

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/New Yrs

Worldwide 70mg caffeine/person/day (tea > coffee)

80% of adult population consumes caffeine daily

Summary: Xanthine use is worldwide & daily!

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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

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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 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, delirium
usually seen at > **500-1000 mg/day** (= 5-10 cups coffee/day)

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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 rein-
forcing 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

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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

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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

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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

