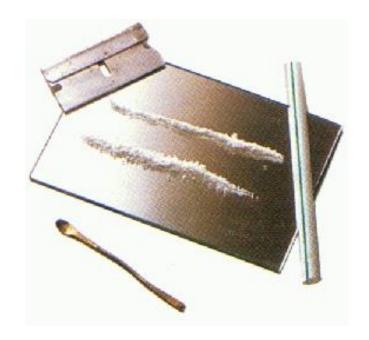
Major Stimulants

Cocaine Amphetamine



History of stimulant use

Coca and the Inca

Freud and cocaine

- Cocaine for depression and...
- morphine addiction
- Cocaine psychosis
 - ◆ Formication syndrome
 - ◆ Paranoid state

Annie C. Meyers

- A "well-balanced Christian women" before becoming a "cocaine fiend"
- "I deliberately took a pair shears and pried loose a tooth that was filled with gold. I then extracted the tooth, smashed it up, and the gold went to the nearest pawnshop, blood streaming down my face and drenching my clothes, where I sold it for 80 cents to buy cocaine.

Amphetamines

- Amphetamine (6-8 hrs)
- Dextroamphetamine (8-10 hrs)
- Methamphetamine (12+ hrs)

Cocaine in the Seventies

 "Cocaine is not an addictive or especially dangerous drug. It should be legalized" (Ashley, 1976)

- "Cocaine is not an addictive or especially dangerous drug. It should be legalized" (Ashley, 1976)
- Cocaine is the most dangerous drug on earth (Inciardi, 1988)

- 2000-2005:FARC & Cartels weaken in Colombia...
- But, coca production went up in Bolivia and Peru
- Bolivia's President, Evo Morales took office in 2006 with a pledge to decriminalize the cultivation of coca
- 2014: Coca flour, tea and other products legal and readily available throughout Bolivia, Peru and much of SA

- "Cocaine is not an addictive or especially dangerous drug. It should be legalized" (Ashley, 1976)
- Cocaine is the most dangerous drug on earth (Inciardi, 1988)
- The effects of cocaine depend on the form of cocaine that is used

Form Chemistry Method

Coca leaf ---- Oral

Coca Paste Cocaine Smoking (Basuco) Sulfate

Street Cocaine Injection Cocaine hydrochloride Intra-nasal

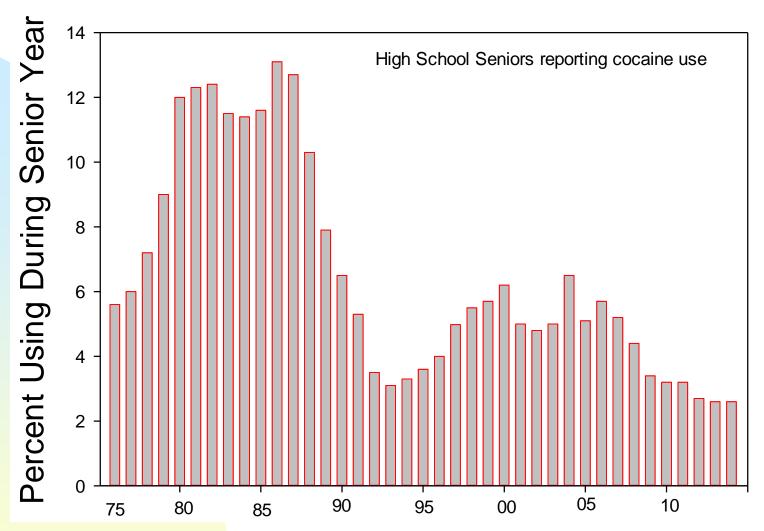
Crack Freebase smoking Cocaine

The Crack Phenomenon

- Shorter duration of action
- Less expensive
- More intense effects
- More risk of overdose
- Much higher rate of addiction
- 1988 Anti-Drug Abuse Act—5-yr mandatory sentence for crack possession

Cocaine and Crack Today

- Crack and Cocaine remain major dependence problems
- July 2010—5-year mandatory sentence for crack possession repealed
- Use relatively stable



Percentage of High School Seniors Reporting Use of Cocaine During the Past Year

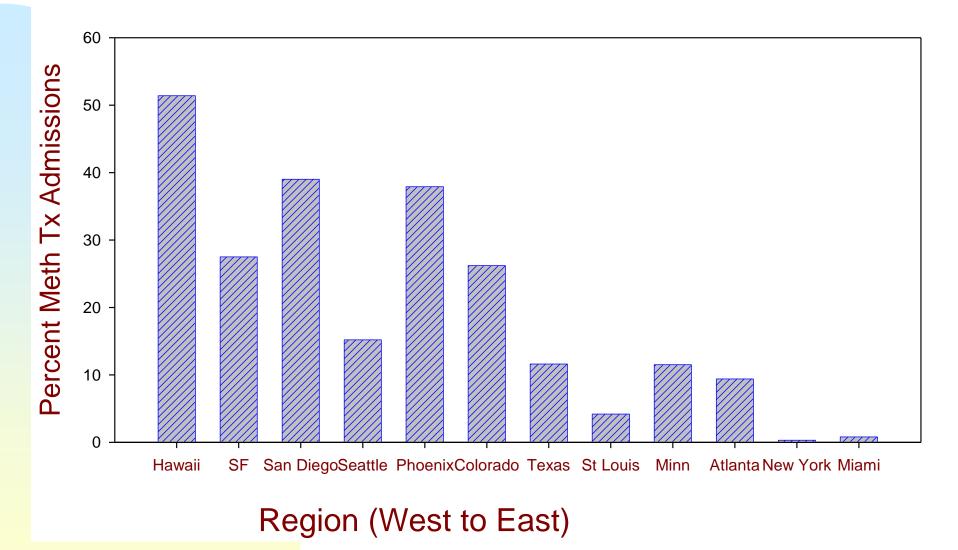
Methamphetamine
Speed
Crank
Ice
Crystal meth

Breaking

Bad

New Season MARCH 21 Sundays 10/9c

Percent of drug admissions involving meth--2010



COMBAT METHAMPHETAMINE EPIDEMIC ACT

- Federal law in effect 2006
- All products containing ephedrine and pseudoephedrine sold behind the counter
- Purchasers over 18 and must show ID and sign log; only limited quantities may be purchased
- 2014: most meth now comes through Mexico

Mechanism of Action

 Blocks reuptake of monoamines: dopamine, serotonin and norepinephrine

Mechanism of Action

- Blocks reuptake of monoamines: dopamine, serotonin and norepinephrine
- Mesolimbic dopaminergic pathway--short cut to the pleasure center
- Monoamine depletion in withdrawal

Sympathomimetic Effects

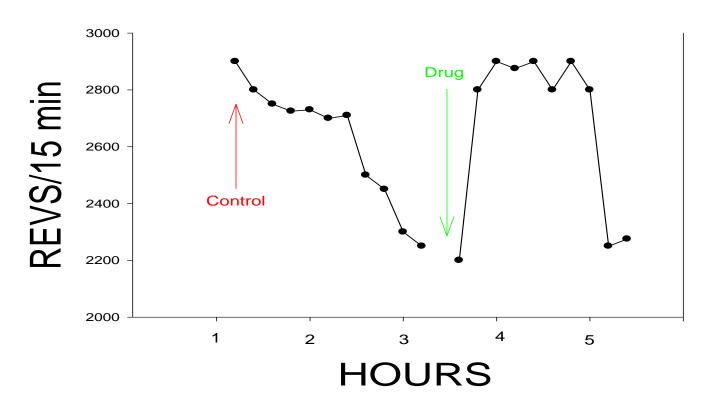
- Increased heart rate
- Increased blood pressure
- Increased respiratory rate
- Pupil dilation
- Changes in blood flow
- Increased sweating

- Insomnia
- Anorexia
- Dry mouth—"meth mouth"

- Insomnia
- Anorexia
- Mood elevation
- Alertness and arousal
- Sexual effects
 - ◆ Impotence in men
 - ◆ Sextasy: Viagra and Meth/MDMA

- Insomnia
- Anorexia
- Mood elevation
- Alertness and arousal
- Reduced reaction time
- Increased strength and endurance

Performance on bicycle machine after control and 10 mg methamphetamine injections



- Insomnia
- Anorexia
- Mood elevation
- Alertness and arousal
- Reduced reaction time
- Increased strength and endurance
- Effects on learning & cognition

State-Dependent Learning

Information learned under the influence of a drug is best recalled under the influence of that same drug

Stimulant Overdose

- Convulsions; seizures
- Cardiac failure

Sublethal Overdose

- Stimulant psychosis
 - ◆ Confusion/anxiety
 - ◆ Paranoid state
 - ◆ Formication syndrome

Cocaine/Methamphetamine Dependence & Abstinence

- Crash
- Depression
- Extinction

Attention Deficit Disorder

- Hyperactivity and the "paradox"
- Amphetamine (Adderall)

Attention Deficit Disorder

- Hyperactivity and the "paradox"
- Amphetamines (Adderall; Vyvanse)
- Methylphenidate (Ritalin, Focalin, Concerta--extended release, Daytrana-patch)
- 10 million + prescriptions per year for ages 10-19 alone: more than \$8 billion per year!
- >6% American children between 4 and 17 years old receive ADHD meds

The ADHD Controversy

- Is it a disease?
- Do stimulants work?
- No evidence for improved grades after the first year of tx (Sharpe, 2014)
- ADHD in adults
- Side effects: growth suppression
- Abuse

UNCW student quotes Seahawk, Apr 2010

- If I have too much studying to do, I'll pop an Addy and it's all good!
- I feel like everyone uses Adderall
- It gets hard to come by at the end of the semester...
- You can bet I plan to use it through my last set of finals...

Khat



- East African plant (Yemen, Ethiopia, Somalia
- Chewing leaf produces mild stimulation
- Cathinone is major active ingredient
- Synthetic methcathinone (cat) is Schedule I
- Numerous analogs of methcathinone have been synthesized

BATH SALTS: METHCATHINONES





Note warning on label

Chemicals typically in Bath Salts

- Synthetic derivatives of cathinone (Khat)
 - ◆ Mephedrone (4-MMC)
 - ◆ Methylone (MDMC)
 - ◆ 3,4-Methylenedioxypyrovalerone (MDPV)
 - ◆ 4-Methylethcathinone (4-MEC)
 - ◆ 4-Fluoromethcathinone (3-FMC)
 - ◆ 3-Fluoromethcathinone (4-FMC)
 - ◆ Ethcathinone

First Encountered in Europe Meow

- Spring 2009 law enforcement & ERs note increasing incidents with bath salts
- British Crime Survey (2010) 7% of adolescents & young adults report using bath salts
- 2010 "Clubbers" Survey (nonscientific) up to 42% using
- Legally obtained online then distributed at clubs
- Made illegal in Britain in 2010
 - ◆ 2011 about 5 % report usage



Emerged in USA in 2010 Me Meow

- Legally available on web: not for human consumption
- Calls to Poison Centers re bath salts:
 - **◆** 2009----0
 - **◆** 2010---304
 - **◆** 2011---6137



Drug Effects

- Mephedrone , Methylone, MDPV:
 - ◆ Effects 15–45 min after oral ingestion and last approximately 2–7 h
 - ◆ Effects 5-30 min after intranasal administration and last approximately 2–3 h.
 - ◆ High lasts approximately 10–15 min after intravenous injection, with an overall duration of 30 min

Synthetic Cathinone Effects

- Stimulate release and/or block reuptake of dopamine
- Sympathomimetic
- ◆ Alertness, arousal, mood elevation
- High doses: confusion, paranoia, panic, seizures
- ◆ NIDA (2014) reports craving and dependence not unlike Meth

Bath Salts Adverse Effects

- Tachycardia & Elevated BP
- Anxiety and panic attacks
- Extreme paranoia, violent behavior
- Acute psychosis
- Self-mutilation
 - ◆ But not cannibalism—Randy Eugene, Miami cannibal, was not on bath salts!

Synthetic Drug Abuse Prevention Act, 2012

- Adds two methcathinone analogs to Schedule I: mephedrone, methylone, MDPV
- Also adds Spice and THC analogs and several hallucinogens (e.g., 2C-D, 2C-I to Schedule I
- Extended DEA emergency scheduling powers to 2 years (formerly 1 yr)

Bath Salts since the 2012 Act

- > 70 other cathinones have been siezed as of Jan 2015; most are legal
- M-PEP, a-PVP (gravel) and 8 other cathinones temporarily banned in 2014 using emergency powers

Bath Salts since the 2012 Act—is it working?

- Calls to Poison Centers re bath salts:
 - **◆** 2009---0
 - **◆** 2010---304
 - **◆** 2011---6137
 - **◆** 2012---2691
 - **◆** 2013---996

Methylxanthines

- Caffeine
- Theophylline
- Theobromine





Cup of coffee 100-150 mg
Cup of tea 40-100 mg
Cola drink 15-25 mg

Energy drinks

shot

◆ Red Bull 80 mg

◆ Rockstar/Jolt 80-229 mg Monster

◆ 5-hour ENERGY 207-242mg

◆ Starbucks double 162 mg

Energy drinks

- Over 20,000 ER visits linked to energy drinks since 2007
- FDA investigating 13 deaths in 2013—cardiac failure linked to caffeine OD
- LD50 for caffeine is about 5 g—but some are more sensitive to caffeine

Caffeine effects

- Alertness and arousal
- Insomnia
- Sympathomimetic

Sympathomimetic Effects

- Increased heart rate
- Increased blood pressure
- Increased respiratory rate
- Pupil dilation
- Changes in blood flow
- Increased sweating

Caffeine effects

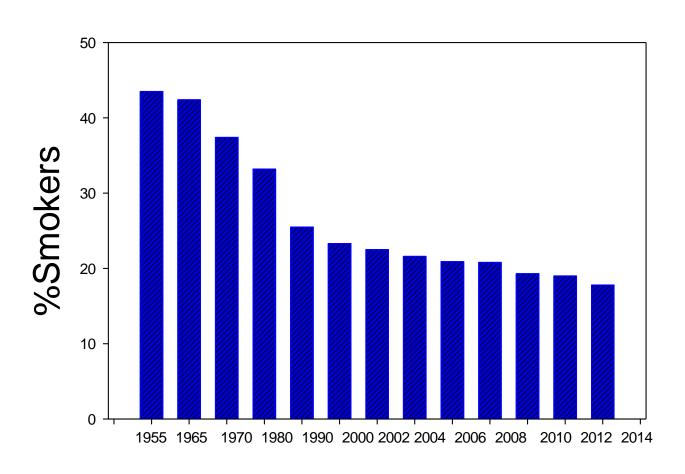
- Alertness and arousal
- Insomnia
- Sympathomimetic
- Neural Mechanism:Blocks adenosine (inhibitory transmitter)

Caffeine Withdrawal

- Headache
- Sleepy
- Yawning
- Miserable

Comer, Haney, Foltin & Fischman (1997) "The use of tobacco is growing greatly and conquers men with certain secret pleasure so that those who have once become accustomed thereto, can later hardly be restrained therefrom..." (Sir Francis Bacon)

Smoking Prevalence Among U.S. Adults



Nicotine paradox

- Stimulant effects
- Relaxing/tranquilizing effects

Nicotine Actions

- Stimulates norepinephrine release:Sympathomimetic
- Mimics acetylcholine--nicotinic receptors
- Dopamine?

Cigarettes and Health

- Lung and other cancers
- Increased risk of CHD
- Emphysema and related lung disease
- Passive smoking

Causes of Avoidable Death in US (PLoS 2009 study)

- 1. Tobacco use
- 2. High Blood Pressure
- 3. Obesity
- 10. Alcohol use

- 455,000
- **390,000**
- **225,000**
- **70,000**

The World Health
 Organization estimates that at
 current rates of use, there will
 be over 1 billion deaths due to
 cigarette smoking during the
 next 100 years

Regulation of Tobacco

- Historically, tobacco products were not regulated as a drug (Bureau of Alcohol Tobacco & Firearms
- Suits against tobacco companies reveal nicotine added to cigarettes
- Tobacco regulation moved to FDA (June, 2009)
- FDA bans flavored cigarettes (Sept, 2009) from USA
- FDA imposed graphic label requirement to begin 2012



- •Tobacco companies appeal this requirement (2011)
- •Found unconstitutional Feb 2012

Regulation of Tobacco

 CVS announces it will not sell cigarettes after October 1, 2014

Quitting: everything works!

- Nicotine gum; patch; E-Cigs
- Hypnosis
- Cognitive Behavior therapy
- Chantix (varenicline)
- But, 6-mo follow-up: 80% relapse;
 90% with placebo…linked to depression/suicide
- Mark Twain was right! Quitting is easy....

Quitting

- Switch brands
- Set quit date
- Quit





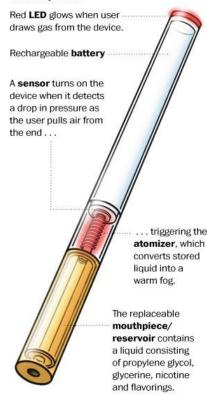


HOW COES IT WOLK like a cigarette and deliver dose of nicotine, but that's where the similarity and a

- A heating element activated by a sensor detecting airflow
- A cartridge containing a nicotine solution is heated
- Nicotine is vaporized an aerosol is generated & inhaled
- Hence the verb: "Vaping"

The electronic cigarette

It may look like a cigarette and deliver a similarity ends.

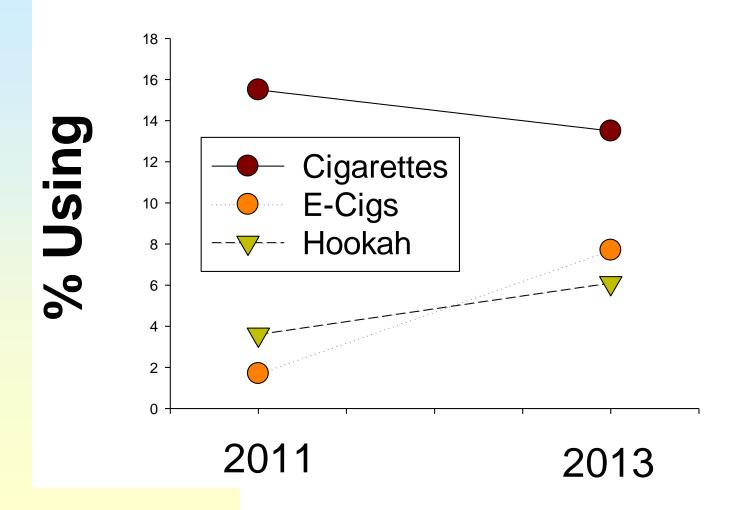


An FDA study found that e-cigarettes release carcinogens and toxic chemicals. However, they might be safer than regular cigarettes because they don't release tar, carbon monoxide, hydrogen cyanide and other poisons found in cigarette smoke.

Sources: Tobacco Control, FDA

Adolescent Use

High School Tobacco/Nicotine Use in NC



Adolescent Use

 2014—More High School Seniors smoked ecigs (17.2%) than tobacco cigarettes (13.1%)

The Perception Among Users – and what advertisements claim





What is in an Ecig?

- Nicotine levels vary widely; not clear how much nicotine is absorbed from vaping
- No tar should translate into reduced risk of cancer, but CHD not affected
- Other chemicals in Ecigs (e.g., Propylene glycol) may pose risk

Regulation



- Ecigs are not currently regulated by the FDA
- Sales not currently restricted to 21 and over
- Advertising is not regulated and ecigs are untaxed in many states

Regulation

- 2014 FDA issued a proposed rule extending FDA's tobacco product authorities to include e-cigarettes.
- FDA would regulate advertising, limit access to minors, could restrict flavored Ecigs, etc.
- Some states, communities and institutions (e.g., UNCW) now treat Ecigs as tobacco products

Alcohol

 America's "love-hate" relationship with alcohol...



Alcohol

- The worlds largest drug business:
 - > \$ 60 billion dollars/year in USA



- The worlds largest drug business:
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- 8 million junior high and high schoolers drink every week



- The worlds largest drug business:
 - > \$ 60 billion dollars/year in USA
- 8 million junior high and high schoolers drink every week
- Undergraduates in US spend \$4.2 billion on booze: more than they spend on textbooks!

- The worlds largest drug business:
 - > \$ 60 billion dollars/year in USA
- Alcohol advertising targets virtually everyone in our society especially youth

- The worlds largest drug business:
 - > \$ 60 billion dollars/year in USA
- Alcohol advertising targets virtually everyone in our society especially youth
- One in twelve will develop alcoholism or alcohol abuse disorder

Ethyl alcohol or ethanol



Computing BAC

- 1 Standard drink = .5 oz pure ethanol
 - ◆ 1 beer (12 oz)
 - ♦ 4 oz wine
 - ◆ 1 oz 100 proof liquor

Computing BAC

- Alcohol metabolization
 - ◆ 1 drink every 2 hrs
 - ◆ .01% every 40 min
 - ◆ BAC=NSD X (.025%) NHD X (.015%)

BAC .04% **Drinks**

1-2

Effects

Relaxed

.04%

.08%

Drinks

1-2

3-4

Effects

Relaxed

High

.04%

.08%

Drinks

1-2

3-4

Effects

Relaxed

High

Computing BAC

- Alcohol metabolization
 - ◆ 1 drink every 2 hrs
 - ◆ .01% every 40 min
 - ◆ BAC=NSD X (.025%) NHD X (.015%)

.04%

.08%

.15%

Drinks

1-2

3-4

7-10

Effects

Relaxed

High

Drunk

.04%

.08%

.15%

.30%

Drinks

1-2

3-4

7-10

11-15

Effects

Relaxed

High

Drunk

Dead drunk

.04%

.08%

.15%

.30%

.40%

Drinks

1-2

3-4

7-10

11-15

16-20

Effects

Relaxed

High

Drunk

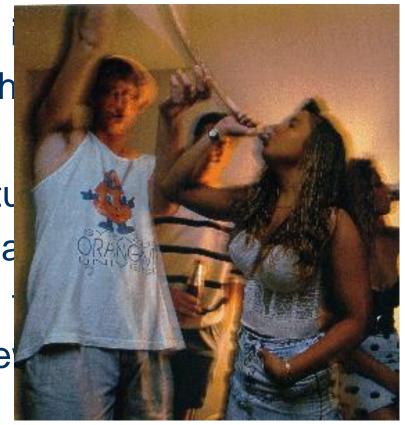
Dead drunk

Dead

Binge Drinking

4-5 drinks i setting (3-4 h

College sture
 reported an a
 9 drinks in a
 episode (Breine)

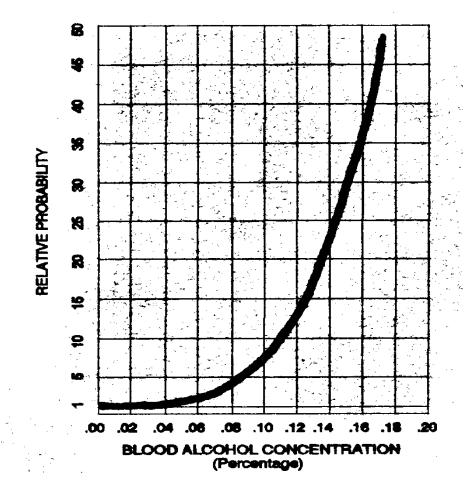


Binge Drinking

Drinking ar



FIGURE 1. RELATIVE PROBABILITY OF CAUSING A CRASH

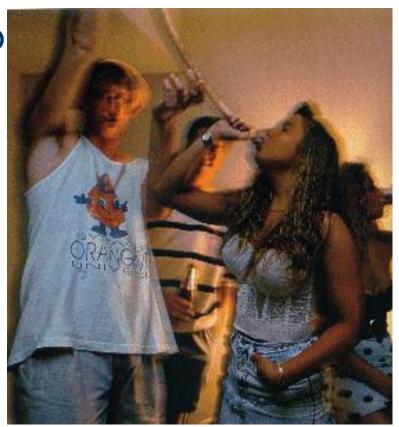


(From the <u>Role of the Drinking Driver in Traffic Accidents</u>, by R. F. Borkenstein, R. F. Crawther, R. P. Shumate, W. B. Ziel, and R. Zylman, Indiana University Department of Police Administration: Bloomington, 1964.)

44% of all traffic Fatalities (2011)

Binge Drinking

- Memory: b
- Hangover
- Overdose



Effects of Chronic Drinking

- Cirrhosis of the liver
- Wernicke-Korsakoff syndrome
- Fetal Alcohol s



Effects of Chronic Drinking

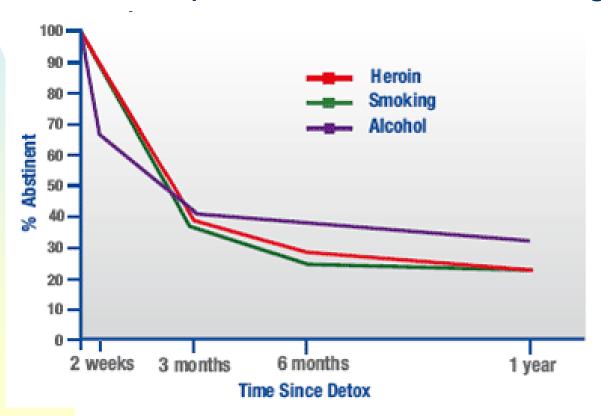
- Cirrhosis of the liver
- Wernicke-Korsakoff syndrome
- Fetal Alcohol syndrome
- Alcoholism

Delirium Tremens

- Tremors
- Confusion and irritability
- Hallucinations
- Anxiety and insomnia
- Seizures and convulsions
- Detoxification: cross-dependence and cross tolerance with other depressants

Alcoholism

Relapse rate of 70% following



Alcoholism

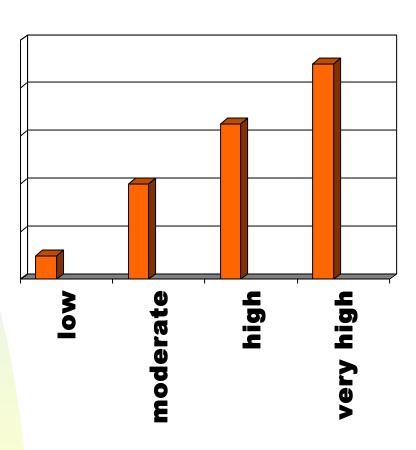
- Relapse rate of 70% following detox
- 6-10% of adults diagnosed with Alcoholism
- Children of Alcoholics 4 times more likely to develop alcoholism
- Nature? Nurture? What is inherited?

Psychiatric Drugs

- Require prescription
- Prescription privileges for Psychologists?
- \$329 billion in 2013
- \$3 billion spent in marketing to physicians

Depressant Drug Action

Death
Anesthetic
Sedative
Anxiolytic



Benzodiazepines: Anxiolytics/Hypnotics

```
Librium
chlordiazepoxide
  >48 hrs
                      Valium
 diazepam
     >48 hrs
                      Xanax
 alprazolam
     >12 hrs
                      Ativan
  Iorazepam
     >12 hrs
                      Halcion
 triazolam
```

hrs

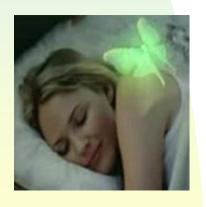
Benzodiazepine-like Compounds-

Short acting, side-effects less severe...

zolpidem Ambien

zaleplon Sonata

eszopiclone Lunesta



Benzodiazepines

- Anxiolytic effects
- Sedative effects—BZ hangover
- Tolerance and dependence
- Synergy

Synergy

- Michael Jackson's MD
 prescribed 50 mg propofol every night for weeks
- Cut down to 25 mgs June 25 2009
- But, added midazolam and lorazepam when Jackson couldn't sleep
- Death NOT propofol OD: but synergy



Benzodiazepines

- Anxiolytic effects
- Sedative effects—BZ hangover
- Tolerance and dependence
- Synergy, cross-tolerance and cross-dependence
- GABA

Benzodiazepine-like Sleeping Pills

- Nearly 40 million prescriptions per year
- \$2.5 billion per year



Depressant drugs: All BZ Sleeping Pills

- Inhibit REM sleep
- REM rebound
- Rebound insomnia
- Amnesia, sleep-



Benzodiazepines: Anxiolytics/Hypnotics

chlordiazepoxide Librium

diazepam Valium

alprazolam Xanax

triazolam Halcion

flunitrazepam Rohypnol (Roofies)
 Common date rape drug

Depressant drugs: All BZ Sleeping Pills

- Inhibit REM sleep
- REM rebound
- Rebound insomnia
- Amnesia, sleepwalking/driving
- High ris

Lunesta Free Trial Offer

Note: OTC Sleep Aids are NOT benzodiazepines

- Most OTC sleeping pills are antihistamines (e.g., diphenhydramine) or melatonin
- Both produce drowsiness, but do not pose high risk for dependence
- Main side effects are feeling sleepy and groggy the next day



Major Psychiatric Disorders

- Schizophrenia
- Depression
- Bipolar Disorder
- Case examples of disorders

Antipsychotic drugs

chlorpromazine

thioridazine

haloperidol

Thorazine

Mellaril

Haldol

Antipsychotic drugs

- Relieve symptoms of schizophrenia
- Block dopamine
- Parkinson-like side effects
- Tardive dyskinesia

Atypical Antipsychotics

clozapine

Clozaryl

(agranulocytosis)

risperidoneRisperdal

olanzapine Zyprexa

quetiapine Seroquel

aripiprazole Abilify

Linked to weight gain/diabetes

Off-Label Uses of Antipsychotics

- Atypical Antipsychotic Abilify was the best selling drug of 2013.
 Zyprexa and Seroquel also big sellers—together > \$16 billion!
- Odd, because schizophrenia is relatively uncommon (1% of population)
- Off-label (unapproved) uses include depression, dementia, sleep disorder, stress, OCD.
- Limited support for these uses—

Antidepressants

- MAO-inhibitors--phenelzine (Nardil)
- Cyclics—third most commonly prescribed drug class—taken by 11%:
 - ◆ fluoxetine (Prozac)--SSRI
 - ◆ citalopram (Celexa, Lexapro)---SSRI
 - sertraline (Zoloft)--SSRI
 - duloxetine (Cymbalta) serotonin/norepi
 - ◆ venlafaxine (Effexor, Ixel)—

Cyclic Antidepressants

- Produce immediate elevation in serotonin/norepi
- Antidepressant action appears only after 1-5 weeks of daily use
- Side effects include drowsiness, dry mouth, constipation, urinary difficulties, dizziness, weight gain and sexual dysfunction
- Withdrawals symptoms can include nausea, headache, insomnia, flu-like symptoms,

Antidepressant's in children

- Effective in children and adolescents
- Suicidal ideation and suicide attempts more common during first few weeks of SSRI treatment than in general population
- Black box warning for suicide risk required 2004
- 2007 study (Bridge et al., JAMA) suggests suicide rates higher in untreated depression

Bipolar Disorder:

- Lithium
- Depakote (divalproex)
- Tegretol (carbamazepine)
- Atypical