STIMULANTS: Nicotine (p.1)

1. History of Use

mostly derived from the tobacco plant (*Nicotiana tobacum*)
native to So. Amer., used by Mayans probably B.C.
taken to Europe by Spanish explorers in 1500s
returned to No. Amer. in 1600s (by British & others)

wherever it was used, its use went through predictable stages:
medicinal use & praise
glamour/recreational use & faddism
protest against its use (as unhealthy, unsafe, monetary fines)
taxation, government control of access
government continues to depend on revenue from taxation
and does not outlaw tobacco access
acceptance… (“in bed with the devil”!)

history of use in USA:
1938 first study linking smoking to lung cancer
1954 relation between smoking & heart/lung disease noted
1964 “Cigarette smoking may be hazardous to your health” warning
1969 smoking permitted anywhere on CSUF campus, incl. classrooms
1970 Public Smoking Act (restricted smoking in some public places)
1971 tobacco ads banned on radio & TV
1971 “Cigarette smoking is dangerous to your health” warning
*1995 smoking in CSUF classrooms banned (OK in hallways)
*1979 smoking & non-smoking sections on domestic airlines
*1981 smoking banned on all domestic flights within California
*1985 smoking banned on all domestic flights within USA
1987 Surgeon General Koop issues warning – “nicotine is addicting”
*1991 smoking banned in California restaurants
*1995 smoking banned in California bars
1994 FDA takes position that it should regulate cigarettes as a “drug”
1996 smoking banned in all major European airports
*2000 smoking not permitted in CSUF buildings/balconies anywhere
*approx. dates (subject to vagaries in my LTM)
STIMULANTS: Nicotine (p.2)

2. Demographics of Users (USA)
__the 3 most widely used psychoactive drugs are: caffeine, nicotine, ETOH
4K cigarettes/year/person 18 yrs. or older
approximately 25% of population smokes cigarettes
   vs. 74-92% of schizophrenics!
   vs. an even higher % of alcoholics & persons Dx w/ depression!
implications…

mean age of onset of smoking = 13 years…implications…
9 out of 10 smokers were addicted before the age of 21 years
6000 teens/day smoke their first cigarette
50% will go on to become habitual users
33% of these habitual users will eventually die of smoking-related causes

approximately 2000 persons/day quit smoking
but > 3000 persons/day start smoking
thus, about a 2-3% yearly increase in smokers #s
34% of smokers try to quit smoking/year…2.5% succeed
eventually about 50% of all smokers manage to quit
proportion of adults who smoke as been decreasing (now about 25%,
was 50% in 1965)

smoking is directly responsible for about 1100 deaths/day
while it is the nicotine which causes the dependence, it may be other
ingredients (e.g. tars) that are the most toxic (e.g. cause cancer and cardiovascular damage)
3. **Pharmacokinetics**

**Absorption:**

nicotine is *water soluble* and is *readily absorbed*
- if smoked, is an *aerosol* (liquid dispersed in a gas)
- absorbed into lungs, mucous membranes (chewed, inhaled as *snuff*)
- note: can be absorbed through skin (e.g. nicotine based insecticides)

mean of 0.5 to 2.0 mg nicotine/cigarette
- absorb about 10-20% of that dose (0.05 to 0.4 mg/cigarette) into bloodstream
- 80-90% of original nicotine in cigarette goes off in uninhaled smoke but this “uninhaled” smoke can also be inhaled later by smoker in badly ventilated room or by a “non-smoker” in the vicinity
- 90% of nicotine in bloodstream passes BBB (0.045 to 0.36 mg), average of about 0.18 mg/cigarette with a latency of about 10 sec.
- also crosses placental barrier

**Metabolism & Elimination:**

nicotine is metabolized by liver enzyme CYP2A6

- smoking induces liver enzymes (*only if smoked*)
- some SSRIs inhibit formation of CYP2A6
- note: lower levels of CYP2A6 found in African Americans metabolized to “cotinine”
- ½ life is about 2 hours (in a chronic smoker)

excretion is via the *kidneys*

*LD50* is 60 mg of nicotine
STIMULANTS: Nicotine (p.4)

4. Pharmacological Effects

nicotine is a “stimulant” because it excites the CNS, but paradoxically it is felt as a calming agent (at lower dose levels, at least)

note: in initial/early stages of smoking, nicotine produces very aversive effects: nausea, vomiting (is an irritant to GI tract)
but tolerance develops quickly to this response

nicotine --- attaches to ACh “nicotinic” RSs in PNS (somatic NS)
initially --- stimulates the post-synaptic cell
but as nicotine stays attached to RS, eventually becomes a RS blocker
--- blocks cholinergic PNS RS --- muscle relaxation (at low doses)
at high doses --- increased muscle activity (tremors, spasms)

also stimulates preganglionic SNS RS (uses ACh) in PNS
--- increased release of NE, E in postganglionic SNS neurons
--- increased release of NE, E from adrenal medulla
both of which --- increased BP, HR
increased heart force
peripheral vasoconstriction of cutaneous vessels

vasodilation in skeletal muscle bloodvessels
vasodilation in coronary arteries

increased tendency to form blood clots

increased motility in gut --- diarrhea
initial increase in salivation, followed by decreased salivation & bronchial secretions

increased respiratory rate (low doses)
decreased respiratory rate (high doses)
STIMULANTS: Nicotine (p.5)

4. Pharmacological Effects (cont.)

Effects in CNS:

- Increases the release of ADH (by hypothalamus) --- fluid retention
- Increased CNS activity generally initially --- excitation, increased alertness, attention; followed by decreased CNS activity --- depression
- Stimulation of area postrema (medulla) --- increased nausea/vomiting (followed by rapid tolerance)
- Stimulation of medullary breathing centers and reduced O2 in bloodstream --- increased respiratory rate
- Increased release of NE & DA in hypothalamus
  - DA released in mesolimbic system, nucl. Accumbens, forebrain --- reinforcing effects, addiction, focus on nicotine (DA2 RSs)
  - Builds up tolerance --- increasing doses
- Increased release of glutamate --- agitation, improved memory?
- Increased release of 5HT --- sedation, decreased aggression
- General effects from CNS changes --- decreased appetite (& mild weight loss)
- Increased motor activation, restlessness, figiting
- Increased cognitive functioning
- Improved sensory-motor performance (on simple tasks)
- Increased memory consolidation (esp. STM vs. LTM)
  - Nicotine activates frontal lobes
  - As an ACh agonist, may affect hippocampus, frontal lobes

**Increased anxiety & panic attacks** (via activation of cingulate gyrus & locus coeruleus, the latter structure related to control of vigilance, alertness, REM sleep, major source of ACh)

Nicotine may have an antidepressant effect...implications

There are many co-morbidities (dual Dxs) with smoking:
- Conduct disorders, ADHD/ADD, depression
- Smoking & adverse childhood events (divorce, mentally-ill parent, jailed parent, abuse, battering, etc.)
5. Tolerance & Dependence

*does not show much biological tolerance to physiological effects*
although does develop tolerance to nausea/vomiting
*does develop tolerance to reinforcing effects* --- increasing drug doses

does develop dependence --- *adverse withdrawal Sxs* upon D/C drug
thus, is aversive to D/C drug
use of nicotine patches help with w/d effects (2x success rate)
adverse w/d responses *can last many months after D/Cd drug*:

- irritability
- decreased concentration
- increased appetite
- anger
- restlessness
- weight gain
- anxiety
- impatience
- insomnia, fragmentation
	often increases use of caffeine when w/ding from nicotine

6. Toxicity

**acute toxicity (=> 10 mg):**

- nausea
- cold
- disturbed vision
- salivation
- sweaty
- disturbed hearing
- abdominal pain
- headache
- mental confusion
- vomiting
- dizziness
- muscle weakness
- diarrhea
- faintness
- labored breathing
- hypotension
- irregular EKG
- weak/rapid pulse

**chronic toxicities:**

- increased risk of cancer, esp. to lungs, bladder, mouth, tongue, etc.
- increased risk of pulmonary diseases (e.g. COPD, emphysema, asthma)
- increased risk of cardiovascular disease
  - increased CO exposure --- heart muscle anoxia
  - increased atherosclerosis (narrowed arteries) --- heart muscle anoxia
  - increased risk of thrombosis (clotting, “sticky” platelets)

above are all increased even more in pt. w/ dual diagnosis of diabetes

summary – increased risk of blockage of vital arteries to heart/brain
**STIMULANTS: Nicotine** (p.7)

6. **Toxicity** (cont.)

   and blockage of blood supply to rest of body areas/organs as well
   450,000 persons die/year of smoking-related causes
   “passive smoke” inhalation also a major health risk
   4,000 deaths/year due to lung cancer in non-smokers
   37,000 deaths/year due to heart disease in non-smokers

7. **Pregnancy & Reproduction**

   nicotine reduces fertility & conception (interferes with fallopian cell
   cilia)
   increased risk of spontaneous abortions, stillborns
   increased risk of post-partum deaths
   increased risk of preterm deliveries
   decreased rates of intrauterine growth rates (up to 40%)
   increased low birth-weight babies (although normal by 1½ years)

   2,000 infant deaths/year rel. to mother smoking
   *fetal hypoxia* (high CO levels, low O2 levels)

   increased risk of lowered IQ in child, increased risk of Dx of ADHD/ADD,
   & other behavioral problems later on (as damaged brain areas come
   “on-line”?)

   could mother smoking during pregnancy lead to changes in fetal RSs?
   greater risks for addictions, depression, conduct disorder, etc.?

8. **Miscellaneous**

   cigarette smoke is made up of 4,000+ *compounds* (from tobacco & paper)
   including CO, CO2, ammonia, cyanide, formaldehyde, nicotine, tars
   and others
   more than 43 *known carcinogens* with the 4,000+

   smokers, esp. heavy smokers *titrate their dose levels* w/i a range
9. Therapy for Nicotine Dependence

quitting – not easy…
success rates @ 6 months are 22-42%
success rates of smoking cessation clinics is 12-28%
of 41 million ex-smokers in USA, 90% quit on their own

use nicotine replacement (w/ transdermal patches, gum, nasal sprays, inhalers)
helps to slow down process of readjustment (up/down regulation of RSs, etc.)

use DA/5HT/NE agonists to help reduce “cravings”

Wellbutrin, Zyban (buproprion)
this drug inhibits reuptake of DA & NE
SEs includes increased risk of seizures
note: naloxone increases cravings…implies endogenous opioids involved somehow

use antidepressants (e.g. SSRI) if depression is also present

support groups, behavioral charting, cognitive therapy, etc.
e.g. avoiding triggers (e.g. coffee, ETOH, driving)

10. Is nicotine “good” for anything?... Yes!
a pesticide/insecticide
smoking correlated with lowered risk of PD & Alzheimer’s disease