1. History of amphetamine development
   
   first synthesized in 1887 (in Germany)
   seeking a synthetic form of ephedrine
   marketed first in 1932 as a *Benzedrine inhaler*, for tx. of asthma, congestion
   (Benzedrine = d,l – amphetamine)
   in 1935 dextroamphetamine (*Dexedrine*) was marketed for tx of narcolepsy
   (Dexedrine = d-amphetamine)
   by 1940s amphetamines were widely used as “diet pills”
   do decrease food/drink intake for short term (& increase duration of times
   between meals), but eat more rapidly and same amounts overall when do eat
   overall, not helpful for long-term weight loss/control

   **used in WWII by military** to decrease fatigue (Germans, USA, Japanese, etc.)
   the **Rebuilding of Japan after WWII**:
   after WWII Japanese government sold large stock piles of amphetamines to
   its citizens w/o Rx
   by 1954 it is estimated that 2/100 persons in Japan were abusing amphetamine.
   and the abuse potential of the drug was finally acknowledged
   by 1960 Japanese government had decreased public access to drug and # of
   abusers had begun to decrease

   by 1960s in **USA** also began to recognize abuse potential for amphetamines…
   made a Schedule II drug in late 1960s… and abusers switched to cocaine!
   in **1970** 10 billion amphetamine pills were produced in USA per year
   **at least 10% of USA population > 14 years old had used some** form of this
   drug (dieters, students, truck drivers, laborers, etc.)
   in 1954 methylphenidate (Ritalin) was synthesized, followed by pemoline
   (Cylert)
   both have abuse potential, Ritalin > Cylert

   now used for several specific medical conditions:
   ADHD/ADD, narcolepsy (although this is changing), and IHS
   Not used for weight loss
STIMULANTS: Amphetamines, Cocaine (p.2)

2. **General effects** of taking amphetamines:
   - in PNS – vasoconstriction, hypertension, tachycardia
   - in CNS – agitation, insomnia, anorexia, increased alertness
   - tremor, restlessness, increased motor activity

   note: cocaine users cannot distinguish between the subject effects of 8-10 mg. cocaine vs. 10 mg. dexadrine, both administered IV

3. **Mechanisms of Action:**
   - these are sympathomimetic agents
   - are NEpi, Epi, & DA agonists
   - increase the release of NE & DA from presynaptic neurons in CNS
   - increase the release of NE & E from post-ganglionic neurons in SNS
   - may have medium effects (<cocaine) on blocking reuptake of DA

   release of DA in mesolimbic pathway --- reinforcing effects
   release of DA in basal ganglia (caudate nucl. & putamen) --- **stereotypic behavior**
   “punding”

   note: in S with ADD/ADHD amphetamines seem to have a paradoxical
   “calming” effect (actually, S is **more focused**, not calm *per se*)

4. **Effects of drug vs. dose levels:**
   - **low doses** (< 20 mg)
     - increased BP, HR
     - relaxation of bronchial muscles (opening of airway)
     - increased alertness, euphoria, wakefulness, mood, decreased fatigue
       - note: amphetamine < cocaine in producing euphoria (less reinforcing)
     - increased motor activity & speech production
     - increased sense of well-being & power
     - may improve performance on simple motor tasks, esp. repetitive “boring” tasks
     - but impairs fine motor skills; usually improves athletic performance
     - can detect in urine up to 48 hours after use
4. **Effects/Dose levels (cont.)**

**Moderate doses (20-50 mg)**
- all of the above, plus increased respiration rate
- increase in tremors & motor restlessness
- increase in insomnia, agitation
- decreased appetite

**High doses (> 50 mg)**
- all of the above, plus sudden aggression & violence
- marked increase in purposeless, repetitive acts (“punding”, stereotypies)
- paranoid delusions
- severe anorexia --- wt. loss, malnutrition, skin sores, infections
- psychosis (esp. with abuse of methamphetamine)
- lack of sleep
- progressive deterioration of social, personal, job skills

5. **Use in pregnancy**
- no clear teratogenic effects
- but lower birth weights, retarded growth rates postnatal
- can see an increase in intracerebral hemorrhages in fetus
- increases in school/behavioral problems, cognitive slowing & general maladjustments later on in infant/child

6. **Pharmacokinetics**
- can take PO (unlike cocaine)
- lipid soluble
- onset of effects w/i ½ hour
- ½ life is 5 to 20/30 hours (mean = 10 hours)
- a single dose is detectable in body for 3 days
- metabolized by liver enzymes
STIMULANTS: Amphetamines, Cocaine (p.4)

7. Pharmacodynamics:
   withdrawal effects – hypersomnia (increased REM, increased NREM)
   hyperphagia & wt. gain
   lethargy, fatigue
   depression & increased risk of suicide (for months)
   requires tx w/ antidepressants & careful monitoring

   tolerance develops esp. to euphoric effects, to anorexia, & to some of the cardiovascular effects
   tolerance develops fairly rapidly, so increased doses frequently seen
   increased risk for OD

   toxic effects that mimic paranoid psychosis occurs at dose levels 60-300 mg/day
   and can last for longer duration than that seen with cocaine
   requires tx with high-potency antipsychotics (e.g. Haldol/haloperidol)

   shows state-dependent learning effects

8. Use of “ICE” (free-base methamphetamine)
   (analogous to use of free-base cocaine or “CRACK”)
   both of these forms of the drug are smoked/inhaled, which because of an almost immediate effect in the brain are markedly more addictive than when the drugs are taken by some other route (PO, absorption through nasal mucosa, etc.)
   changes in the CNS (e.g. in RSs) may be irreversible…e.g. drug “craving” behs.
   see >1yr. after D/Cd drug
   also see long-lasting (permanent?) changes in sleep architecture, sexual beh., mood (depression), movement disorders, and schizophrenic Sxs
   deaths due to pulmonary edema and/or heart failure
9. Amphetamines Used in Clinical Treatment

For ADD/ADHD, use Dexedrine, Adderall (Dexedrine + amphetamine)
also use Ritalin, Concerta (methylphenidate),
newly released drug Provigil (modafinil) is also now being tried
is not a DA agonist --- no/low abuse potential
may be a glutamate agonist and/or a GABA antagonist
used in order to improve mental focus, concentration in these Ss
which has the happy side effect of decreasing distractability, restlessness, etc.

For narcolepsy or idiopathic hypersomnia, use Dexedrine, Ritalin, Provigil,
or Cylert (pemoline, although must do frequent liver function tests)
used in order to counter EDS in these patients
note: exciting recent discovery of NT that may produce “wakefulness”
is perhaps not a NT that simply blocks sleep…
orexin = hypocretin, cell bodies in anterior hypothalamus

For weight loss, no currently supported use for stimulants
Do not use Fastin/Adipex (phentermine)
Do not use Redux (dexfenfluramine)
Do not use Pondimin (fenfluramine)
Do not use ephedrine (Ma Huang), seudephedrine
Use Meridia (sibutramine)
ise a reuptake inhibitor of 5HT, NE & DA (< amphetamines)
structurally similar to amphetamine molecule but is not an amphetamine
parent molecule rapidly metabolized --- active metabolite
so far seems to have a low abuse potential
does increase BP & HR
10. **History of Cocaine Use**

obtained from leaves of *Erythroxylon coca* plant (So. America)
  fresh, green leaves chewed by native peoples --- less fatigue, greater
  endurance, more resistance to cold
  about a 200mg/day “dose” at most
1855 – the active ingredient (cocaine) isolated
1850-1860 – invention/perfection of syringe & hypodermic needle
1880 – cocaine used as a local anesthetic
1885 – cocaine & caffeine both used in USA as “helpful nerve tonics”
  e.g. Coca-Cola (60 mg cocaine/8 oz.)
  to give S energy, sense of well-being!
late 1880s – Freud used cocaine himself & recommended it for his pts.
  addition potential unrecognized at first
  by early 1900s Freud was discouraging its use
1910 – President Taft speaks out against use of cocaine specifically
1914 – passage of the *Harrison Narcotic Act* (includes prohibition against cocaine)
  cocaine banned for use in medicines or beverages
1918 – 1st synthetic local anesthetic developed (*Novocaine/procaine*)
  procaine has no dependency-producing effects
1930s – use of cocaine had decreased
1940s – to be replaced by use of newly synthesized “ephedrine-like” drugs

11. **“Typical” Cocaine User in USA**

  young (12 to 39 years)
  dependent on cocaine + 2 other drugs (multiple drug use)
  male (75%)
  comorbid conditions – depressed (67%), paranoid (25%), ETOH dependent
    (85-90%)
  at increased risk for premature (& violent) death (homicides, suicides, accidents)
  at increased risk for cardiovascular morbidity/mortality
12. **Pharmacokinetics:**

**absorption** – is slow when “snorted” because drug causes vasoconstriction of nasal blood vessels
peak plasma levels reached 30-60 min. after snorting
20-30% of snorted drug absorbed into bloodstream

- is very fast when **smoked/inhaled**, via lungs
peak plasma levels reached w/i 5 min. & “rush” felt w/i a few seconds
6-32% of smoked drug absorbed into bloodstream

- is also very fast if **injected IV**, enters plasma directly
100% enters bloodstream
30-60 seconds to feel onset of effects

- PO route is rate, reduced absorption, very mild effects after 30-60 minutes

**distribution** – crosses the BBB easily
initial concentration in brain > plasma concentrations
after cocaine leaves brain it redistributes to other body tissues (is water soluble)
easily passes placental barrier

**metabolism & excretion**
½ life = 30-90 minutes
metabolized extensively by liver & plasma enzymes
removed more slowly from brain vs. body tissues (is still present in brain > 8 hrs. after administered)
can detect cocaine in urine for up to 12 hours after administration
can detect cocaine **metabolite** (inactive, benzoylecgonine) up to 48 hours after use (in acute user), and after 2 weeks (in chronic user) because inactive metabolite accumulates in body tissues
**STIMULANTS: Amphetamines, Cocaine** (p. 8)

13. **Mechanism of Action**

   cocaine is a **major DA agonist**
   
   **blocks the reuptake** of DA
   
   increases the DA activity, esp. in nucl. Accumbens
   
   cocaine itself directly can also affect post-synaptic membranes of neurons
   
   end result is a decrease in discharge rate of nucl. Accumbens neurons & of ventral-tegmental pathway neurons

   cocaine is also a **major 5HT & NE agonist**
   
   blocks the reuptake transporter protein for 5HT & for NE
   
   seems also to produce reinforcing effects (although the 5HT1a RS may decrease reinforcing effects)
   
   note: may cause the DA,5HT,NE transporter protein to reverse, & carry NTs to outside of neuron (to synaptic cleft) from presynaptic membrane…

   **clinical issue** - What if S had a “faulty” 5HT/DA transporter system that resulted in too great an uptake of 5HT/DA?
   
   Would this person be “self-medicating” by using cocaine?
   
   Would this person be more susceptible to cocaine use & depression?
   
   both cocaine & ETOH abusers do seem to have faulty 5HT transporter proteins...

14. **Effect of Cocaine on the Body/Behavior**

    3 of importance:
    
    potent local anesthetic effect (prevents uptake of Na+ into neurons)
    
    potent vasoconstrictor (incl. cardiac/coronary arteries)
    
    potent psychostimulant with reinforcing properties

    Effects of **short-term, low-dose use: physiological/bodily effects**
    
    increased alertness                hypertension
    
    motor hyperactivity              bronchodilation
    
    tachycardia                      increased body temperature, increased BMR
    
    vasoconstriction                 pupillary dilation
    
    increased blood glucose          decreased blood flow to organs
    
    increased blood flow to skeletal muscles & brain
14. **Effects** (cont.)

**Short-Term, Low-Dose Use** (cont.)

**Psychological Effects** – usually occur within the first 30 minutes
- euphoria (marked)
- giddiness
- increased self consciousness
- forceful boasting

Secondary Effects – that occur within 60-90 minutes
- milder euphoria
- anxiety
- rapid speech, “pressured” speech, incoherence

Protracted Effects – that last for hours – incl. **anxiety, and depression** later on

**Appetite** is initially suppressed, later rebounds
**Sleep** is quite delayed, but fatigue is reduced initially & then rebounds later on

initially motor activity increases, with agitation, restlessness

And the urge to take more cocaine increases – “**cocaine cravings**”
- Which as tolerance increases (esp. to euphoria) --- larger/more frequent doses
  --- greater toxicities & risk of death

Note: former cocaine users show **classically conditioned cocaine cravings**
- when shown stimuli associated with prior cocaine use blood flow increases to **limbic system** structures (esp. amygdala, anterior cingulated gyrus, orbito-prefrontal cortex) & S experiences “cravings”)

**specific toxicities to CNS:**
- anoxia in CNS 2ndary to decrease in blood flow
- increased risk of vascular thrombosis
- intracranial hemorrhage & strokes
- cerebral atrophy    seizures    risk of movement disorders 2ndary to brain damage
STIMULANTS: Amphetamines, Cocaine (p. 10)

14. Effects (cont.)

**cardiovascular toxicities:**
hypertensive crisis
cardiac ischemia, cardiac arrhythmias
MIs, heart failure, infected heart tissue
ruptures aorta

**nasal problems** (degeneration of nasal septum)

**Long-Term, High-Dose Effects:** “toxic paranoid psychosis”
anxiety
severe sleep deprivation
hypervigilance
suspiciousness
paranoia, persecutory fears
impulsive
repetitive, compulsive behavior (“punding”)
altered perception of reality – delusions, hallucinations
aggression, homicidal thoughts/behaviors
depression & dysphoria (which will worsen when S D/Cs cocaine)
   can last for days-weeks +

“cocaine psychosis” – paranoia, impaired reality testing, anxiety
   stereotyped, compulsive, repetitive behaviors
   vivid hallucinations (visual, auditory, tactual)
   disturbances of eating, sleeping

note: w/ chronic cocaine use there is likely to be a **comorbid Dx**
bipolar, unipolar depression, schizophrenia, other drug use (esp. ETOH &
heroin), personality disorders (reckless, rebellious, poor frustration tolerance,
risk taking, impulsive)
often a + family pedigree for drug abuse, psych. disorders
15. Cocaine & Pregnancy

vasoconstriction --- **decreased placental blood flow** --- decreased O2 to fetus
increased risk for placental detachment, preterm labor, stillborns, decreased birth weight, microcephaly, cardiovascular damage to fetus

*teratogenic* effects & fetotoxic effects are noted

*question* – would fetus have reduced #s of 5HT, DA, NE RSs?
would fetus thus be at greater rish for depression postnatal?

*note*: overall 11% of pregnant women use cocaine during pregnancy
inner city women in low SEL – may be as high as 68-70%
in these women, 15-25% of neonates have detectible cocaine in their bloodstream/urine at birth

cocaine still present in breast milk 60 hours after woman last used cocaine

16. **Pharmacologic Treatment** of Cocaine Dependency

tax for **depression** – antidepressants (e.g. desipramine, imipramine, fluoxetine)

tax for **cravings** – e.g. buproprion (Wellbutrin) that block DA RSs

tax for **comorbid disorders** – e.g. antidepressants, mood stabilizers
e.g. ReVia (naltrexone) to decrease ETOH/heroin craving

*note*: prolonged cocaine use is likely to have --- **down regulation of DA (NE,5HT) RSs**; thus, when D/C cocaine --- these NT systems are **hypoactive**
--- **depression**, **anhedonia**, **fatigue**, etc.? & have to again up regulate…

*note*: have these Ss been “self-medicating” for “too active” a DA/5HT/NE system?
35% of cocaine abusers have a Hx of ADHD in childhood, 15% in adult yrs.
thus, if these Ss were given e.g. Ritalin, do they usually improve…yes
16. Treatment (cont.)

**psychosocial interventions**, added to pharmacologic txs, make for better results than either intervention alone.

these psychosocial interventions should include cognitive-behavioral therapy, coping skills, interpersonal skills, social support, environment changes, etc.

Use **Harm Reduction Model**

note: all of our interventions have relatively poor treatment outcomes in the long run…**most addicts return to using**…& their **craving beh. never stops**

…a permanent brain change?
be very careful what you expose you CNS to…
an ounce of prevention may be worth a pound of cure…