioid system (i.e. buprenorphine, naltrexone), compounds targeting the serotonergic system (i.e. fluoextine, sertraline, ondansetron), compounds targeting the glutamatergic system (i.e. Dizocilpine, memantine), cortisol synthesis inhibitors and glucocorticoid receptor antagonists (i.e. ketaconazole), calcium channel blockers (i.e. nimodipine), anti-depressants (i.e. SSRIs, TCAs, venlafaxine, bupropion) and anti-convulsants (i.e. carbemazepine)-- there is no conclusive data to support the efficacy of any particular pharmacologic agent to treat stimulant use disorders in unselected human populations.

Pharmacology of Cocaine Addiction

Pharmacologic Treatment of Cocaine Use Disorders

Dopamine based treatments: Replacement therapy, Antagonism, and Aversive Conditioning

Replacement Therapy & Antagonism

Cocaine

•Replacement treatments make theoretical sense with cocaine dependence including replacing cocaine's effects at the DAT and replacing post-synaptic DA with DA agonists.

•Vanoxerine was a promising agent as a replacement therapy and possessed all the favorable pharmacologic properties of such an agent: slower onset, longer duration of action, low motoric stimulation compared to cocaine as well as having higher selectivity for the DAT as compared with the SAT and NAT.

•Despite promising pre-clinical data trials were suspended in humans because of QT prolongation.

•D1 agonists demonstrated anti-addictive properties in preclinical and human subject studies, but also increase the risk of seizures limiting their use.

Pharmacology of Cocaine Addiction

Pharmacologic Treatment of Cocaine Use Disorders

Cocaine

Dopamine based treatments: Replacement therapy, Antagonism, and Aversive Conditioning

Replacement Therapy & Antagonism

- **Among the dopamine enhancing agents, amantadine has shown some promise in treating patients with cocaine dependence but has not been a reliable finding.**
- **A final replacement approach involves substituting amphetamine for cocaine as agonist therapy where dextroamphetamine has been shown to reduce cocaine use in cocaine-dependent humans.**
- **This would be similar to replacing heroin with methadone as amphetamine has a longer half-life than cocaine but still has addictive liability as does methadone.**

Pharmacology of Cocaine Addiction

Pharmacologic Treatment of Cocaine Use Disorders

Cocaine

Dopamine based treatments: Replacement therapy, Antagonism, and Aversive Conditioning

Replacement Therapy & Antagonism

•Similar to the use of buprenorphine for opiate addiction, partial dopamine agonists have the potential to mimic some of the reinforcing properties of cocaine without producing toxicity and could act to reduce DA activity when it is too high acting as a relative antagonist and could increase DA activity when it is too low.

• One such agent BP-897, a partial D3 agonist decreases cue-induced cocaine seeking in animals and is currently being tested in phase II clinical studies.

•Aripiprazole, a partial dopaminergic agonist used to treat schizophrenia, has been associated with decreased cocaine craving in open label trials of patients with schizophrenia and co-morbid cocaine dependence.

•Antagonism at the DAT remains a theoretical point of intervention while non-selective DA receptor antagonists have yielded some positive but non-reliable findings.

Pharmacology of Cocaine Addiction

Pharmacologic Treatment of Cocaine Use Disorders

Cocaine

Aversive Conditioning: Disulfiram

•The initial idea to test disulfiram to treat cocaine dependence came from the observation that in samples of cocaine dependent patients, there is a very high co-occurrence of alcohol use disorders, up to 85% in some epidemiologic studies.

•The idea was that a reduction in alcohol consumption as part of the DER would indirectly lead to a reduction in cocaine consumption.

• Several studies in patients with co-occurring alcohol and cocaine use disorders have shown that disulfiram is associated with a reduction in both alcohol and cocaine use and in a placebo-controlled trial, disulfiram was associated with greater treatment retention and reductions in cocaine and alcohol use compared to placebo along with a sustained reduction in both cocaine and alcohol use at 1-year follow-up.

• However, several recent placebo-controlled trials have called into question the indirect effect of disfulfiram on the reduction of cocaine use and have suggested a more direct effect.

• In one of these studies disuliram (250mg/day) treatment was found be more effective in reducing the amount and frequency of cocaine use in the nonalcoholic cocaine dependent group as compared to the alcohol + cocaine dependent group.

Pharmacology of Cocaine Addiction

Pharmacologic Treatment of Cocaine Use Disorders
Cocaine
Aversive Conditioning: Disulfiram

•A possible explanation relates to disfulfiram's ability to inhibit *dopamine beta hydroxylase* (DBH), the enzyme that converts dopamine to norepinephrine, leading to a build-up of DA and producing an effect similar to a non-specific dopamine agonist.

•Based on findings that cocaine administration along with disulfiram causes an elevated rate of adverse psychological and physiological reactions some have suggested a disulfiram-cocaine aversive reaction, similar to the DER, causing aversive counter-conditioning.

• There is also some evidence to suggest that similar to pharmacogenetic differences in the mu-opioid receptor predicting treatment response to naltrexone in alcoholics a polymorphism in the DBH gene (-1021C->T) associated with low DBH activity has been associated with a reduction in cocaine use compared to placebo in a randomized controlled trial.

Pharmacology of Cocaine Addiction

Pharmacologic Treatment of Cocaine Use Disorders
Cocaine
***GABA-ergic agents:* Baclofen, Tiagabine, Vigabatrin, Topiramate, Valproic Acid**

•GABAergic interneurons provide inhibitory modulation on the release of DA in the VTA and NA.

•While cocaine abuse diminishes GABA levels, activation of GABA B receptors inhibits DA release in the VTA and NA and decreases cocaine self-administration in rats

• 2 promising strategies that enhance GABAergic function in cocaine addicts are: direct stimulation of GABA B receptors with an agonist and enhanced GABAergic transmission by either inhibiting the GABA re-uptake transporter or via inhibition of GABA transaminase, the main enzyme involved in GABA catabolism.

•A promising agent actively being studied for cocaine dependence is *baclofen*, a selective GABA-B agonist. In addition to promising pre-clinical data showing decreased cocaine self-administration and decreased cocaine-seeking behavior, open-label and controlled human trials have demonstrated a reduction in cocaine use.

•*Tiagabine* is a GABA re-uptake transport inhibitor that has shown efficacy in reducing cocaine use in several placebo-controlled clinical trials including 2 in cocaine dependent patients enrolled in a methadone maintenance program

Pharmacology of Cocaine Addiction

Pharmacologic Treatment of Cocaine Use Disorders

Cocaine

GABA-ergic agents: **Baclofen, Tiagabine, Vigabatrin, Topiramate, Valproic Acid**

•*Vigabatrin* (gamma-vinyl-GABA), an irreversible inhibitor of GABA transaminase that dramatically raises the levels of GABA has been shown to have anti-addictive properties pre-clinically and in two open-label human clinical studies.

• Placebo-controlled phase II trials of vigabatrin are currently underway in several sites in the US.

•*Topiramate* (enhanced GABAergic activity as well as antagonist properties at the AMPA and kainite glutamate receptors) in a 13-week, double-blind, placebo-controlled trial of 40 cocaine abusing subjects, at a dose of 200mg/day, was superior to placebo in achieving and maintaining abstinence from cocaine (59% vs 26% respectively).

•Given the above mentioned promising results for the use of topiramate as a relapse prevention treatment for alcoholism, future studies to see if topiramate can reduce alcohol and cocaine use in patients with the co-occurring SUDs are warranted.

•*Valproic acid* (an antiepileptic agent that increases the synthesis of GABA and potentiates its pre-synaptic release and post-synaptic response) has been associated with decreased cocaine use in several open label trials as well as some evidence of decreased affective symptoms along with decreased cocaine use in patients with co-occurring bipolar disorder and cocaine dependence

Pharmacology of Cocaine Addiction

Pharmacologic Treatment of Cocaine Use Disorders

Cocaine

Serotonergic agents:

•Given that cocaine inhibits the SAT and has a high affinity for the 5HT3 receptor as an agonist, both sites have been targets for clinical intervention.

•While the results of SSRIs in controlled trials have failed to provide promising results ondansetron , a 5HT3 antagonist, has shown efficacy in reducing cocaine self-administration in lab animals and a randomized, 10-week controlled pilot study in cocaine dependent patients found a reduction in cocaine use and enhanced treatment retention

Pharmacology of Cocaine Addiction

Pharmacologic Treatment of Cocaine Use Disorders

Cocaine

Glutamatergic Agents:

•In psychostimulant addiction, several aspects of glutamatergic dysregulation occur that likely represent potential pharmacotherapeutic options: a final common pathway to drug seeking behavior is associated with a large release pre-synaptically of glutamate in projections from the PFC to the NA, upregulation of post-synaptic AMPA receptors, and a downregulation in signaling in release-regulating presynaptic metabotropic glutamate receptors (mGluR2/3).

• An example of an agent that prevents some of these processes is N-acetylcysteine, a cystine/glutamate exchanger that restores extracellular levels of glutamate, which may in turn restore inhibitory tone by activating mGluR2/3 receptors that prevents synaptic glutatamte release associated with drug-seeking and has been shown to reduce cocaine craving in a trial of cocaine dependent patients.

• Moreover, specific mGluR2/3 agonists have been associated with diminished cocaine seeking in animals.

Pharmacology of Cocaine Addiction

Pharmacologic Treatment of Cocaine Use Disorders
Cocaine

Glutamatergic Agents

•Modafinil, a wake-promoting agent used to treat narcolepsy, as one of several pharmacologic properties increases extracellular glutamate levels which could theoretically restore tone on mGluR2/3 receptors and potentially decrease glutamate surges associated with drug reinstatement.

•Several small clinical trials have suggested a role in promoting cocaine abstinence for modafinil with a double-blind placebo-controlled trial associated with good treatment retention and prolonged abstinence from cocaine compared to placebo

Pharmacology of Cocaine Addiction

Pharmacologic Treatment of Cocaine Use Disorders
Cocaine

Other future options

Endogenous Cannabinoid System

•The endocannabinoid system has been implicated in cocaine addiction. CB1 knockout mice had diminished acquisition and maintenance of intravenous cocaine administration and rimonabant reduced cue- and drug-primed conditioned cocaine relapse in animals.

•Although there is no human data on the use of CB1 antagonists/inverse agonists in cocaine use disorders, they remain a potential area of further inquiry.

Pharmacology of Cocaine Addiction

Pharmacologic Treatment of Cocaine Use Disorders
Cocaine

Other future options

Immune Therapy

•Cocaine vaccination produces antibodies to cocaine preventing the drug from reaching the central nervous system.

• Studies in rats have shown that with sufficient anti-cocaine antibody levels, cocaine reinstatement was reduced and a phase II open label study in humans over a 14-week period with the Xenova vaccine revealed that subjects who received the more intense vaccination schedule (total of 2000 micrograms) used significantly less cocaine than those receiving a total of 400 micrograms.

Ethical Issues in Treatment

- Personal relationships
- Confidentiality
- Dangerousness to self and others
- Informed consent
- Financial conflict of interest

Ethical Issues: Confidentiality I

- Interdisciplinary treatment teams
- Supervision in and outside of program
- Outside agencies/practitioners
- Family members
- Teaching/sharing experiences

Ethical Issues: Confidentiality II

- Legal protection of records
- Illegal activities by patients and reporting to police
- Drug use itself as illegal activity
- Group and family meeting risks

Ethical Issues: Personal Relationships

- No sexual relationships with patients
- Meetings outside treatment program
- Group versus individual meetings
- Ongoing contacts after patient leaves treatment

Ethical Issues: Dangerous

- Duty to inform threatened persons
- Conflict with confidentiality
- Who and when to notify
- Medical emergencies - limited disclosure
- High risk behaviors - AIDS

Ethical Issues: Informed Consent I

- Written informed consent
- Release of written records
- Oral communication - dangerousness
- Need to document released information
- Program policies, HIV testing

Ethical Issues: Informed Consent II

- Capacity to provide consent
- Surrogate consent (e.g., family members)
- Full disclosure of risks and benefits
- Parole, probation and criminal justice reports

Ethics: Conflict of Interest

- Financial most common with treatment extension or discharge due to insurance
- Favoring one easily available treatment mode
- Pre-treatment relationship to patient
- Dual reporting to criminal justice, employer, etc.

Ethics: HIV Testing

- Negative consequences: medical services, housing, employment, school admission
- Contact tracing and partner notification
- Associated sexual diseases, tuberculosis

Ethics: Methadone Programs

- Retention vs. discharge: non-compliance
- Blind withdrawal only on request
- Pregnancy and continued drug use
- Child protective services

Post-Lecture Exam Question 1

1. **Which of the following statements is false:**

A. Physical dependence is synonymous with addiction.

B. One can be addicted without being physically dependent.

C. Once a patient has met criteria for Substance Dependence, they should not be diagnosed in the future with Substance Abuse.

D. A critical feature of addiction is compulsive use in spite of harm.

Question 2

2. Which of the following statements is false:

A. Psychiatric disorders can cause substance abuse.

B. Substance abuse can cause psychiatric disorders.

C. If both substance abuse and a psychiatric disorder are present, treating the psychiatric disorder is usually not necessary.

D. Treating an underlying psychiatric disorder usually does not adequately treat the substance abuse.

Question 3

3. **The most common comorbid psychiatric diagnosis in patients with substance abuse is:**

A. Schizophrenia
B. Antisocial Personality Disorder
C. Anxiety Disorder
D. Major Depression

Question 4

4. Which one of the following is false:

A. Cocaine decreases negative symptoms in schizophrenics.

B. When cocaine free, schizophrenics have more negative symptoms.

C. Chronic cocaine use increases depression in schizophrenics.

D. Chronic cocaine decreases positive symptoms of schizophrenia.

Question 5

5. **Which of the following are considered "Gateway Drugs"?**

A. Alcohol

B. Marijuana

C. Nicotine

D. A & C only

E. A, B, & C

Question 6

6. **Adolescent substance abuse is associated with:**

A. Increased school dropout

B. Increased depression and suicidality

C. Premature involvement in sexuality

D. All of the above

Question 7

7. **The proportion of users who ever became dependent is as follows (from high to low):**

A. Nicotine, alcohol, heroin, cocaine, marijuana.

B. Alcohol, nicotine, cocaine, heroin, marijuana.

C. Nicotine, heroin, cocaine, alcohol, marijuana.

D. Nicotine, alcohol, marijuana, cocaine, heroin.

Question 8

8. Which of the following is not used as a maintenance agent in heroin addiction:

A. Methadone

B. Clonidine

C. Naltrexone

D. Buprenorphine

Question 9

9. Which category of medications is <u>not</u> yet available for treatment of heroin addiction:

A. Agonists
B. Antagonists
C. Partial agonists
D. Anti-craving agents
E. Anti-withdrawal agents

Question 10

10. Which of the following statements are true:

A. Naltrexone blocks the effects of alcohol.

B. Drinking while on naltrexone can make one very ill.

C. Benzodiazepines are the usual agents used for alcohol withdrawal.

D. All of the above

Answers to Pre & Post Competency Exams

1. A
2. C
3. B
4. D
5. E
6. D
7. C
8. B
9. D
10. C