

Prescription Stimulants

nonmedical use, Abuse, addiction

C. Chapman Sledge, MD, FASAM

Cumberland Heights

Nashville, TN

Chapman_sledge@cumberlandheights.org

Historical Perspective

- Chinese medicine – MaHuang (ephedra) – 5000 years ago
- South America – Coca leaves (cocaine) – 2000 years ago
- Eastern Africa / Arabian Peninsula – Khat (cathinone) – thousands of years ago, ancient Egypt

Historical Perspective

- 1860 – Albert Niemann isolated cocaine as the active ingredient in the coca leaf
 - Vin Mariani – wine containing cocaine
 - 1884 – cocaine used as ophthalmologic anesthetic
 - 1884- Freud published *Uber Cocaine* – details psychological effects of cocaine and suggests treatment of morpine addiction
 - 1886- John Pemberton combined cocaine and caffeine in a sugary syrup -Coca Cola
 - 1886- first reported cocaine induced MI /CVA
 - 1903 – cocaine removed from Coca Cola
 - 1914 – Harrison Narcotic Act banned cocaine from OTC preparations

Historical Perspective

- 1887 – Amphetamine synthesized
- 1919- Methamphetamine synthesized
- 1930 – Amphetamine gained popularity in OTC bronchodilator, Benzadrine Inhaler
- 1933 – CNS stimulant properties recognized and OTC's promoted for weight loss, narcolepsy, depression, and childhood hyperactivity
- Amphetamine largely replaced cocaine by illicit users: cheaper, readily available, longer duration of action
- 1937 – Abuse led to prescription only status

Historical Perspective

- World War II – Allied forces widely used amphetamine, Axis force use methamphetamine, to enhance performance of troops and factory workers
- Widespread abuse of stockpiles in Japan and Sweden after the war
- 1959 – FDA banned benzadrine inhalers due to IV abuse of extracted amphetamine
- 1970 – Controlled Substances Act placed cocaine, amphetamine, and methamphetamine in Schedule II
- In 1970 – 65 prescription stimulants marketed by 40 companies
- In 1995 – 8 prescription stimulants available in US

Pharmacology

- Plant-Derived Stimulants:
- Naturally occurring
- Widely available for traditional use
- Traditional use:
 - Adheres to cultural sanctions
 - Lower potency
 - Slow onset route of administration
 - Less often associated with abuse and addiction

Pharmacology

- Plant-Derived Stimulants:
- Cocaine
 - Natural plant alkaloid
 - Leaves of coca bush, *Erthroxylon coca*, contain 0.2% to 1% cocaine
 - Coca bushes grow at altitude in Andean region of South America
 - Leaves are crushed and heated in organic solvent to extract cocaine, after several steps the paste reaches 80-90% purity
 - Salt (cocaine hydrochloride) is powder form and water soluble and is snorted or injected
 - Base form has low melting point and is readily smokable

Pharmacology

- Plant-Derived Stimulants:
- Ephedra
 - Ephedrine and pseudoephedrine are naturally occurring alkaloids that are found in several *Ephedraceae* species
 - Widely used in Asia, Europe, North America
 - Marketed as “safer herbal” products
 - Severe CNS and CV effects led to ban from US market in 2006

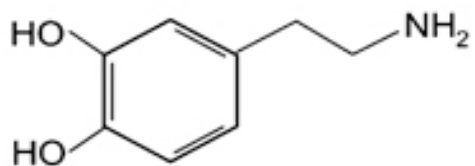
Pharmacology

- Plant-Derived Stimulants:
- Khat
 - Preparation of *Caha edulis*, native to East Africa and southern Arabian peninsula
 - Two active substances:
 - Cathinone
 - Cathine (norpseudoephedrine)
 - Leaves are chewed to reduce fatigue and suppress appetite
 - Substituted cathinones, mephadrone, sold as MDMA, molly, bath salts, plant food

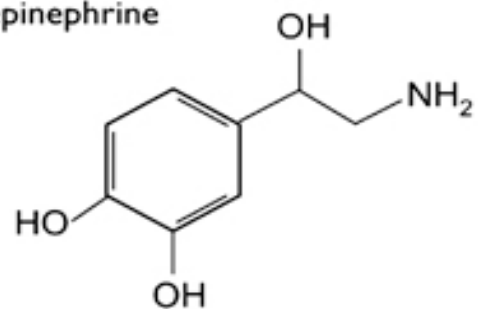
Pharmacology – Synthetic Stimulants

- Dextroamphetamine
 - Desoxyn, ProCentra
- Amphetamine / Dextroamphetamine
 - Adderall, Adderall XR
- Methamphetamine
 - Desoxyn
- Methylphenidate
 - Ritalin, Ritalin LA, Concerta, Daytrana, Metadate CD/ER, Methylin
- Dexmethylphenidate
 - Focalin, Focalin XR
- Lisdexamfetamine
 - Vyvanse

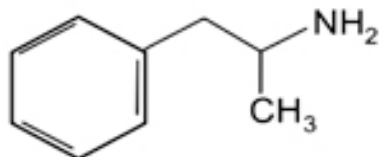
Dopamine



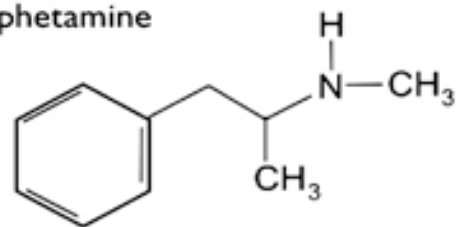
Norepinephrine



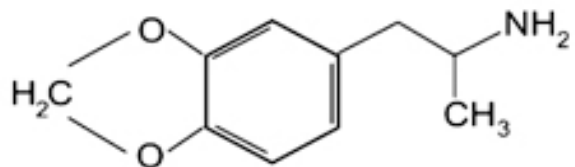
Amphetamine



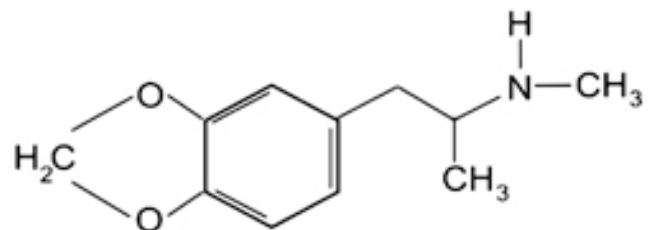
Methamphetamine



3,4-Methylenedioxyamphetamine (MDA)



3,4-Methylenedioxymethamphetamine (MDMA)



Pharmacology – Synthetic Stimulants

- Indications
 - ADHD
 - Narcolepsy
 - Weight Control

Pharmacology

- Route of administration
 - Smoking produces peak effect within minutes
 - Intravenous administration produces peak in 4-7 minutes
 - Intranasal and oral administration produce onset in 30-45 minutes, longer peak, and gradual decline from peak
 - Extended release formulations provide:
 - Improved compliance and effectiveness because of longer duration of action
 - Reduced abuse liability because of slower onset of action and weaker peak effects

Pharmacology

- INTOXICATION
 - Increased energy, decreased fatigue
 - Alertness
 - Sociability
 - Elation / Euphoria
 - Sleep disturbance
 - Anorexia
 - Paranoia / hallucinations
 - Tactile hallucinations (formication / delusional parasitosis)

Pharmacology

- INTOXICATION
 - Tachycardia
 - Pupil dilation
 - Diaphoresis
 - Nausea
 - Restlessness
 - Agitation
 - Tremor
 - Dyskinesia
 - Stereotyped behaviors

Pharmacology

- WITHDRAWAL
 - Depressed mood
 - Anhedonia
 - Fatigue
 - Difficulty concentrating
 - Somnolence
 - Increased appetite

Pharmacology

- CHRONIC EFFECTS
- Psychosis – may persist for up to two years
- Cognitive impairment
 - Diminished visuomotor performance, attention, inhibitory control, and verbal memory

Pharmacology

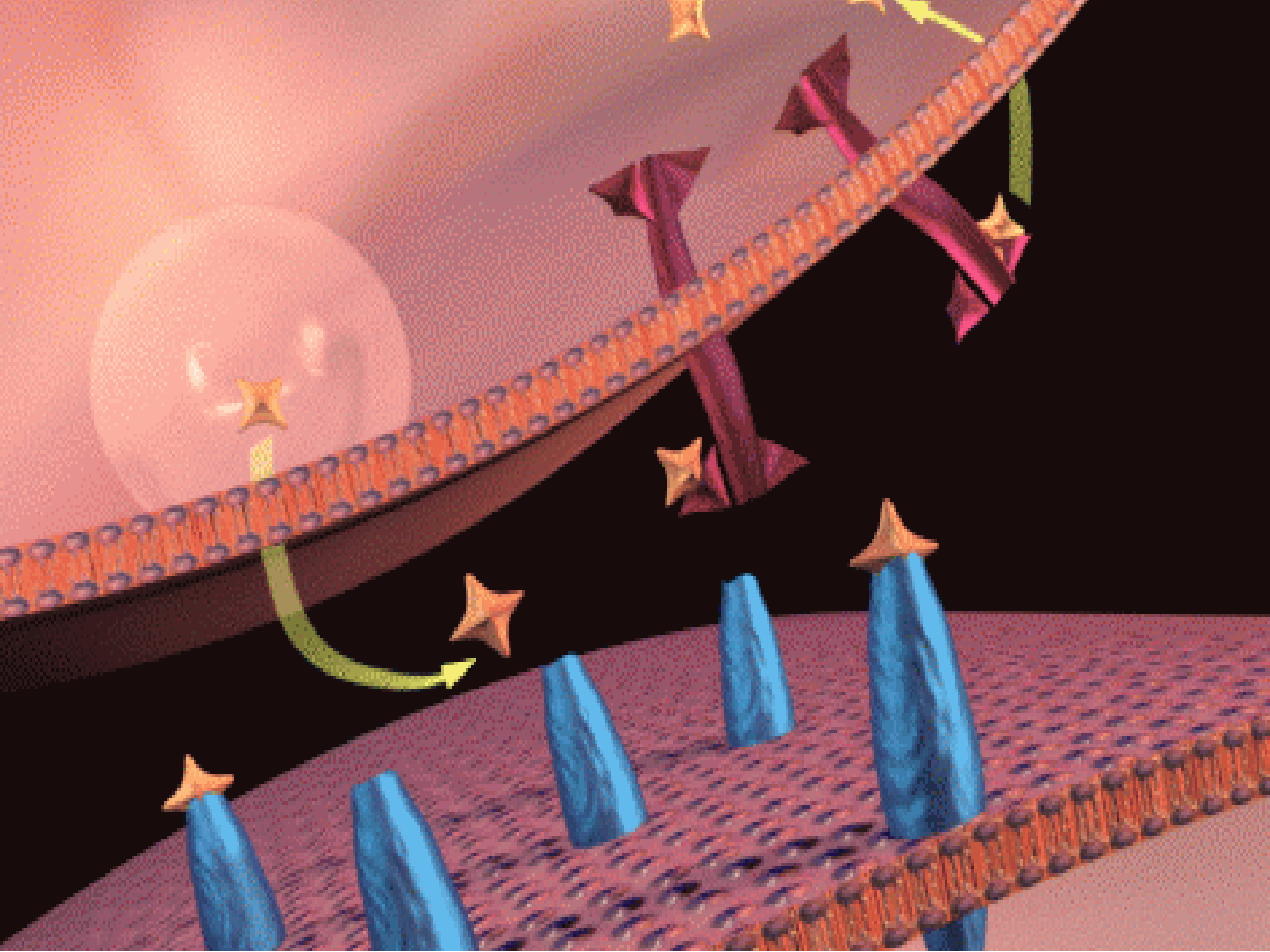
- **CARDIOVASCULAR SYSTEM**
 - Increased heart rate
 - Increased blood pressure
 - Increased systemic vascular resistance
 - Arrhythmias
 - Cardiomyopathy
 - Myocarditis
 - Cocaine user 7x more likely to have MI than non-user

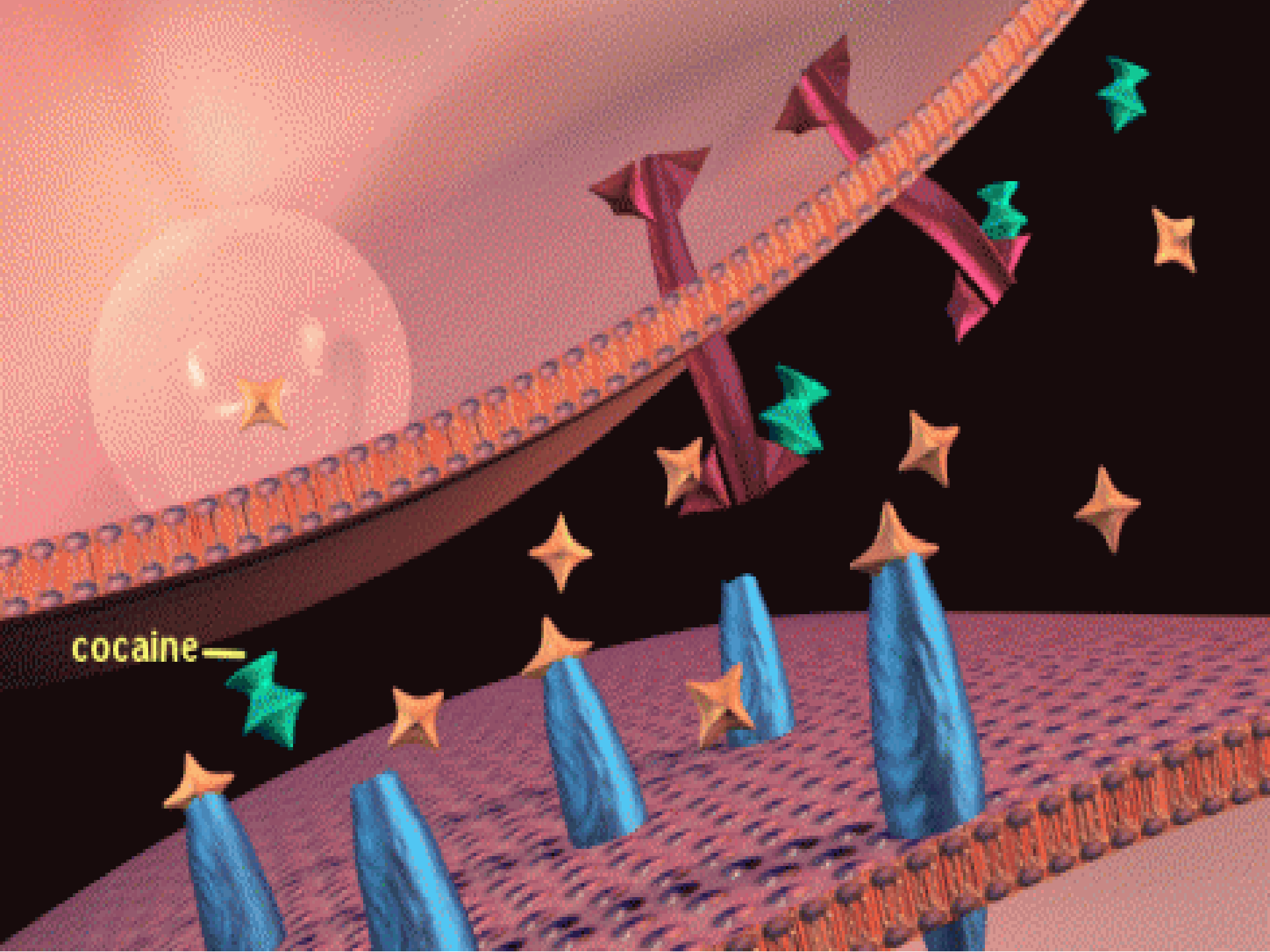
Neurobiology

- All stimulants act to enhance monoamine activity in the central and peripheral nervous system
 - Dopamine
 - Norepinephrine
 - Serotonin

Neurobiology

- Potent stimulants: amphetamines, methylphenidate, and cocaine act indirectly by increasing monoamine activity in the synapse
- Increased monoamine activity is accomplished by a combination of presynaptic release and reuptake blockade





cocaine —

Neurobiology

- Less potent stimulants, ephedrine, pseudoephedrine, phenylephrine, and phenylpropanolamine, act directly by binding to and activating norepinephrine receptors

Neurobiology

- Increased Dopamine activity in the mesocorticolimbic reward circuit mediates the behavioral effects of stimulants
 - Stimulant self administration is correlated to Dopamine activity
 - Euphoria is a function of Dopamine activity

Neurobiology

- Psychological and Physical effects of stimulants are related to Norepinephrine and Serotonin activity
- Glutamate activity plays a role in environmentally induced cues and triggers

Neurobiology

- Neuroadaptation
 - Prior intermittent use of stimulants may lead to *Sensitization* which results in an enhanced response to later exposure
 - Prior continuous use of stimulants leads to *Tolerance* to behavioral and physiologic effects

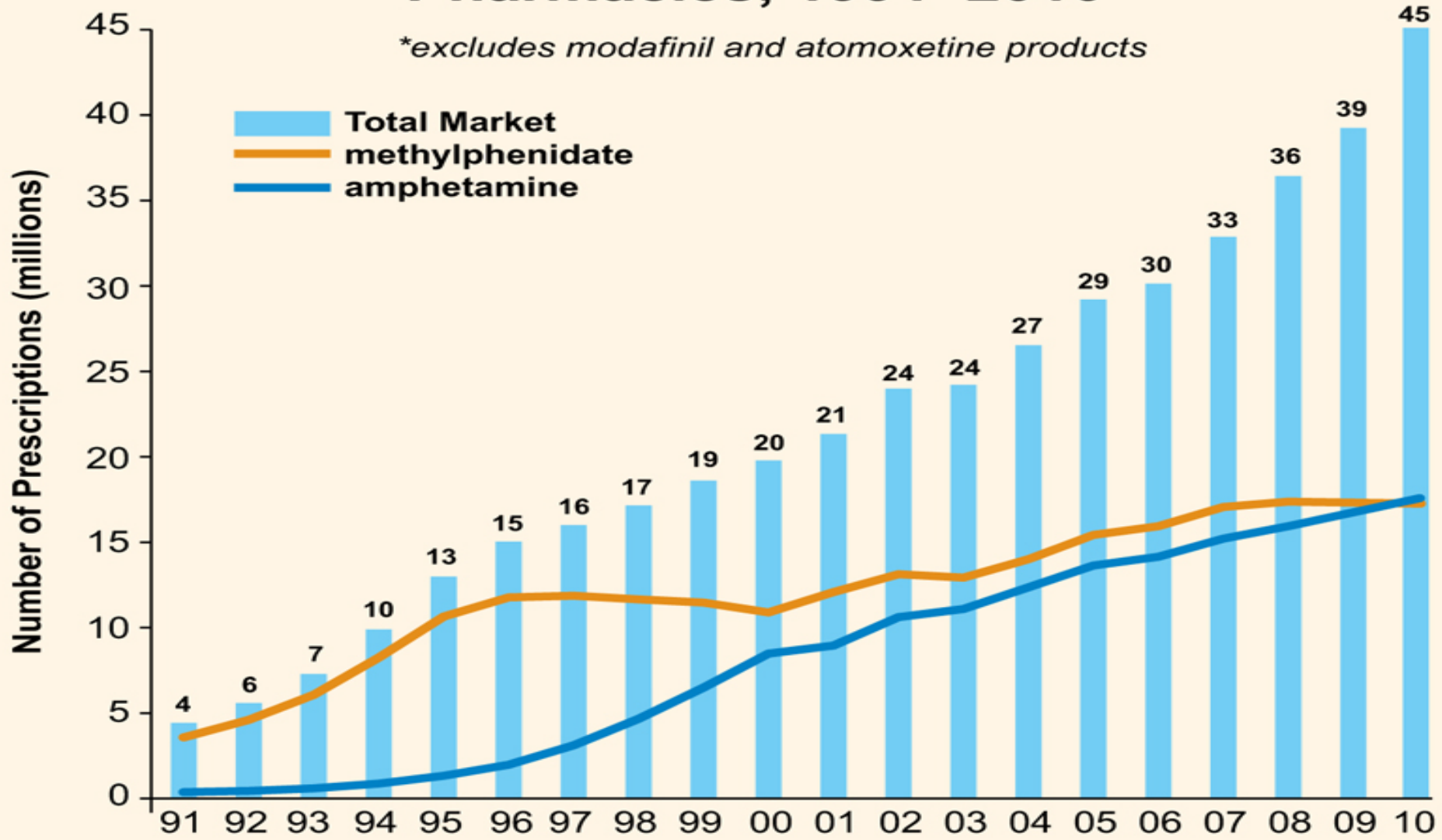
Neurobiology

- Neurotoxicity
- High doses of amphetamine and methamphetamine produce substantial dopamine and serotonin neurotoxicity
- Cocaine and methylphenidate do not produce appreciable neurotoxicity of dopamine or serotonin neurons

prevalence

Total Number of Prescriptions for Stimulants* Dispensed by U.S. Retail Pharmacies, 1991–2010

**excludes modafinil and atomoxetine products*



Source: SDI's Vector One®: National (VONA)

Prevalence

- Top 200 drugs for 2012 (Sales)
 - 33. Vyvanse
 - 37. Methylphenidate ER
 - 70. Adderall XR
 - 105. Focalin XR
 - 132. Amphetamine salts ER (Global)
 - 135. Amphetamine salts ER (Teva)
 - 137. Provigil
 - 175. Nuvigil
 - 183. Amphetamine salts (Teva)

Prevalence

- DEA allows only a certain amount of amphetamine to be commercially produced each year.
- Quota approved by congress each year

Prevalence

- DEA allows only a certain amount of amphetamine to be commercially produced each year.
- Quota approved by congress each year
- 1990 – 417 Kg produced

Prevalence

- DEA allows only a certain amount of amphetamine to be commercially produced each year.
- Quota approved by congress each year
- 1990 – 417 Kg produced
- 2000 – 9007 Kg produced

Prevalence

- DEA allows only a certain amount of amphetamine to be commercially produced each year.
- Quota approved by congress each year
- 1990 – 417 Kg produced
- 2000 – 9007 Kg produced
- 2012 – 25,300 Kg produced

Prevalence

- DEA allows only a certain amount of amphetamine to be commercially produced each year.
- Quota approved by congress each year
- 1990 – 417 Kg produced
- 2000 – 9007 Kg produced
- 2012 – 25,300 Kg produced
- *AND THEY RAN OUT!!!*

Prevalence

- Department of Defense
- Active Military
- 10 fold increase in stimulant prescriptions from 2005 to 2010
 - 18 million prescriptions for stimulants in 2010

The Selling of Attention Deficit Disorder

- New York Times
 - December 14, 2013

The Selling of Attention Deficit Disorder

- New York Times
 - December 14, 2013
- 15% high school age diagnosed with ADHD

The Selling of Attention Deficit Disorder

- New York Times
 - December 14, 2013
- Children on prescription stimulants
 - 1990 – 600,000
 - 2012 – 3,500,000

The Selling of Attention Deficit Disorder

- New York Times
 - December 14, 2013

- Sales of prescription stimulants
 - 2002 – \$1.7 billion
 - 2012 - \$9 billion

The Selling of Attention Deficit Disorder

- New York Times
 - December 14, 2013
- New Market?

The Selling of Attention Deficit Disorder

- New York Times
 - December 14, 2013

- New Market?
 - Adults 20-39
 - 2007 – 5.6 million prescriptions
 - 2012 – 16 million prescriptions

The Selling of Attention Deficit Disorder

- New York Times
 - December 14, 2013
- New Market?
 - Adults 20-39
 - 2007 – 5.6 million prescriptions
 - 2012 – 16 million prescriptions
 - Women 20-39
 - 750% in stimulant prescriptions

The Selling of Attention Deficit Disorder

- New York Times
 - December 14, 2013
- Response in NEJM:
 - Stein, January 6, 2014
 - Get the diagnosis right!
 - Adequate time allotment in primary care setting for proper evaluation
 - Refer to AAP toolkits on website

The Selling of Attention Deficit Disorder

- New York Times
 - December 14, 2013
- Response in NEJM:
 - Stein, January 6, 2014
 - Get the diagnosis right!
 - Adequate time allotment in primary care setting for proper evaluation
 - Refer to AAP toolkits on website
 - *Remember that pharmacy representatives who visit offices and clinics are typically biased sources of information*

Definition

- Non-Medical Use

Definition

- Non-Medical Use
 - Use of the drug without a prescription

Definition

- Non-Medical Use
 - Use of the drug without a prescription
 - Use of one's own prescription medication that is not consistent with how it was prescribed

Definition

- Non-Medical Use
 - Use of the drug without a prescription
 - Use of one's own prescription medication that is not consistent with how it was prescribed
 - More than prescribed
 - More frequently than prescribed
 - In a manner not prescribed

Non-Medical Use

- N=1253
- Medical use for ADHD – 3%
- ADHD with Non-Medical Use – 33% (F>M)
- Non-ADHD with Non-Medical Use – 18%

– Arria, 2008

Non-Medical Use

- Mixed Amphetamine Salts – 89%
- Methylphenidate – 26%
- Methylphenidate ER – 14%

– Arria, 2008

Non-Medical Use

- Route of Administration
 - Oral – 77%
 - Crushed / snorted – 15%

- Arria, 2008

Non-Medical Use

- How obtained
 - Friend with prescription – 79%
 - Friend without prescription – 16%
 - Free – 72%
 - Stealing - <1%
 - Internet – 0%
 - Arria, 2008

Non-Medical Use

- Non-Medical Use was strongly associated with alcohol and marijuana dependence
 - ADHD with Non-Medical Use were more likely cannabis dependent than non-ADHD with Non-Medical Use
- Non-Medical Use was associated with past year use of Cannabis, Inhalants, Hallucinogens, Cocaine, MDMA, Opioids, Sedative Hypnotics
 - ADHD with Non-Medical Use demonstrated strongest association with illicit drug use

Arria, 2008

Non-Medical Use

- No statistical significant differences in Non-Medical Use for those reporting active symptoms of ADHD

– Sepulveda, 2011

Non-Medical Use

- Non-Medical Use significantly associated with higher rates of binge drinking and higher rates of adverse consequences of alcohol use
 - 50% Non-Medical User with positive CAGE screen
- Non-Medical Users 65% positive screen (DAST-10) with 3 or more drug-use related problems compared to 18% Non Users

– Sepulveda, 2011

Non-Medical Use

- For ADHD, Non-Medical Use higher (55% v. 33%) for those who were diagnosed and prescribed stimulants in college as opposed to prior to college
- 80% of Non-Medical Users who identified “to get high” as motivation for Non-Medical Use initiated treatment in college

– Sepulveda, 2011

Non-Medical Use

- Diversion
 - 36% ADHD reported diversion of stimulant medication
 - 57% Non-Medical Use reported diversion
 - 20% non-use reported diversion
 - Adderall and Adderall XR most often diverted
 - Sepulveda, 2011

Non-Medical Use

- Diversion
 - For ADHD, 54% have been approached to sell, trade, or give away stimulant medication each year
 - For ADHD, 61% have diverted prescription stimulants
 - For Non-Medical Users without ADHD, 92% identified obtaining prescription stimulants from a friend
- Sepulveda, 2011

Non-Medical Use

- Demographic Characteristics of Non-Medical Use
 - White
 - Male
 - Jewish
 - Fraternity / Sorority affiliation

- Sepulveda, 2011

motivation

Motivation

- PHP Participants
- Not stimulant specific, but of n38, n31 used stimulants
 - Manage physical pain
 - Manage emotional / psychiatric distress
 - Manage stressful situations
 - Serve recreational purposes
 - Avoid withdrawal symptoms
 - Merlo, 2013

Motivation

- N=689 college students
- Help concentration 58%
- Increase alertness 43%
- Counteract effects of other substances 8%
- To get high 43%
- No significant difference in gender

– Teter, 2005

Motivation

- N= 1253 College Freshmen
- Improve concentration / study – 73%
- Curiosity – 18%
- Enhance wakefulness to party / drink / go out – 9%
- Get high / feel good / have fun – 7%
- Peer pressure – 5%
- Others:
 - weight loss, stay awake to drive, pass breathalyzer, stay awake for no particular reason
 - Arria, 2008

Nature poll, 2008

- 1400 respondents to online poll
- From 60 countries

Nature poll, 2008

- 1400 respondents to online poll
- From 60 countries
- Asked specifically about three different drugs
 - Methylphenidate
 - Modafanil
 - Beta Blockers

Nature poll, 2008

- 1400 respondents to online poll
- From 60 countries
- Asked specifically about three different drugs
 - Methylphenidate
 - Modafanil
 - Beta Blockers
- One in Five reported Non-Medical Use

Nature poll, 2008

- 1400 respondents to online poll
- From 60 countries
- Asked specifically about three different drugs
 - Methylphenidate
 - Modafanil
 - Beta Blockers
- One in Five reported Non-Medical Use
 - 62% Methylphenidate
 - 44% Modafanil
 - 15% Beta Blockers

Nature poll, 2008

- One in Five reported Non-Medical Use
 - 62% Methylphenidate
 - 44% Modafanil
 - 15% Beta Blockers
- 80 respondents reported “other use”
 - Amphetamine most common, then dextroamphetamine
- No difference across age groups
 - Prevalence greatest in 18-25 “real world”

Nature poll, 2008

- One in Five reported Non-Medical Use
 1. Improve concentration
 2. Improve focus on a specific task
 3. Combat jet lag
 4. Party
 5. Clean house

Nature poll, 2008

- One in Five reported Non-Medical Use
- 80% thought that healthy adults should be allowed to take the drugs “if they want to”
- 86% thought access should be restricted to minors
- 35% felt pressured that their own children should use cognitive enhancing medication if their classmates were

Cognitive Enhancement

- American Academy of Neurology, Committee on Ethics, Law, and Humanities:
- Physicians are allowed to grant requests for stimulant drugs to improve cognition in healthy patients...

Cognitive Enhancement

- American Academy of Neurology, Committee on Ethics, Law, and Humanities:
- Physicians are allowed to grant requests for stimulant drugs to improve cognition in healthy patients.....BUT, they are not obliged to do so.

- Lavierre, 2009

Cognitive Enhancement

- Stimulant use improved impairment of episodic memory in ADHD diagnosed undergraduates
- Reduced emotional reaction to frustration
- Improved ability to detect errors
- Increased effortful behavior

- Advocat, 2013

Cognitive Enhancement

- Stimulant use improved impairment of episodic memory in ADHD diagnosed undergraduates
 - Reduced emotional reaction to frustration
 - Improved ability to detect errors
 - Increased effortful behavior

 - BUT

 - Promoted risky behavior
 - Increased susceptibility to environmental distraction
 - Used to overcome poor preparation
- *LITTLE LONG TERM INTELLECTUAL BENEFIT* (Advocat, 2013)

Cognitive Enhancement

- ADHD undergraduates are capable of performing just as well in college as their non-ADHD peers, *if they acquire well-established effective study skills.*

Cognitive Enhancement

- Non-medical use linked to lower grades by end of freshman year (effect of skipping class)

- Arria, 2008

Black Box Warning

- High Abuse Potential, Dependency
- High abuse potential' avoid prolonged treatment, may lead to drug dependence, potential for non-therapeutic use or distribution to others; prescribe / dispense sparingly; serious cardiovascular adverse events and sudden death reported with misuse.

Black Box Warning

- ***High Abuse Potential, Dependency***
- High abuse potential' avoid prolonged treatment, may lead to drug dependence, potential for non-therapeutic use or distribution to others; prescribe / dispense sparingly; serious cardiovascular adverse events and sudden death reported with misuse.

Black Box Warning

- High Abuse Potential, Dependency
- High abuse potential' ***avoid prolonged treatment***, may lead to drug dependence, potential for non-therapeutic use or distribution to others; prescribe / dispense sparingly; serious cardiovascular adverse events and sudden death reported with misuse.

Black Box Warning

- High Abuse Potential, Dependency
- High abuse potential' avoid prolonged treatment, ***may lead to drug dependence,*** potential for non-therapeutic use or distribution to others; prescribe / dispense sparingly; serious cardiovascular adverse events and sudden death reported with misuse.

Black Box Warning

- High Abuse Potential, Dependency
- High abuse potential' avoid prolonged treatment, may lead to drug dependence, ***potential for non-therapeutic use or distribution to others***; prescribe / dispense sparingly; serious cardiovascular adverse events and sudden death reported with misuse.

Black Box Warning

- High Abuse Potential, Dependency
- High abuse potential' avoid prolonged treatment, may lead to drug dependence, potential for non-therapeutic use or distribution to others; ***prescribe / dispense sparingly***; serious cardiovascular adverse events and sudden death reported with misuse.

Black Box Warning

- High Abuse Potential, Dependency
- High abuse potential' avoid prolonged treatment, may lead to drug dependence, potential for non-therapeutic use or distribution to others; prescribe / dispense sparingly; ***serious cardiovascular adverse events and sudden death reported with misuse.***

DAWN – Prescription Stimulants

- “Sharp Rise in Emergency Department Visits involving ADHD Medications”
- Overall, ER visits doubled from 2005 - 2010
 - 2005 – 13,379
 - 2010 – 31,244
- No change for under 18 y/o
- 18 – 25 y/o – from 2131 to 8148
- 26 – 34 y/o – from 1754 to 6094
- >35 y/o – from 2519 to 7957

DAWN – Prescription Stimulants

- Non-Medical Use – 50%
- Adverse Reaction – 29%
- Other – 21%

DAWN – Prescription Stimulants

- Other prescription drugs involved – 45%
- Illicit drugs involved -21%
- Alcohol involved – 19%
-

Prevalence

- Amphetamine-type Stimulant Disorder
 - 12 month prevalence:
 - 12-17 y/o – 0.2%
 - 18-29 y/o – 0.4%
 - >45y/o – 0.1%
 - Non-Medical Use
 - High School 5-9%
 - College – 5-35%
- DSM - 5

Risk

- Recent review
 - Bulk of evidence suggests that stimulant treatment of Childhood ADHD does not increase risk of SUD

Risk

- Recent review
 - Bulk of evidence suggests that stimulant treatment of Childhood ADHD does not increase risk of SUD
 - BUT

Risk

- Recent review
 - Bulk of evidence suggests that stimulant treatment of Childhood ADHD does not increase risk of SUD
 - BUT
 - Most recent studies suggests that stimulant treatment of ADHD does not mitigate risk (in contrast with 2003 meta-analysis, Wilens)
- Kollins, 2008

Risk Factors for Stimulant Use Disorder

- Comorbid:
 - Bipolar disorder
 - Schizophrenia
 - ASPD / childhood Conduct Disorder
 - Childhood Conduct Disorder
 - Other SUD

- DSM-5