1. **Tetrahydrocannabinol (THC)**
   active ingredient in marijuana (MJ)
   now classified as an anandamide partial agonist (ligand)
   420+ ingredients in smoke from MJ
   psych. active ingredients include THC, cannabionol, & cannabidiol
   (cannabinoids – synthetic THC mimics)

2. **Anandamide**
   1992 ligand was isolated
   prior to 1992 MJ had been classified as a mild sed-hyno, sort of = to
   BZDs or ETOH
   although even high doses of MJ do **not** suppress respiration, not lethal
   little cross-tolerance with GABA agonists

3. **Unique Effects**
   decreased attention span decreased motor control
   decreased STM increased appetite (?)
   changes in sensory awareness increased bronchodilation
   analgesia decreased body temperature
   decreased Sxs of RA decreased libido & sperm count(hi dose)
   decreased nausea, vomiting decreased fertility (hi doses)
   decreased androgens (secondary gyncomastia at hi doses)

4. **Mechanisms of Action**
   THC --- indirectly **inhibits adenylene cyclase**
   adenylene cyclase involved in G-protein 2\(^{nd}\) messenger RSs
   which normally --- influx of Ca++ and efflux of K+
   with this pathway inhibited, there is less release of NTs from presynaptic
   axon terminals
   THC --- also decrease release of glutamate in hippocampal neurons --- ?

   there are many anandamide RSs in CNS, maybe 10-20x the # of opioid RSs
   may be tied with GABA as most numerous RSs (≈ 1/3 of all RSs)
5. **Major CNS Areas with THC Effects**
   - hippocampus (--- decreased STM)
   - cerebral cortex (esp. frontal lobes) (--- attention span, distorted sensory perceptions)
   - cerebellum & basal ganglia (decreased motor performance)
   - spinal cord (--- analgesia)
   - “none” in brainstem (medulla) (no effect on respiration, heart)
     but must have some effect on medulla…why?

6. **Major PNS Areas & Others with THC Effects**
   in PNS have both cannabinoid RS1s and RS2s
   - RS2s are found in lymph cells (WBCs) (depressed I.S. functioning?)
   in heart, lungs, arteries, endocrine system, & reproductive organs
   - increased HR, BP, vasodilation
   - bronchodilation
   - decreased sperm count, libido, gynecomastia

7. **Pharmacokinetics**
   - ¼ to ½ of THC is available in smoke
   - one MJ “joint” = 0.4 to 10 mg of THC into bloodstream
     (assuming 1 gram of plant material & 50 mg of THC)
   - rapid onset of effects when smoke **inhaled** (about 5 seconds)
   - bodily effects last about 3-4 hours when inhaled (e.g. effects on HR)
     but psych effects (“high”) can last 12+ hours
   - if taken **PO**, absorption is much slower and doses reduced
     - 30-60 minute onset latency
     - likely subject to 1st pass metabolism in liver
   - distributed through out body tissues, esp. into fat tissues (**very fat soluble**)
     easily crosses BBB & placenta
7. **Pharmacokinetics** (cont.)
   THC is metabolized by P450 enzymes --- active metabolite --- inactive metabolite --- eliminated
   this process extends ½ life of THC to **30-60 hours**
   thus, urine drug screens can be done for relatively long time after S MJ and still get a + result (2 to 14 days after, in acute user; 30 days for a chronic user…and even longer in an obese S)...why?

8. **Pharmacological Effects of THC**

   a. *in non-human animals*
      mice – bred to lack cannabinoid RSs --- higher mortality rates, decreased activity levels, increased sensitivity to pain

      cannabinoids **potentiate morphine-induced analgesia**
      THC --- decreased release of substance P, decreased release of glutamate --- decreased pain signals
      --- increased activity in “opiate” RSs --- decreased pain

      THC --- potentiates sed-hypn effects
      decreased aggression
      decreased seizures (increased seizure threshold)
      increased reaction times, decreased reflexes
      decreased motor performance on complex tasks
      increased hallucinations/sensory distortions (of time, audition, color, taste)
      increased social interactions
      increased eating
      at high doses --- decreased ovulation, decreased sex hormones, decreased sperm, decreased fertility
8. **Pharmacological Effects** (cont.)

b. *in humans*

**CNS effects** – perception of senses being enhanced
- time distortion (time duration is overestimated)
- increased sense of well-being, mild euphoria
- relaxation, usually reduced anxiety, sedation
- reduced RTs, reduced motor skills, poor coordination
- dissociation of ideas, deceased ability to focus
- decreased attention, decreased STM
- decreased cognitive function (reduced learn/memory)
- rare hallucinations (often visual)

**at high doses** – acute depression, panic reactions, mild paranoia

**long-term, chronic use:**
- some tolerance develops to motor effects & to cognitive effects
- but still show impairment of information-processing skills
- esp. cannot filter out irrelevant stimuli
- decreased spatial skills
- decreased ability to “map” the environment
- poor organizing skills, e.g. poor routines of daily living
- \( S \) feels out of control, alientated, life lacts focus/meaning
  (part of the “amotivational syndrome”?)
- note: above all show improvement when d/c drug
  back to baseline?...

**addiction:** Is MJ addicting?

THC does --- increased release of DA in reward/attentional focus
brain areas (basal ganglia, nucl. Accumbens, prefrontal cortex)
& maybe increases activity at the \( mu \) opioid RS (ventral
tegmentum) --- **so concern re. dependency is warranted,**
based on CNS mechanisms…
8. **Pharmacological Effects** (cont.)

“*amotivational syndrome*” seen in heavy chronic MJ users may really be depression…

**Cardiovascular** effects:
- increased BP & HR, peripheral vasodilation --- decrease in BT
- no lethal/dangerous effects usually, TI = 1000

**Pulmonary** effects:
- no risk of respiratory depression
- increased risk of lung damage if MJ smoked
  - MJ has tars/carcinogens > tars/carc. in tobacco!
  - bronchial irritation & inflammation (& dilation)
  - thus, despite dilation, is overall not helpful for asthma when inhaled

**Immune System** effects:
- immunosuppression (as also do other sed-hypns)
- inhibit in particular *NKC*s (tumor-killing cells)

**Reproductive System** effects:
- in males --- decreased testosterone & sperm
- in females --- decreased FSH, LH, & ovulation
- decreased fetal growth/maturation (mild effect)
- may decrease executive (frontal) functioning in child (4 yrs +)
  - if child was exposed prenatally (poor planning, organizing, impulse control)
9. **Tolerance & Dependence**

Tolerance does occur via:
- **down-regulation** (# & sensitivity) of cannabinoid RSs
- with synthetic agonists, see rapid RS “internalization” process
  (RS protein taken back into cell?)

When d/c MJ --- **w/d effects** (so dependence does occur)
- restlessness
- irritability
- anxiety
- insomnia
- agitation
- depression
- anorexia
- nausea, abdominal cramping
- increased sleep disturbances
- drug craving

w/d effects begin about **2 days after d/c**…why so long?
w/d effects last about 4-6 days

As with other drugs, user often uses MJ + other drugs
User often has co-morbid Sxs of w/d that are a combination of MJ w/d
plus w/d from other drugs

10. **Clinical Uses of THC**
**dronabinol** (Marinol) – synthetic THC
- increase appetite (e.g. in anorexic cancer pts)
- decrease nausea, vomiting (e.g. in chemotherapy pts)
- decrease muscle spasms (e.g. MS pts)
- decrease pain (e.g. MS, cancer, RA)
- suppress IS (e.g. RA, MS pts)
- decrease intraocular pressure (e.g. glaucoma pt)
- decrease glutamate release (e.g. post-stroke pts, head trauma)