STIMULANTS: Amphetamines, Cocaine (p.1)

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 Rxs
      by 1954 it is estimated that 2/100 persons in Japan were abusing amphetam. 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 l960s 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

STIMULANTS: Amphetamines, Cocaine (p.3)

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

STIMULANTS: Amphetamines, Cocaine (p.5)

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), pseudephedrine
use *Meridia (sibutramine)*
is 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

STIMULANTS: Amphetamines, Cocaine (p.6)

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
l850-1860 – 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 speakes 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

STIMULANTS: Amphetamines, Cocaine (p.7)

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

STIMULANTS: Amphetamines, Cocaine (p.9)

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 2^{ndary} 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 & heroine), personality disorders (reckless, rebellious, poor frustration tolerance, risk taking, impulsive)
often a + family pedigree for drug abuse, psych. disorders

STIMULANTS: Amphetamines, Cocaine (p. 11)

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

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

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

tx for **comorbid disorders** – e.g. antidepressants, mood stabilizers
e.g. ReVia (naltrexone) to decrease ETOH/heroine cravings

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

STIMULANTS: Amphetamines, Cocaine (p. 12)

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, enrironment 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…