Understanding Drug and Alcohol Abuse and Addiction

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Substance Use, Abuse, and Addiction

- Inexorably intertwined in socioeconomic fabric of most cultures
- Differential diagnosis of diverse medical and psychiatric illnesses
- Elucidates fundamental brain mechanisms of mood, thought, perception, and cognition
- Molecules to Man to Society

History

Medical, religious, or recreational uses for indigenous psychoactive substances:

- **Beer -** archeological traces 4000 BC
- **Opium** - *Papaver sominferum*
- **Marijuana -** *Cannabis sativa*
- **Tobacco -** *Nicotiana tabacum*
- **Cocaine -** *Erythroxylon coca*
- **Stimulants -** *Ephedra* plant

"Modern" Era

- Blending of cultures and technological "advances"
- Synthesis of ephedrine analogues (e.g., amphetamine) and new CNS stimulants and depressants, hallucinogens, and anesthetics
- Epidemics of marijuana (60's), heroin (70's), cocaine (80's); alcohol and drugs trend up (70's), down (80's), up (90's)

Societal and Healthcare Costs of Substance Abuse

- Estimated $177 billion/year for medical care and lost productivity
- Abuse of alcohol, tobacco, and drugs contribute to **each** of the ten leading causes of death in U.S.
- Large potential cost-savings in a capitated healthcare environment

Past Year Prevalence Rates of Substance Use in the General Population

Drug	Male (%)	Female (%)
Alcohol	73	64
Cigarettes	35	30
Marijuana	12	8
Psychostimulants	6	3
Tranquilizers	2	2
Any illicit drug	15	11

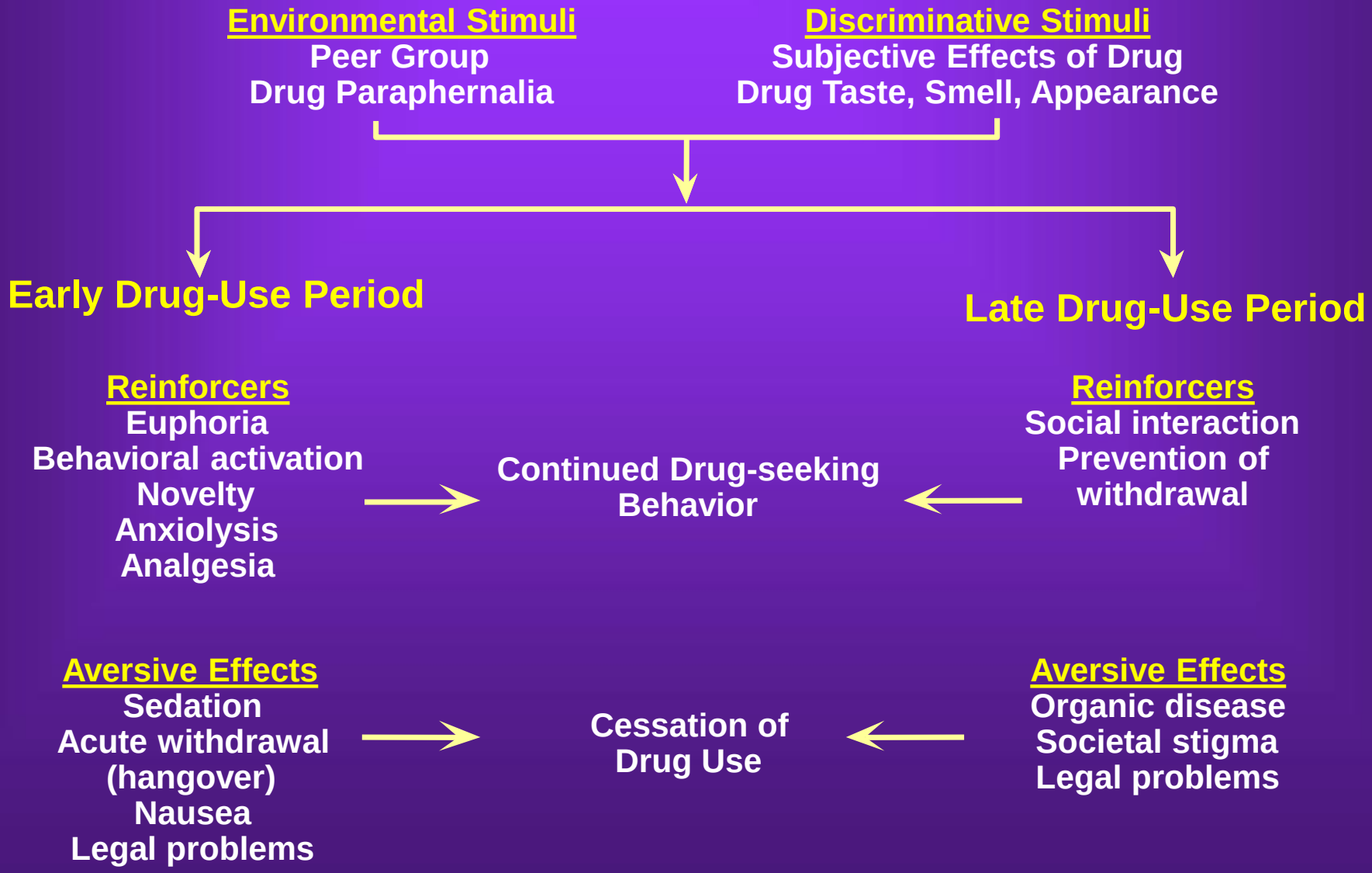
Adapted from Kandel (1992)

Lifetime prevalence of substance use disorders per 100 persons ≥ 18 years in U.S. population

Substance Use Disorders	Lifetime Prevalence
Any substance use disorder	16.7
Any alcohol disorder	13.5
Any drug disorder	6.1
Marijuana dependence/abuse	4.3
Cocaine dependence/abuse	0.2
Opiate dependence/abuse	0.7
Barbiturate dependence/abuse	1.2
Amphetamine dependence/abuse	1.7
Hallucinogen dependence/abuse	0.3

Adapted from Regier et al (1992). Diagnoses based on DSM-III.

Factors Contributing to Drug-Seeking Behavior



Psychoactive Substances with Abuse Liability

- **CNS Depressants:** alcohol, benzodiazepines (Valium, Librium, Xanax, Halcion, Ativan, Klonopin, etc), barbiturates (seconol, butalbatol), nonbarbiturate hypno-sedatives (qualudes, Placidyl, Ambien)
- **Stimulants:** amphetamine, cocaine, Ritalin
- **Cannabinoids:** marijuana, hashish, THC
- **Tobacco:** nicotine, cigarettes, etc.

Psychoactive Substances with Abuse Liability

- **Opioids:** heroin, morphine, methadone, codeine, Dilaudid, Percodan, Talwin, Demerol, Mepergan
- **Hallucinogens:** LSD, psylocybin, mescaline, mushrooms
- **Anesthetics:** PCP, ketamine, laughing gas
- **Inhalants:** gasoline, glue, paint, paint thinners, spray paint, other volatile compounds

Intoxication

Subjective effects of a drug perceived by the individual as well as changes in a user's behavior observed by others

Intoxication is determined by the pharmacologic actions of the drug, characteristics of the individual, and social situation and expectancies

Effects of Blood Ethanol Concentration on CNS Functions

Whiskey (Oz.) Beer (Drinks)	***Blood Ethanol* (mg/100 ml)**	***Impaired Function***
0.5	15	Vision
1-1.5	30-40	Fine muscle coordination
2-3	80	Reaction time
4	100	Judgment

Tolerance

Greater amounts of a drug are required for the same physiologic, subjective, or behavioral change after repeated exposure than was required when the drug was first used

Tolerance is an adaptive physiologic response which opposes the pharmacologic effects of the drug (molecular, cellular, organism)

Tolerance

- **Acquired:** metabolic, functional, behavioral (learned)
- **Initial** vs **acute**

Initial and/or acute tolerance are innate characteristics of the brain that may influence individual vulnerability to development of addiction

Dependence (Addiction)

Neuroadaptive physiologic changes after repeated exposure to a drug; clinical syndrome of drug-seeking behavior and psychosocial consequences

- **Physical:** occurrence of withdrawal following cessation of prolonged drug use
- **Psychological:** craving for drug
- **Both:** protracted abstinence syndrome

Withdrawal Syndrome

- **Normalization** of the adaptive changes which resulted from chronic presence of the drug in the brain
- Behavioral and physiologic signs are **opposite to** the acute drug effects
- Activation of **autonomic nervous system**
- Severity is related to **cumulative dose**

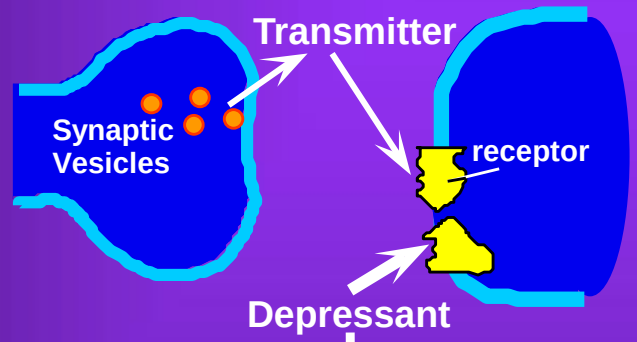
Tolerance *vs* Dependence

- Physical dependence usually develops in concert with tolerance
- Simply different manifestations of the same neuronal changes?

Reacquisition of tolerance and dependence are accelerated following repeated cycles of drug use and withdrawal, suggesting similarities with learning and memory

Neuroadaptation in $GABA_A$ Receptors after CNS Depressants

Allosteric Modulation of Ligand-Gated Ion Channels Enhancing Neural Depression

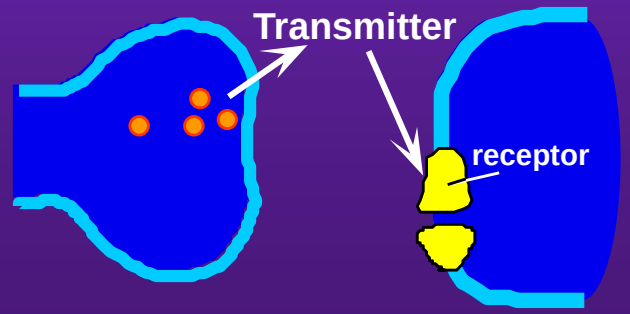


Acute Drug Exposure

Increased inhibitory synaptic communication leading to alterations in expression of receptor subunit proteins

Molecular Mechanisms Activated by Continued Drug Exposure

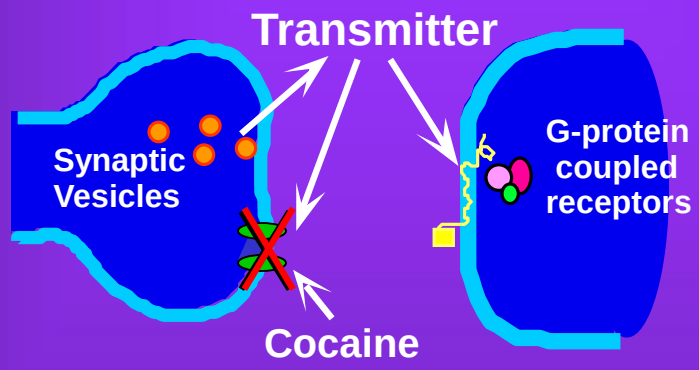
Changes in receptor structure, decreased receptor function and net increase in neural excitation



Chronic Drug Exposure

Neuroadaptation in Dopamine Function after Cocaine

Cocaine: Inhibition of monoamine uptake leads to increased neural excitation

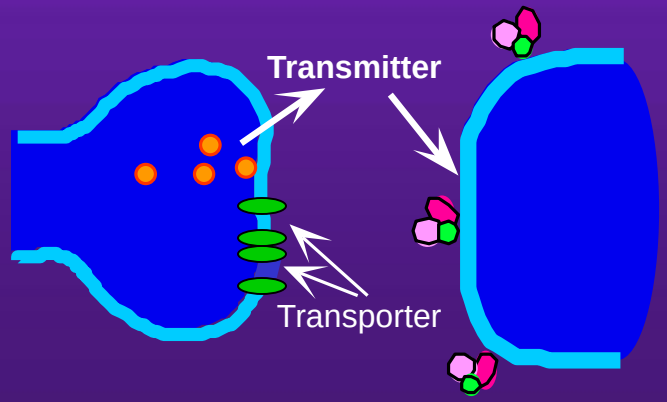


Acute Drug Exposure

Increased neurotransmitter levels lead to changes in receptor and transporter numbers

Molecular Mechanisms Activated by Continued Drug Exposure

Increased expression of neurotransmitter receptors and transporter leading to decreased transmission and neural depression



Chronic Drug Exposure

Clinical Diagnosis of Drug and Alcohol Dependence

- Criteria must be **generalizable** across cultures, substances, avoid value judgements
- **Maladaptive use** leading to significant impairment or distress manifested by $\geq$ 3 symptoms from following clusters:
  - Loss of control
  - Salience to the behavioral repertoire
  - Neuroadaptation

Loss of Control

- The substance is taken in larger amounts or over a longer period than intended
- Persistent desire or unsuccessful efforts to cut down or control substance use

Salience to Behavioral Repertoire

- A great deal of time is spent in activities necessary to obtain the substance, use the substance, or recover from its effects
- Important social, occupational, or recreational activities are given up or reduced
- Use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance use

Neuroadaptation

- **Tolerance**
  - need for increased amounts of the substance to achieve intoxication or desired effect
  - markedly diminished effect with continued use of the same amount of the substance
- **Withdrawal**
  - characteristic withdrawal syndrome
  - substance taken to relieve or avoid withdrawal

Diagnostic Criteria for Alcohol and Drug Abuse

Maladaptive use leading to significant impairment or distress manifested by ≥1 of the following, occurring within 12 months:

- Failure to fulfill major role obligations at work, school, or home (absences, poor performance, suspensions, neglect of family)
- Recurrent use in physically hazardous situations (driving, heavy machinery)

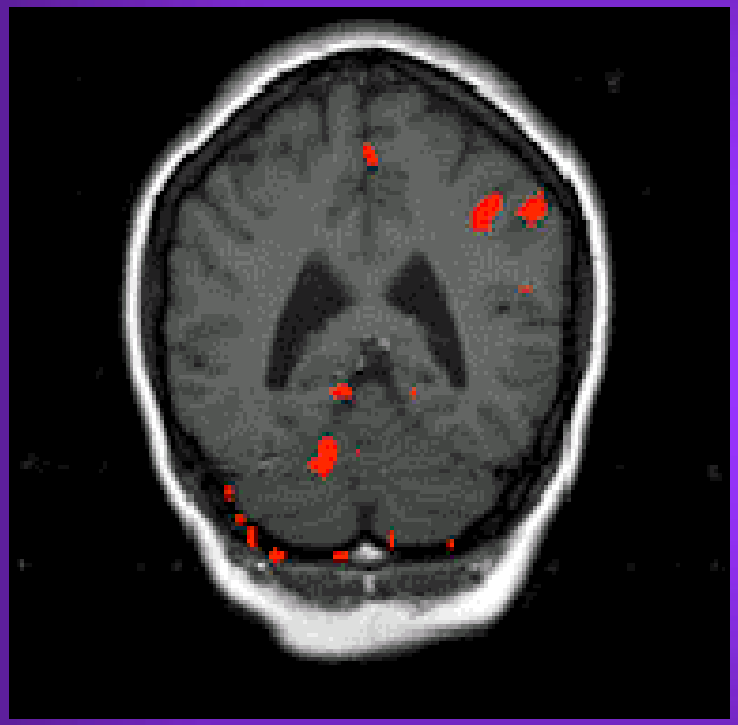
Alcohol and Drug Abuse

- Recurrent substance-related legal problems (e.g., arrests for disorderly conduct)
- Continued use despite persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance (e.g., family arguments)
- **The symptoms have never met criteria for Substance Dependence**

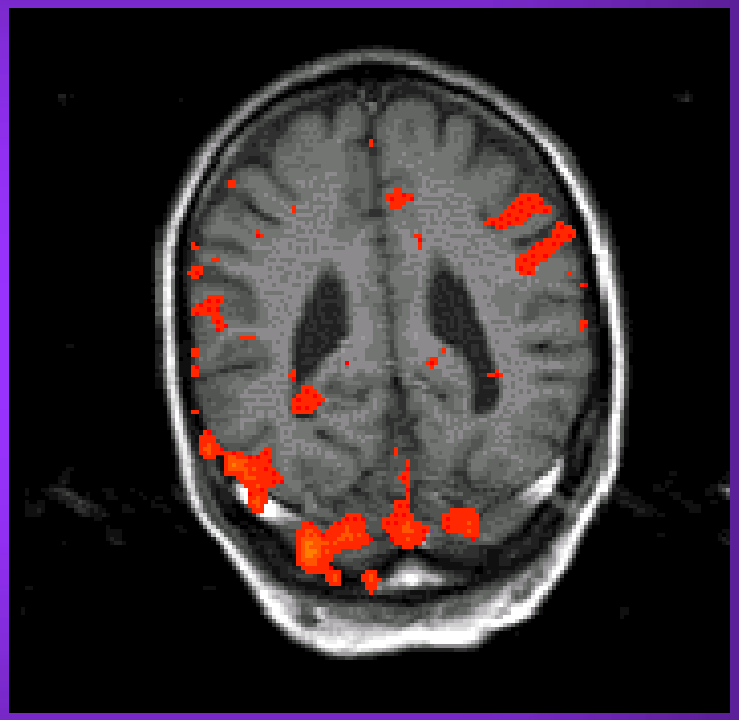
Clinical Presentation

- Acute and chronic **direct pharmacologic actions** of the substance:
  - **overdose**
  - **organ toxicity** (e.g., cirrhosis/ulcer/ pancreatitis, angina/MI/cardiomyopathy, emphysema, stroke/seizures/dementia, depression/anxiety/ psychosis, hypogonadism/infertility/fetal)
  - **metabolic consequences** (gout, diabetes, hypoglycemia, hyperlipidemia)

BRAIN ACTIVATION DURING FINGER TAPPING



Normal Volunteer

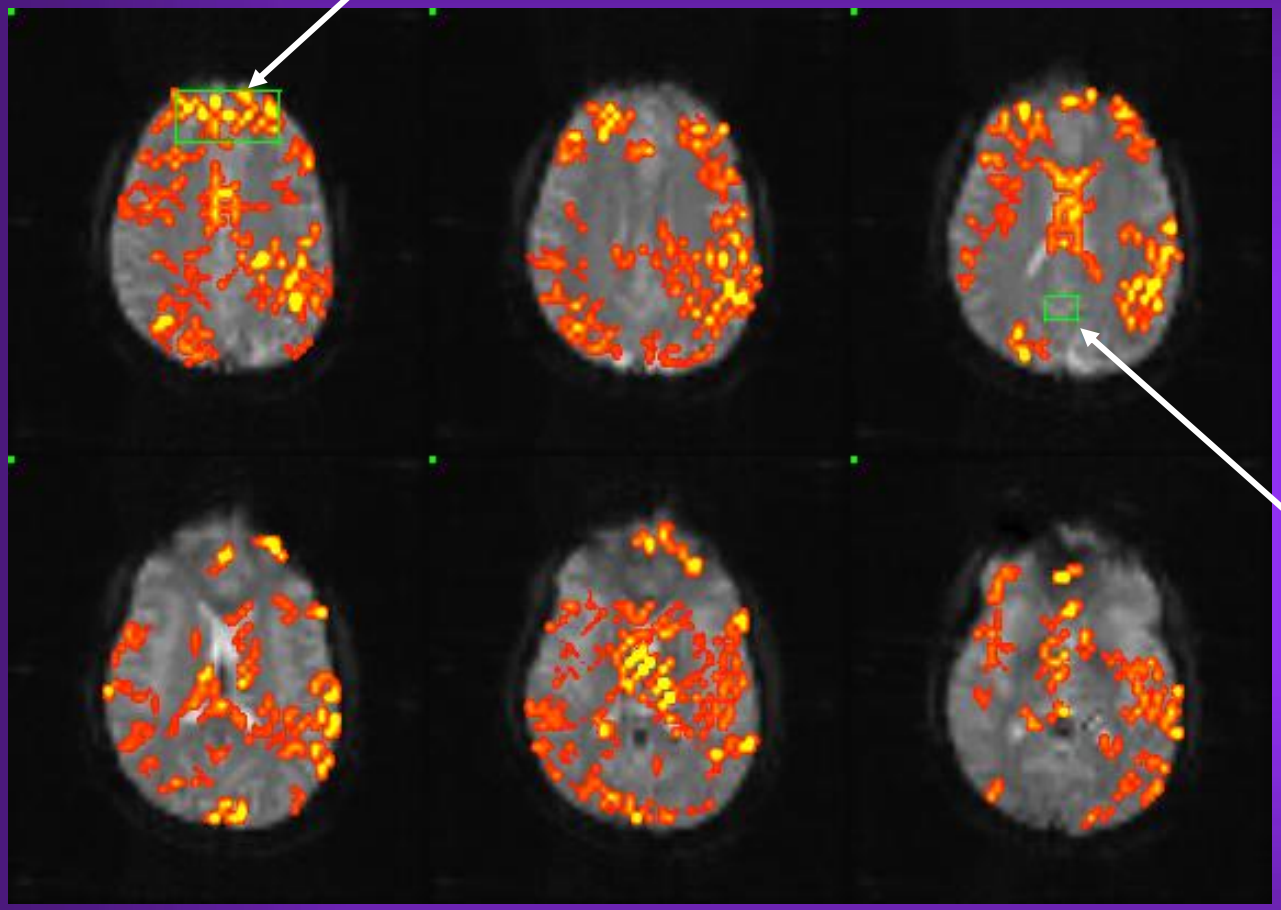


Alcoholic Patient

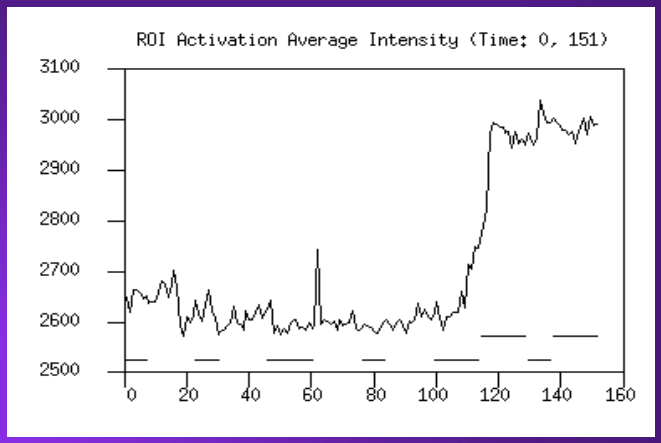
Clinical Presentation

- **Indirect effects** of drug self-administration on life-style:
  - family disruptions and emotional trauma
  - legal problems and physical trauma
  - neglect (e.g., malnutrition, infections)
  - tobacco and inappropriate use of prescribed medication (e.g., analgesics, anxiolytics)
  - lack of compliance with medical regimens for coexistent illnesses

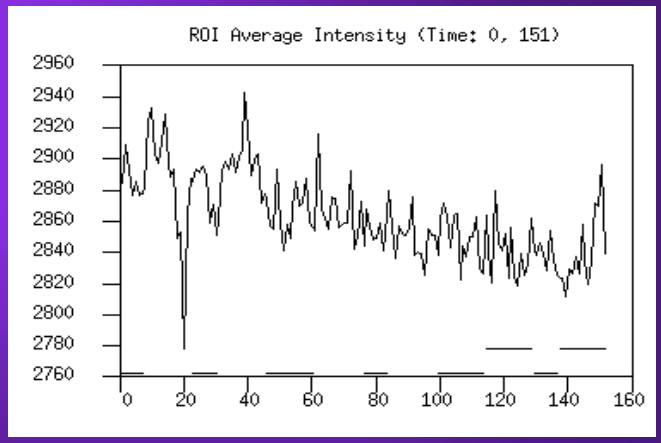
BRAIN ACTIVATION DURING SEXUAL AROUSAL



Normal Volunteer



Activated region

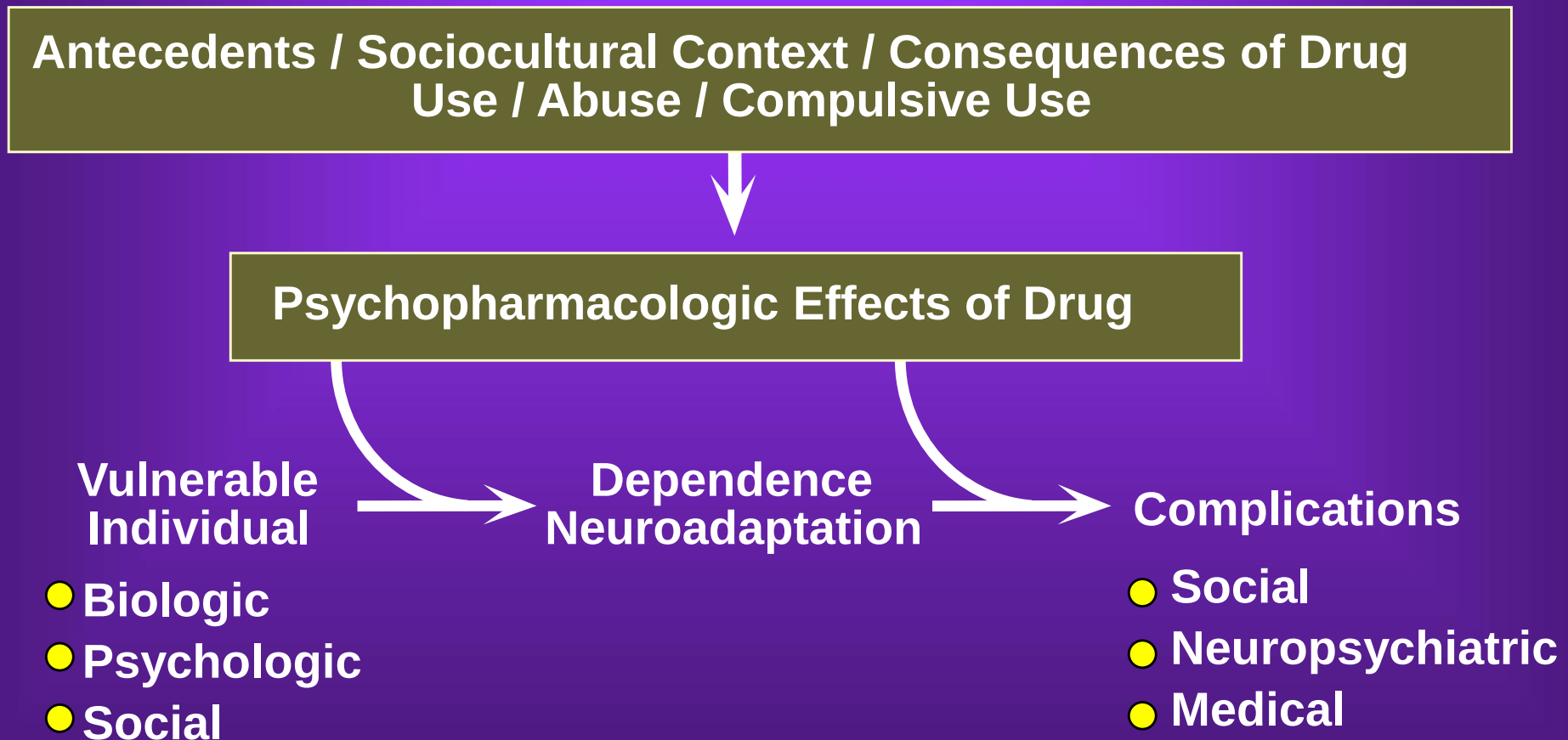


Non activated region

Treatment

- Careful clinical evaluation with emphasis on medical and psychiatric complications
- Treatment of withdrawal syndrome
- Inpatient, outpatient, residential, aftercare
- Psychotherapies (social or milieu, insight-oriented, behavioral, individual, and group)
- Introduce and encourage participation in 12-step self-support groups, e.g. AA, NA, CA

Longitudinal Progression of Substance Use Disorders



Medications Used in Treatment

- Withdrawal (Valium, phenobarb, clonidine)
- Antabuse (disulfiram)
- Revia (naltrexone)
- Antidepressants (Prozac, Zoloft, Paxil)
- Mood stabilizers (Depakote, Tegretol, lithium)
- Antipsychotics (Haldol, Risperdal, Zyprexa)

Future Research Directions

- Environmental and genetic factors in development of addiction and complications
- Co-morbid psychiatric conditions
- New psychopharmacologic treatments
- Combined use of medications and psychotherapeutic approaches
- Prevention and cost-effective treatment