STIMULANTS: Methylxanthines/Xanthines (p.1)
(“minor” stimulants)

1. Plant Sources of Xanthines (alkaloids)
   Coffee – *Coffea Arabica* (Ethiopia originally)
       *Coffea robusta* (African Congo originally)
   Tea – *Camellia sinensis* (China, India, Burma, Thailand, Laos & Vietnam)
   Chocolate – *Theobroma cacao* (Amazon & Orinoco rivers)
   So.Amer. Holly – *Ilex guayusa* (Amazon, Peru, Ecuador)
       Achuar Jivaro tribesmen
   (xanthines act to repel insects)

2. Specific Active Ingredients & Plant Sources
   **Caffeine** – found in coffee, tea, colas, & So.Amer. holly
   **Theophylline** – found in tea
   **Theobromine** – found in chocolate (along with phenylethylamine & caffeine)
   (caffeine > theophylline > theobromine)

3. Users of Xanthines
   Mean age of initial use:
       of coffee = 19 years; of tea = 22 years; of colas = 14 years; of choc?
   In USA > 85% of population consumes caffeine weekly
       > 98% of children/adolescents (5-18 yrs) consume weekly
   210-238 mg caffeine/person/day (all sources)(mostly coffee)
   (Julien says 80-400 mg, = 3 to 5 5oz. “cups” of coffee/day)
   (vs. 444 mg caffeine/person/day in United Kingdom!)(mostly tea)
   coffee consumption was dropping & colas increasing – in early 1990’s (PS)
   In U.K. per capita consumption of chocolate is 16 lbs./year
       (vs. 12 lbs./year in USA)
   in U.K. around 20% of yearly chocolate is consumed at Xmas/NewYrs
   Worldwide 70mg caffeine/person/day (tea > coffee)
   80% of adult population consumes caffeine daily
   **Summary: Xanthine use is worldwide & daily!**
4. General Positive Effects
   increased mental alertness, wakefulness
   increased energy, sense of well-being
   does it have potential for toxicities? YES…
   does it have potential for physical dependence? YES…

5. Pharmacokinetics
   taken PO, rapidly absorbed from GI tract
      are alkaloids…so “should” ionize & get trapped in stomach…but
      do not ionize easily in acidic environment; therefore remain in non-
      ionized form & readily pass out of stomach into bloodstream
      absorbed w/i 15-45 minutes, completely by 1½-2 hours
      peak plasma levels 2 hours after drinking, decrease thereafter

      freely distributed to all body tissues
      crosses BBB easily & quickly
      crosses placental barrier easily & quickly

   90% metabolized by liver enzymes (CYP1A2), 10% excreted unchanged)
      mostly in urine
      small amounts excreted in feces, sweat, breast milk, etc.
   ½ life varies: 3½ to 5 hours (2½ - 7) in most adults
      ½ life increases in infants, pregnant women (3-10 hours), & elderly
      ½ life decreases in smokers (via liver enzyme induction)

   note: some TCAs & SSRIs, & grapefruit can inhibit CYP1A2 production
      which then --- increases caffeine effects
      e.g. Luvox/fluvoxamine (vs. Effexor/venlafaxine)

   caffeine metabolized into 3 active (stimulant) metabolites:
      theophylline & paraxanthine – active, acts like caffeine
      theobromine – active, but does not act like caffeine
STIMULANTS: Methylxanthines (p.3)

6. Pharmacological Effects of Caffeine (at low to medium doses)
   increased alertness, increased wakefulness
   increase in faster, clearer thinking
   increased mood, sense of well being, sociability
   decreased fatigue
   decreased sleep, increased restlessness, sensitivity to stimuli
   increased skeletal muscle activity (increased shaking, tremors --- decreased
   fine motor control)
   increased respiratory drive & rate
   increased urine output (is a diuretic)
   increased HR, cardiac force, BP, dilation of coronary arteries (vs. cocaine)
   decreased smooth muscle activity (is a vasodilator in peripheral blood
   blood vessels, but a vasoconstrictor of CNS blood vessels; opens
   bronchi)
   increased basal metabolic rate

7. Toxic Pharmacological Effects of Caffeine (at medium to high levels)
   usually seen at about 1 to 1.5 grams/day levels (= 12 cups coffee)
   increased agitation, anxiety (esp. in sensitive Ss)
   increased tremors, restlessness
   increased rapid, shallow breathing
   increased insomnia
   increased peripheral vasoconstriction (cold, sweaty hands)

   lethal dose = 10 grams caffeine/day (= 100 cups coffee)
   (therefore, TI = 40)

   “caffeinism” – a clinical pattern seen with caffeine OD
   anxiety, agitation, severe insomnia, labile mood swings (esp. irritability
   to rage), tachycardia, HBP, cardiac arrhythmias, severe GI disturbances,
   incl. diarrhea, gas, & cramping, and acid reflux, SOB, tinnitus, delerium
   usually seen at > 500-1000 mg/day (= 5-10 cups coffee/day)
STIMULANTS: Methylxanthines (p.4)

8. Mechanisms of Action of Caffeine

What NTs are affected by caffeine is dose dependent (Julien, see p. 225)
At usual dose levels (one cup of coffee), caffeine blocks adenosine RSs (A1 and A2a RSs)
adenosine acts presynaptically (on GABA; on ACh, NE, DA, 5HT)

normally, adenosine is a NT that seems to have “sedative” effects; thus, if this RS is blocked --- arousal, alertness, wake

**adenosine** normally --- increased GABA
--- decreased DA, glutamate, ACh
so--- sedative, depressant, & anticonvulsant effects

if block **A1 RS** --- increased DA, glutamate, & ACh
so --- modest reward effects, increased alertness/vigilance, & increased mental acuity/memory
if block **A2a RS** --- increased DA, so modest reward effects
note: the **DA is released in the prefrontal cortex** (not the mesolimbic reward pathway, not nucl. Accumbens), therefore, not as reinforcing as cocaine, amphetamines

in **PNS**, caffeine acts as a NE synergist --- SNS activation (e.g. HBP)
acts at NE beta RS

at much higher dose levels, caffeine also blocks GABA A RSs, increases Ca++ release, and inhibits phosphodiesterase
these effects are thought to underlie toxic responses to caffeine

note: in mice selectively bred to have no adenosine RSs, caffeine acts as a depressant!...
note: in rats daily caffeine use --- up-regulation of adenosine RS #s and increased sensitivity of adenosine RSs
**STIMULANTS: Methylxanthines** (p.5)

9. **Tolerance & Dependence of Caffeine**

daily use of caffeine can induce *significant degree of tolerance* and *physical dependence*

thus, Ss gradually increase daily dose strengths

when D/C abruptly --- w/d Sxs seen in 10-30% of former daily users

tolerance does develop to effects on sleep, to diuretic effect, & to cardiovascular effects

tolerance effects have returned to baseline after about 2 months of abstinence from all caffeine

dependency occurs in 6-15 days of consuming 600+ mg caffeine/day

caffeine w/d Sxs: moderate to severe *headache* (> 50% of Ss)

drowsiness, fatigue, less alert, less active, lethargy

anxiety (10%)

depression (10%)

flu-like Sxs (malaise, muscle aches, abdominal cramps, etc.)

nausea, vomiting

irritability

w/d Sxs begin w/i 12-24 hours after D/C caffeine

usually *last up to 7 days* or so

note: many headache OTC drugs have caffeine in them (e.g. Excedrine)

note: relationship between amount of prior caffeine used daily & severity of w/d Sxs
10. Use of Caffeine in Pregnancy

caffeine is used by 75%+ of pregnant women
unknown if this is really safe…

> 300 mg/day (about 2 ½ cups) --- decreased intrauterine fetal growth
  increased risk of spontaneous abortion

> 600 mg/day --- increased risk of spontaneous abortion
  no/little evidence of teratogenic effects
  no evidence of labor/delivery complications

*caffeine passes into nursing infant in breast milk* --- increased irritability, insomnia, colic in infant

slight negative rel. between increased caffeine intake and decreased fertility (caffeine use may slow conception)

note: pregnancy lengthens the ½ life of caffeine

11. Therapeutic Uses of Caffeine

  for vascular (migraine) headaches
  for diuretic
  for mild assist to memory, concentration, learning
  for ADD/ADHD, for narcolepsy (a “poor man’s speed”)
  for weight loss
  as a respiratory stimulant (e.g. asthma, central sleep apnea)
  prophylactic for Parkinson’s Disease

12. Other Miscellaneous on Caffeine
STIMULANTS: Methylxanthines (p. 7)

13. **Theophylline**
actually *more potent* than caffeine, but rarely is tea brewed (in USA)
at same strength as coffee… except in U.K.!

peak plasma levels reached in 1.5 to 2 hours
½ life is 6 hours

effects are very similar to caffeine
esp. bronchodilation, cardiovascular responses, & CNS stimulation
but theophylline is more relaxing to peripheral smooth muscles,
esp. respiratory smooth muscles
and has a greater effect on increased drive to breathe

thus, *used to treat asthma & central apnea* (more than caffeine is)
e.g. Theo-Dur (theophylline)
in oral, rectal or injectable forms
e.g. aminophylline (no brand name, is a theophylline salt)
e.g. Enprofylline (5x as effective as theophylline)

note: fetal liver converts theophylline to caffeine (adults no not)

*OD/toxicity*: similar to caffeine except w/o headache
nausea, vomiting, tachycardia, arrhythmias, seizures, tremors

14. **Theobromine**
least effective of the three methylxanthines
note: some women crave/binge on chocolate premenstrually
chocolate seems to decrease PMS Sxs
note: naloxone blocks cravings for chocolate… implications?

toxicity seen at >0.8grams (>11mg/Kg)
nausea, vomiting, dizziness, sweating, trembling, headache