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)

where ever 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)

STIMULANTS: Nicotine (p.3)

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 though 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 blood-stream --- 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.)

STIMULANTS: Nicotine (p.6)

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 adversive 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

STIMULANTS: Nicotine (p.8)

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