Stimulants
Cocaine, amphetamines & amphetamine-like drugs
Caffeine & its relatives
Nicotine
NOT a chemically similar family like depressants

Chapter 7

Cocaine (naturally occurring)
Used for > 3000 years
Amphetamines (synthetic)
Developed in the 1920's
These drugs are on the DEA's Schedule of Controlled Substances
Non-amphetamine (but amphetamine-like) stimulants

We will start with:
“Psychostimulants” or
“Monoamine Stimulants”

Cocaine’s Actions

- Local anesthetic (like Novocaine or topical anesthetic mixture (TAC) used on wounds or before getting stitches)
- Vasoconstrictor
- Sympathomimetic: ↑ HR, ↑ BP, pupils dilate
- Psychostimulant – stimulates behavior/CNS
- Blocks reuptake of DA* & 5HT & NE
- DA is key neurotransmitter in reward system; NE is involved in arousal of body and brain, SHT & NE play a role in mood

Cocaine
- Naturally occurring in leaves of coca bush (~1-1.2% concentration)
- Available as powdered salt (cocaine hydrochloride) (~25-30 mg per “line”) – if snorted, effect peaks 15-20 minutes, lasts 60-90. If injected, rush is faster, stronger but shorter (30-40 min. total)
- Crystallized chunks of crack cocaine (doses average 250-1000 mg for this or older version of “freebase”) - intense rush, but short-lived
- In South America 60-80% pure coca paste often combined with tobacco & smoked (bazuco and paco)
- 2009 – 423,000 coke related ER visits in DAWN hospitals

Common Cocaine Adulterants

- Other stimulants (caffeine, theophylline, ephedrine, amphetamine or amphetamine-like drugs)
- Other local anesthetics (lidocaine, benzocaine, procaine, tetracaine)
- White inactives (lactose, sucrose, talc, four, cornstarch, mannitol)
- Miscellaneous (PCP & other hallucinogens, opioids, quinine, strychnine)
Ephedra or “Ma Huang”

- Active ingredient ephedrine was at one time the primary medication for asthma.
- Dilates bronchioles

Amphetamines

- Developed as a synthetic substitute for ephedrine (1927)
- Was sold as OTC asthma inhaler Benzedrine
- Pep pills used worldwide during WWII; still used by armed forces today
- Became a prescription drug in 1965 because of growing abuse, then a “Controlled Substance” in 1971; new wave of meth popularity began in 1990’s

Some Cocaine Risks (more later)

Over half-million ER visits/yr in DAWN

- Risk of overdose; sensitization
- Interacts with alcohol: risk of death 18-25X greater
- #1 single drug assoc. with ER visits & deaths
- The depressive crash as drug effect wanes promotes continued use.
  - Very real risk of suicide
  - During peak use in 80’s – 1/5 NYC suicides were coke users; 1/7 callers of 1-800-Cocaine reported suicide attempts
  - With chronic use, DA depletion occurs – may persist months after withdrawal

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Stereoisomers: Mirror Image Molecules

- A visual example of stereoisomers

Basic Amphetamines

- Molecules come in right (dextro or d)& left (levo or l)-handed varieties or isomers
- Benzedrine was a mix (d,l amphetamine)(5-50 mg.);
today’s Adderal is also such a mix
- Dexedrine is d-amphetamine & is more potent (2-20 mg.)
- Methamphetamine crosses BBB even better.
- “Freebase” dextromethamphetamine (ice or crystal) is smokable crystals like crack, but much longer acting.

Amphetamine’s Actions

- Amphetamines make DA and NE more available at synapses by triggering their release & decreasing reuptake.
Cocaine & Amphetamine Dose-Dependent Effects & Side Effects

• Stimulate body and brain
• Wakefulness, energy, appetite suppression
• Elevated confidence, mood
• Increased movement & speech
• Amphetamine much longer acting (hrs vs mins), because the enzymes that metabolize cocaine are found everywhere

• Common side effects: excess stimulation (anxious, short-tempered, agitated, palpitations (pulse may exceed 200), high BP, stomach ache, dizziness, headache, tremors & twitching, insomnia, bruxism/teeth grinding, dry mouth can progress to “meth mouth”)
• May show repetitive, stereotyped behaviors
• The more you do, the more “side effects” become “adverse effects”

Adverse Effects of Controlled Stimulant Abuse Besides Dependency

• Depression, anxiety
• Paranoia, risk of cocaine/amphetamine psychosis with hallucinations (cocaine or amphetamine “bugs” → constant picking)
• Weight loss, malnutrition, poor health, bruising, poor sleep, impotence possible
• Possible stroke, arrhythmia, heart attack, seizures, respiratory arrest, high fever – overdose common
• Risk to fetus or nursing baby
• Often used with downers, alcohol, heroin – may lead to dual dependency
• Cocaine use with alcohol produces cocaethylene which increases cocaine’s toxic effects

The Meth Problem in Iowa

http://www.resultsiowa.org/drugctrl.html

• Meth lab problem declining but still significant – IA had been 3rd in nation with 1500 labs/yr, now down to ~288 labs in 2013
• 62% IA criminal cases are drug-related and 69% of those are for meth (nationally are 41%, 14%)
• Primary drug related to IA prison admissions (478 in 2013)
• 60% of meth seizures are “ice”; meth twice as common as regular amphetamine
• Meth involved in 46.7% of IA child abuse cases
• In “1002 of these cases meth and other drugs found in child’s body in 2012
• Kids present in 80% homes with meth labs
• 80% of meth sold to users in IA is imported from the southwest (Mexico mostly), not made here

Withdrawal After Regular Use – not physically life-threatening

• Depression (possibly suicidal), irritability
• “Anhedonia” – nothing is rewarding, pleasurable
• Exhausted, no energy, increased sleep
• Headache, stomach pain followed by rebound hunger, binging
• Crave positive drug effects
• Evidence that methamphetamine abuse causes a particularly lasting shortage of DA & 5HT, actual loss of neurons and cortical dysfunction

Labs

• Cold (pseudoephedrine) pills, anhydrous ammonia, ether (starter fluid), sulfuric acid (“Liquid Fire”), lithium batteries, gas can, coolers, coffee filters, rock salt, chemical or urine smell.
• Highly hazardous

Stimulant Abuse Difficult to Treat

• MANY drug approaches have been tried with little success:
  • Substitute DA agents
  • Antidepressants (multiple types)
  • Alternative stimulants
  • New approaches under development: keep the drug out of the brain
  • Enhancing metabolic enzymes
  • Cocaine vaccine – antibody attaches to cocaine making it too big to cross BBB
  • Methamphetamine vaccine
Medical Uses for Amphetamine & Amphetamine-Like Drugs

- Treatment of attention-deficit hyperactivity disorder (ADHD) & its variations, including in adults
- Improve behavior in 70-80% of those correctly diagnosed; one of the most well-documented pharmacotherapies – more effective than intensive behavioral therapy (see treatment links) but not a “cure”
  - *Ritalin – methylphenidate (half-life 2-4 hrs)
  - Adderal – a mix of d & l amphetamine salts
  - Dexedrine – d-amphetamine
  - Must be taken more than once a day for sustained effect

For up-to-date discussion of treatment of ADHD see p 523-531

*New Long-Acting Varieties With a Variety of Time-Course Profiles

- methylphenidate
  - Concerta ~12 hrs.
  - Metadate CD, Ritalin-LA ~8 hrs
  - Focalin – dextro version of methylphenidate, more potent with longer half-life
  - Concerta & Daytrana transdermal patch
  - Quillivant XR – a liquid form of methylphenidate

- amphetamines
  - Adderal XR – 10-12 hrs
  - Dexedrine Spansule – 6-9 hrs

New Variety to Avoid Abuse

- Vyvanse (lisdexamfetamine)
- Amphetamine attached to an amino acid so that it is not psychoactive if snorted or injected.
- Only effective by oral route because amino acid comes off in GI tract

![NIMH Long-Term Study of ADHD Reduced Brain Volume](http://www.health-center.com/english/brain/adhd/default.htm)

ADHD Drug Treatment Risks

- Stomach ache, headache, jitters, dizziness, especially at first
- Appetite-suppression; delayed sleep onset
- Growth reduction possible; motor tics in 1%
- Rare heart attacks, strokes, sudden death in some
- Kids may not receive adequate assessment & follow-up, but data suggest under-prescription more common than over-prescription

*Non-amphetamine alternative treatments

- Strattera (atomoxetine) (selective NE reuptake inhibitor (SNRI)
- Antidepressants (Wellbutrin (bupropion), Prozac (fluoxetine), Cymbalta (duloxetine) (less effective than stimulants)
- Provigil (modafinil) – a newer stimulant unrelated to amphetamines used for narcolepsy, shift work sleep disorder & daytime sleepiness of apnea – not yet approved for ADHD
- 2 anti-hypertension drugs – clonidine (Catapres) & guanfacine (Tenex & longer acting Intuniv) (alpha agonists at NE receptor) – may be used with stimulants
Medical Uses - continued

- Treatment of narcolepsy, shift-work sleep disorder, daytime sleepiness of sleep apnea
- Amphetamines have been used to maintain wakefulness
- Newer non-amphetamine psychostimulant available:
  - Provigil (modafinil) was approved for this use (may ↑ glutamate action, ↓ GABA) – less effect on mood, appetite, HR & BP, less abuse
  - Nuvigil (armodafinil) – just the "right-handed" form of modafinil rather than a mix of R & L

Watch for this drug company trick

- When their patent is about to run out on a popular drug, they release a "new drug" that is just 1 stereoisomer/enantiomer rather than a mix to get a new patent to be able to charge the high "new drug" prices
- Examples:
  - Benzadrine (mix) ———> Dexadrine (just d-amphetamine)
  - Ritalin (mix) ———> Focalin (just d-methylphenidate)
  - Celexa (mix) ———> Lexepro (just S-citalopram)
  - Provigil (mix) ———> Nuvigil (just the R-modafinil)

Controversial Use

- Short-term* adjunct to weight-loss programs – multiple drawbacks means it should only be considered for obese facing serious health risks
  (health risks, tolerance, potential dependence & rebound weight gain limit usefulness)
- Prescription amphetamine-like appetite suppressants
  (note: one after another has been removed from the market because of health risks)
  - phendimetrazine
  - diethylpropion
  - phentermine
  - Now turning to non-stimulant 5HT related drugs, but no wonder drugs out there

Catha edulis - Khat

African/Arabian shrub which contains cathinone.
Leaves (fresh only) chewed for stimulant effects.

“Bath Salts”

- AKA Bliss, Vanilla Sky, Purple Wave, Ivory Wave & others
- Contain synthetic cathinones that are amphetamine-like
- Contain miscellaneous “designer drug” stimulants
  - mephedrone, methylone, and/or MDPV or methylenedioxypyrovalerone (MDPV) (illegal as of Sept 2011 or at least 14 other compounds made illegal in Jan 2014)
  - Like a hallucinogenic methamphetamine

- http://www.youtube.com/watch?v=bKbTbRqXVFg