

MARIJUANA

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Pre-Lecture Exam

1. Cannabis use can lead to all except:
 - a. Euphoria
 - b. Impaired memory
 - c. Weight gain
 - d. Altered perception
 - e. Anxiolysis

Pre-Lecture Exam

2. Cannabis has been used as a therapeutic agent for the following conditions:
 - a. Extreme nausea
 - b. Increased intraocular pressure
 - c. Inflammation
 - d. AIDS-related wasting
 - e. All of the above

Pre-Lecture Exam

3. Which of the following is/are not true:
- a. About 40% of Americans over the age of 12 have tried marijuana
 - b. A single joint can lead to a positive urine test for 8-96 hours
 - c. It is absolutely legal to prescribe marijuana in some states, but not in others
 - d. Marijuana is Schedule 1 substance under the Controlled Substance Act E
 - e. All of the above statements are false

Pre-Lecture Exam

4. Which statement about cannabinoids is/are true:
- a. Cannabinoid agonists can be used for the treatment of obesity
 - b. Cannabinoid antagonists can be used to treat nausea associated with chemotherapy
 - c. Cannabinoid CB1 receptors can be found in the basal ganglia, cerebellum, hippocampus, and cortex D
 - d. All of the above are true

Pre-Lecture Exam

5. Which is true about schizophrenia and cannabis:
- a. The risk for developing schizophrenia is higher for those using cannabis at an early age versus those starting in late adolescence
 - b. The risk for developing schizophrenia is highest for those who use cannabis at an early age and who have the MET-MET COMT genotype
 - c. The risk for developing schizophrenia is higher for those using alcohol at an early age versus those starting in late adolescence.
 - d. All of the above are true

Pre-Lecture Exam

6. Which is true about the endocannabinoids:
- a. In addition to THC, CB receptors respond to endogenous anandamide, which produces similar effects but is less potent.
 - b. In USA, THC content has increased from <2% in 1980, to 8.5% in 2006.
 - c. Amount of THC delivered to lungs varies between 20% and 70%, and to brain, between 5% to 25%.
 - d. The most common adverse effects marijuana are anxiety, panic reactions, and psychosis.
 - e. All of the above.

Teaching Points

- Cannabis has potentially toxic effects regarding cognition, bronchopulmonary irritation, endocrine changes, and immunomodulation
- Cannabis has been used as a therapeutic agent as an antiemetic, for glaucoma, as an analgesic, as a muscle relaxant, and as an anti-inflammatory agent
- Although theoretically “legalized” in several states for medicinal use, cannabis remains a Schedule 1 substance under the Federal Controlled Substance Act, and thus illegal outside an FDA-approved research program

Teaching Points (cont.)

- Synthetic cannabinoid agonists (for example, dronabinol) are commercialized and FDA-approved for chemotherapy-related nausea and AIDS-related wasting
- Cannabinoid antagonists (for example, rimonabant, not approved in the US) may be useful for the treatment of obesity and possibly substance use disorders
- There may be a gene x environment interactions regarding cannabis use and the development of schizophrenia

Outline

- What is marijuana?
- Desirable and undesirable cognitive effects
- Therapeutic and toxic somatic effects
- Chemistry and pharmacokinetics
- Synthetic THC
- Cannabinoid receptors
- Cannabinoids and obesity
- Cannabis and schizophrenia

Marijuana = Dried and shredded *Cannabis sativa* (hemp)

- Native of Central Asia, now worldwide
- Blooming buds of the female plants: highest concentration of THC
- Smoked (joints, bong and blunts) or eaten



Clinical effects - cognitive

Desirable effects

- Euphoria : *“high”*
- Anxiolysis: *“mellowing out”*

Toxic effects

- Disorientation
- Unsteady coordination
- Amotivational syndrome
- Memory loss
- Altered perception
- Decreased consciousness
- But, low lethal potential

Clinical effects - somatic

Therapeutic effects

- Anti-emetic
- ↓ intra-ocular tension
- Analgesic
- Muscle relaxant
- Anticonvulsant
- Anti-inflammatory
- ↑ appetite: “the munchies”

Toxic effects

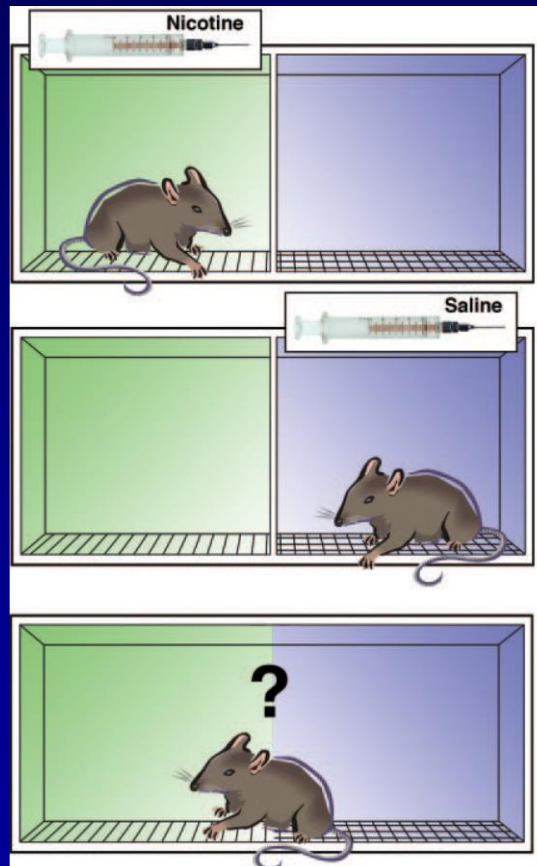
- Xerostomia, Hypohydrosis, Hypertension, Tachycardia
- Conjunctival Irritation
- Bronchopulmonary Irritation
- Endocrine changes
- ↓ Immunomodulation
- LD 50% in rats > 1200 mg/kg

Are cannabinoids like other drugs of abuse?

Preclinical data: YES

Clinical data: Equivocal

- ✓ Is self administered
- ✓ THC seeking can be reinstated over delay
- ✓ ↑CRF & BSR (“brain stimulation reward”)
- ✓ Dopamine
- ✓ Produces Conditioned Place Preference (CPP)



- **Tolerance** rapid on/off
- **Withdrawal syndrome:** atypical, mild
- **Dependence:** Only 9% of those who ever used

Chemical constituents of Cannabis

Chemical classes

Cannabinoids (66)

Nitrogenous compounds (27)

Amino acids(18)

Proteins/ enzymes (11)

Sugars (34)

Hydrocarbons (50)

Simple alcohols (7)

Simple aldehydes (12)

Simple ketones (13)

Simple acids (21)

Fatty acids (22)

Simple esters/lactones (13)

Steroids (11)

Terpenes (20)

Non-cannabinoid phenols (25)

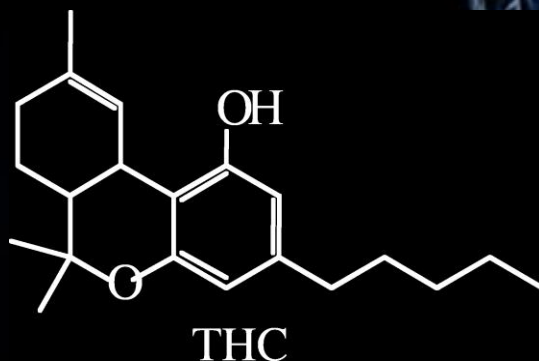
Flavoroids (21)

Vitamins (1)

Pigments (2)

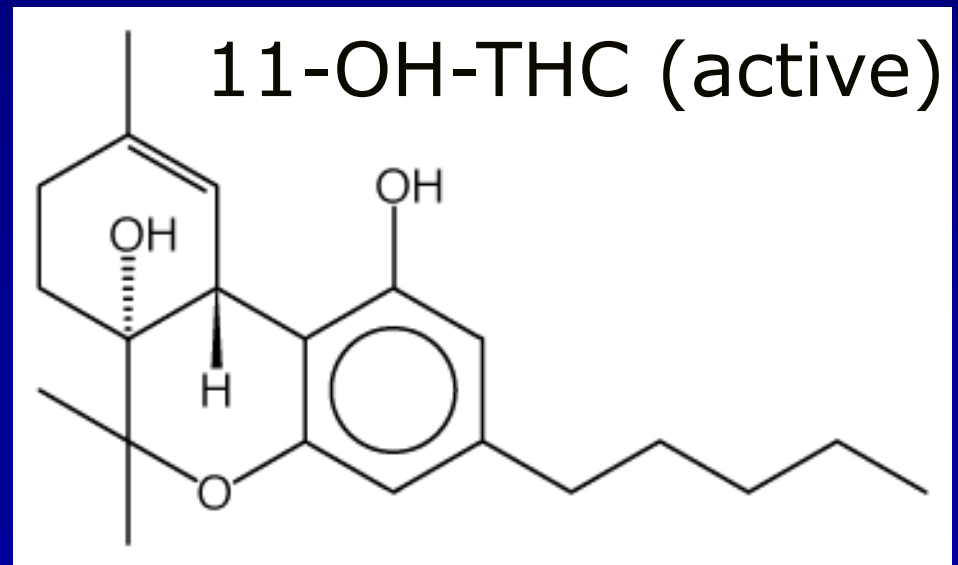
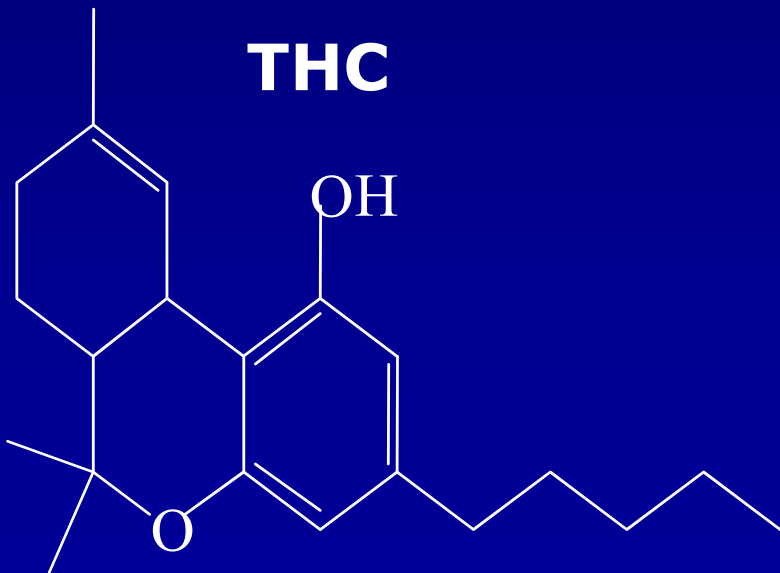
Elements (9)

Total known compounds (483)



- Delta-9-tetrahydrocannabinol (**THC**) is the active ingredient of marijuana
- major metabolites **OH-THC** (11-delta-9-THC) and **THC-COOH** (11-nor-delta-9-THC-carboxylic acid, inactive)

Levo is the more active isomer



Epidemiology: *The Demand*

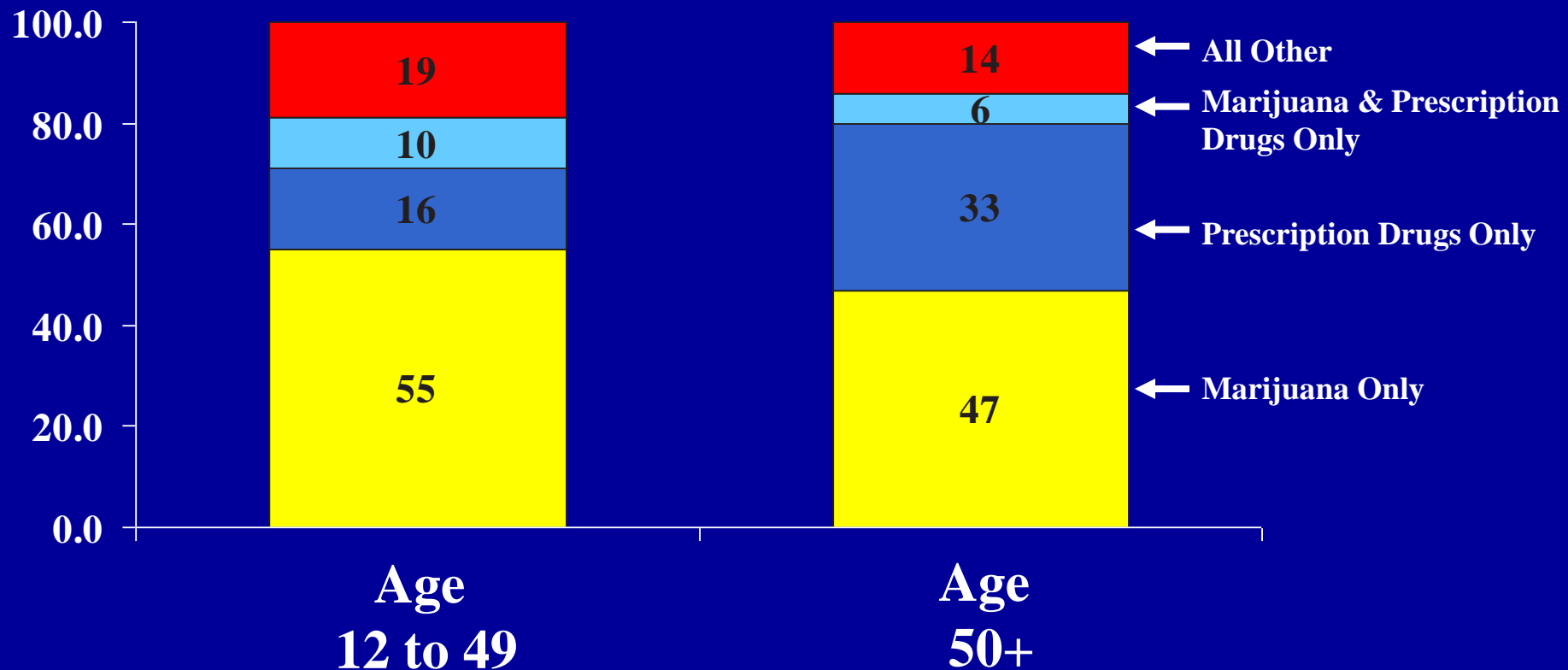
- Most common illicit psychoactive drug worldwide
- 94 million Americans (40 %) over the age of 12-years have tried marijuana

(National Survey on Drug Use and Health, 2003)

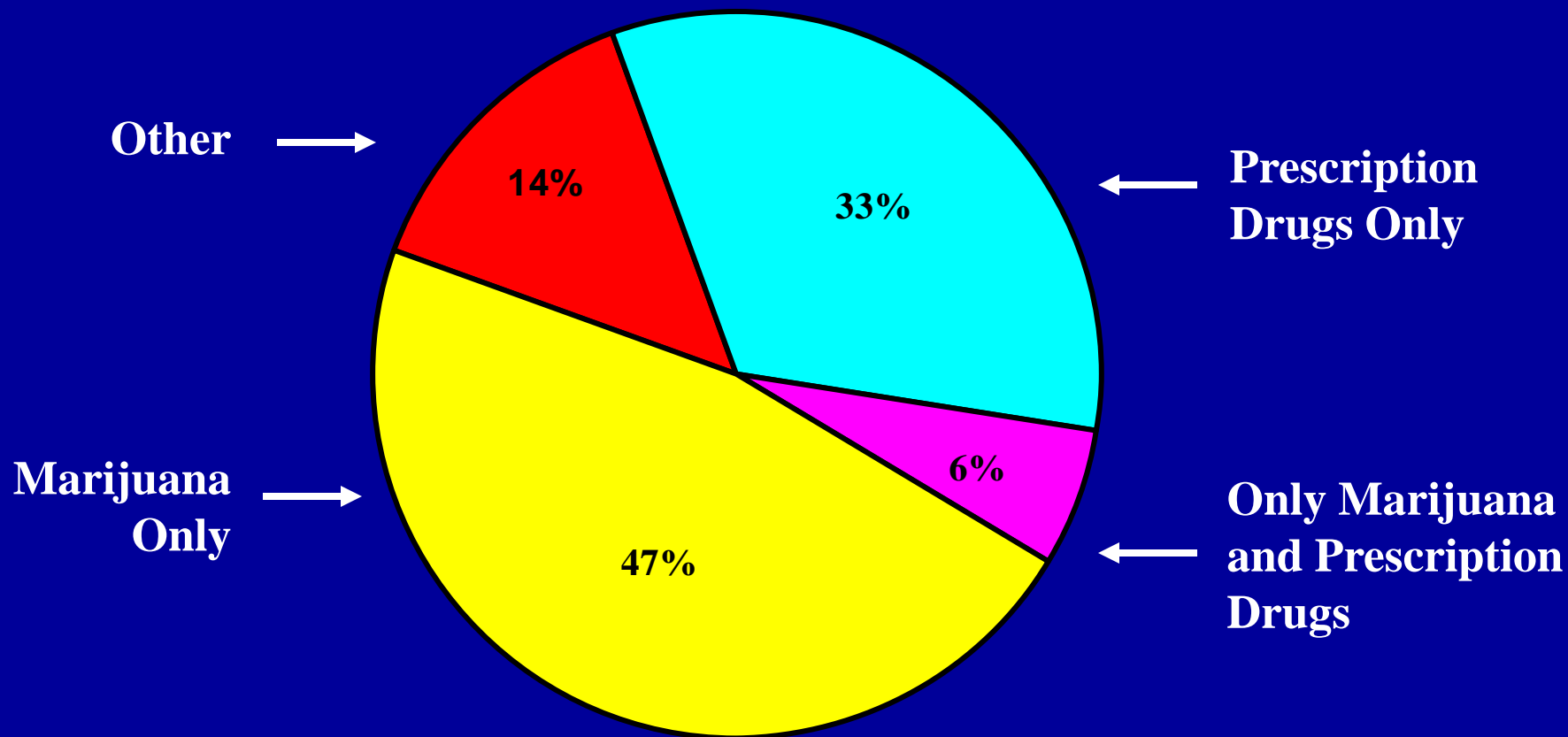
<http://www.marijuana-info.org>

Types of Drugs Used by Past Month Illicit Drug Users: Age 12 to 49 and 50+, 2002-2003 Annual Averages

Percent of Current Users



Types of Drugs Used by Past Month Illicit Drug Users: Age 50+, 2002-2003 Annual Averages

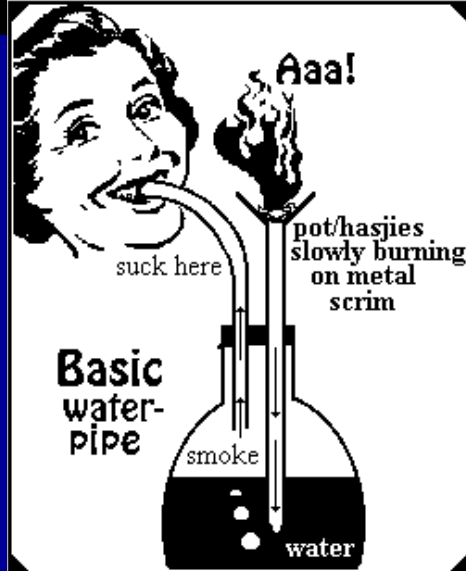


1.4 Million Illicit Drug Users (1.8%)

THC Content in street preparations

> 4% Marijuana

30% Hashish



\$10 billion spent in the US in 2000
\$70 to \$1,200 per pound, \$600 to \$4,000 for sin-semilla

The Supply

- All 50 States, Puerto Rico and Guam reported cannabis cultivation
- Indoor hydroponic operations in every State and Puerto Rico
- Major foreign sources: Mexico (7900 metric tons), Canada, Colombia, and Jamaica (200 metric tons)

Absorption, Metabolism & Elimination

- Psychotropic threshold > 25 ng/ml
- Peak plasma **levels** > 100 ng/ml drop to < 2 ng/ml in 4 hours
- Psychotropic effects lag the plasma level after inhalation
- Peak **effect** (inhaled) <10 min
Peak **effect** (ingested) 2.5+ hrs (first pass yields OH-THC)

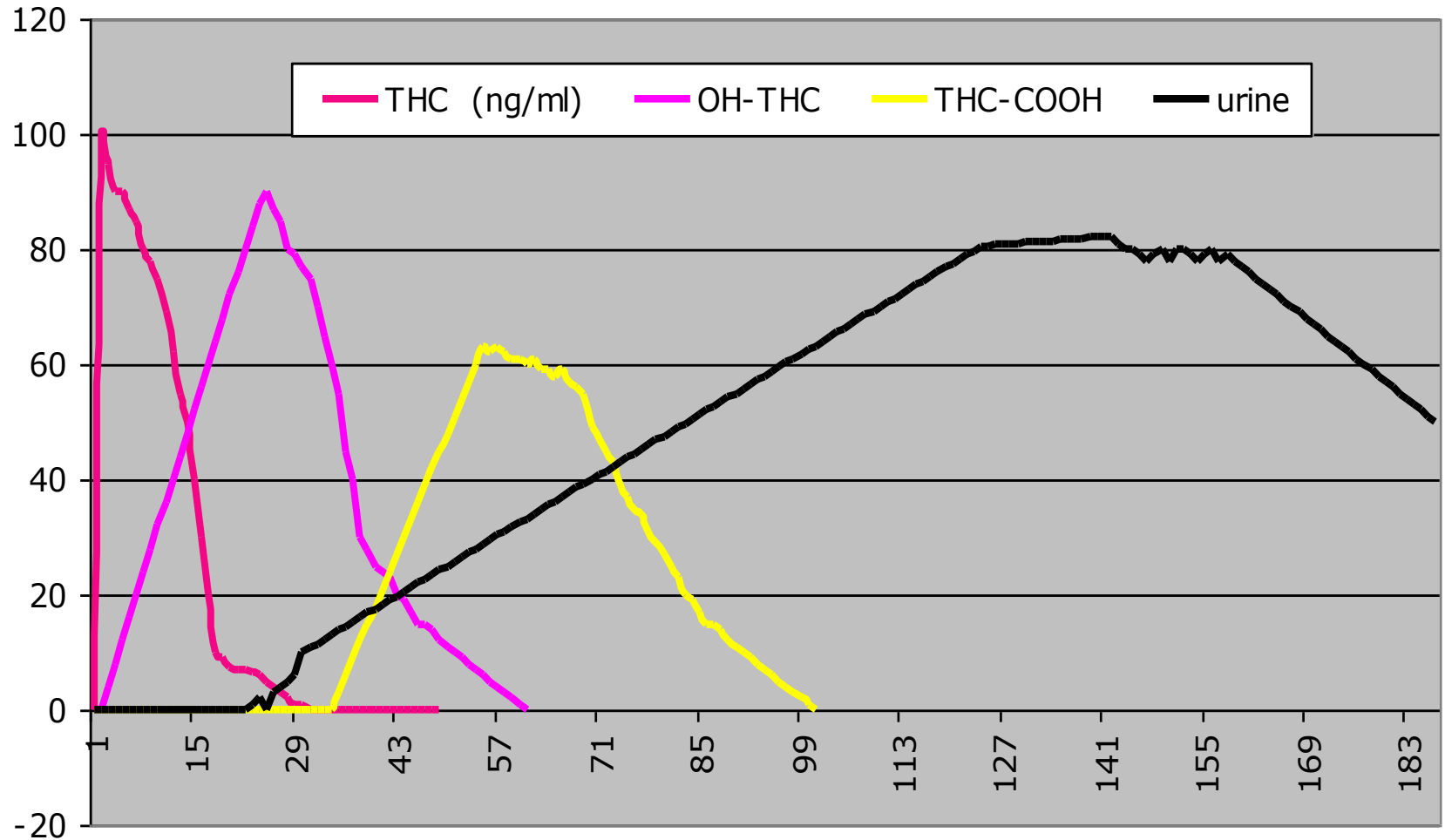
Absorption, Metabolism & Elimination

- Liver - CYT P450
- Lipophilic: redistributed in fatty tissues and could be released back into circulation
- Elimination: 35% urine, 65% feces

Detection

- **Screening** - Immunoassay in urine: sensitivity threshold is 50 ng/ml, does not discriminate THC from the metabolites
- **Confirmation** - Gas chromatography and other specific methods
- Single joint can lead to a positive urine test for 8-96 hrs
- Plasma but not urine samples are correlated with time and amount used

THC and metabolites in plasma and urine



Pharmaceutical THC: then and now

1930: American Cannabis USP “narcotic, analgesic, sedative...” Parke, Davis and Co

No longer legal in the US

2006: Sativex™ oral and spray

GW pharmaceuticals

(UK/Canada)



May I prescribe you a joint?



14 states legalized medicinal use with medical recommendation: AK CA CO HI ME MT NV NJ OR RI VT WA. 35 states allow use by prescription

BUT

Schedule I substance under the Controlled Substances Act: *high potential for abuse, no currently accepted medical use and a lack of accepted safety = illegal, except FDA - approved research programs*

so



Synthetic Cannabinoid Agonists

- **Dronabinol (Marinol)** is synthetic THC used to treat:
 - 1) Anorexia and weight loss in patients with AIDS
 - 2) Nausea and vomiting associated with cancer chemotherapy in patients who have not responded adequately to conventional antiemetic agents

Synthetic Cannabinoid Agonists

- Nabilone (Cesamet): THC analogue
Same indications as Marinol (UK)
- HU-210: x100 to 800 more potent than THC
- WIN-55,212-2: Binds to CB2 > CB1

Cannabinoid Receptors

G protein-coupled, with seven transmembrane regions

- **CB1**

Brain, fat cells, liver, duodenum, muscle

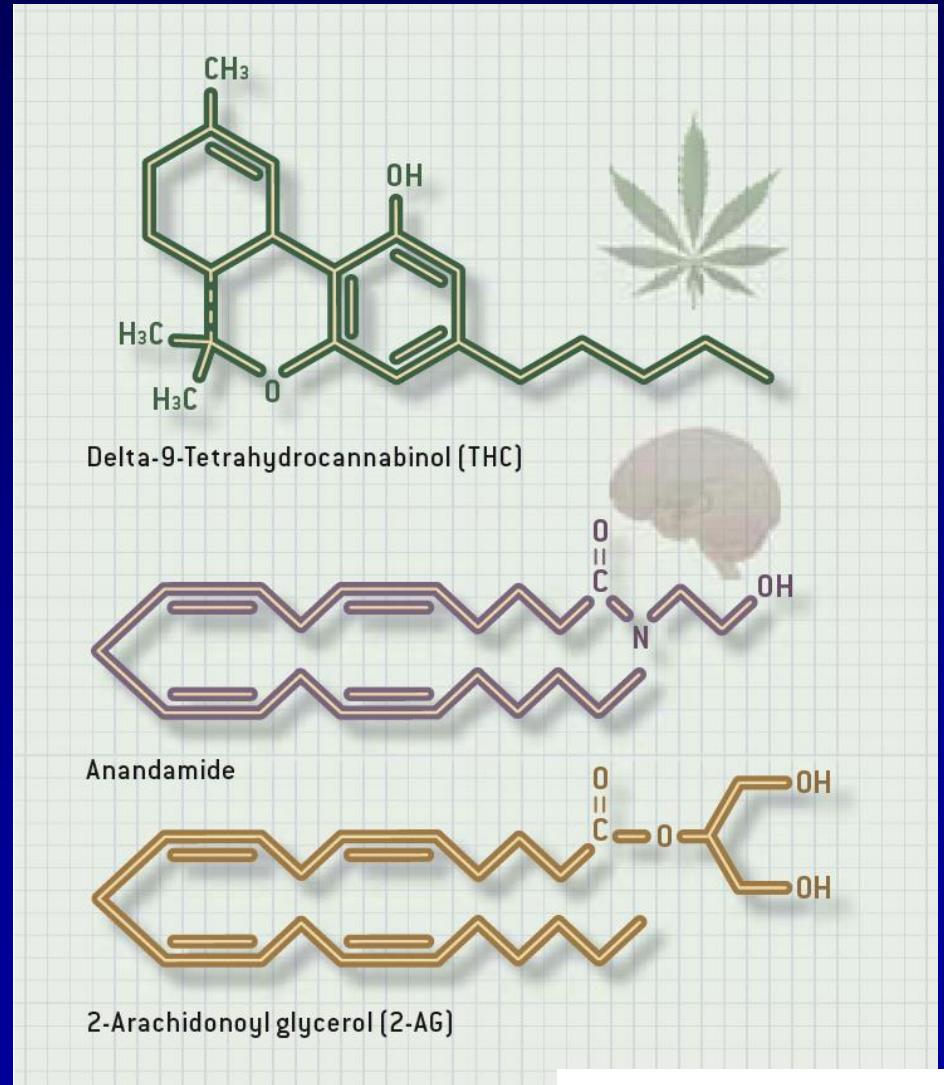
- **CB2**

lymphocytes>macrophages>cytokines

Endocannabinoids: Bind CB1 > CB2

structure, related to prostaglandins

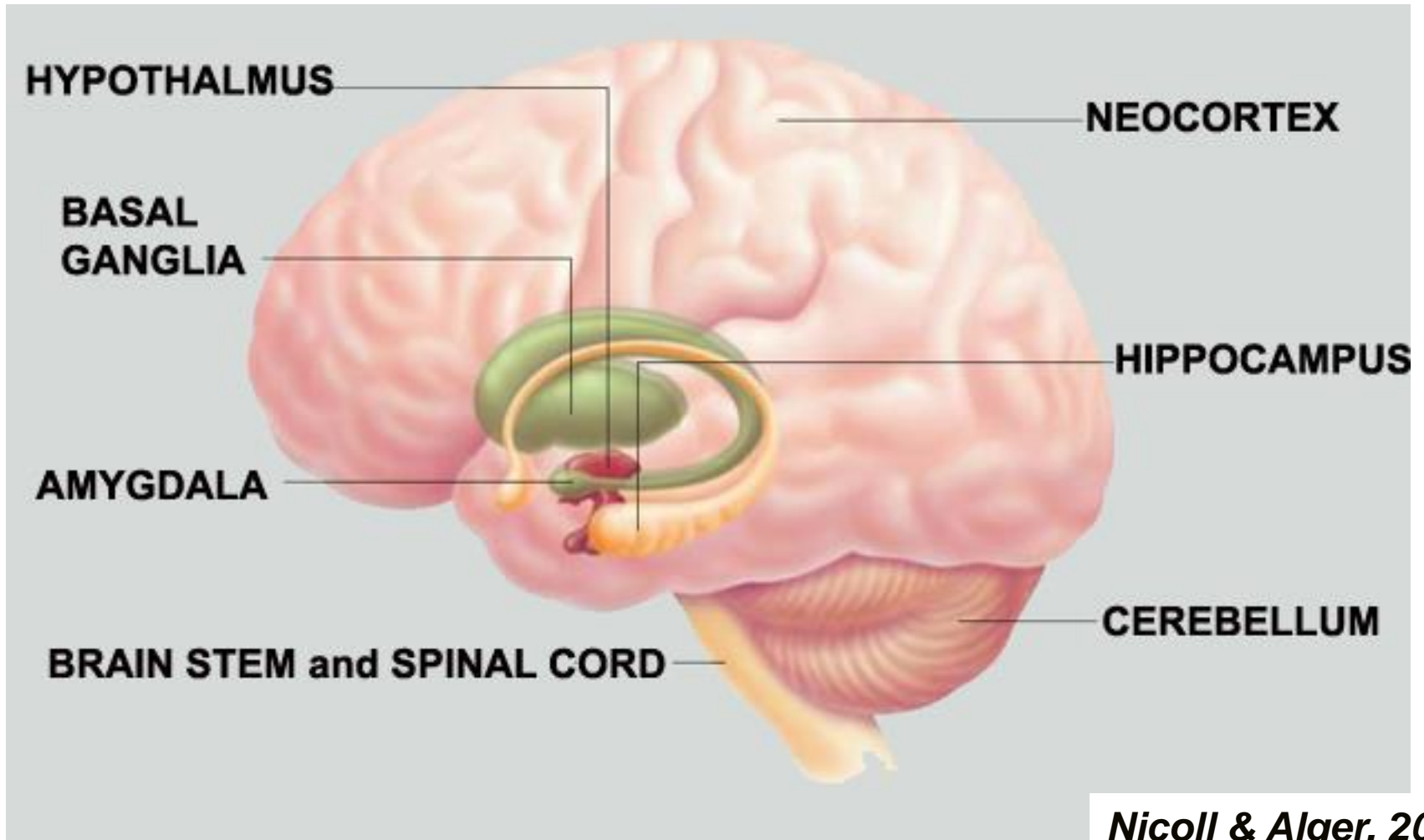
- Anandamide
(arachidonyl-ethanolamid)
- 2-Arachidonoyl -
glycerol (2-AG)
more abundant, less potent



CB1 receptor density in the brain

High density: Basal Ganglia, Cerebellum, Hippocampus, NAcc, Mid-Prefrontal, Parietal Cortex

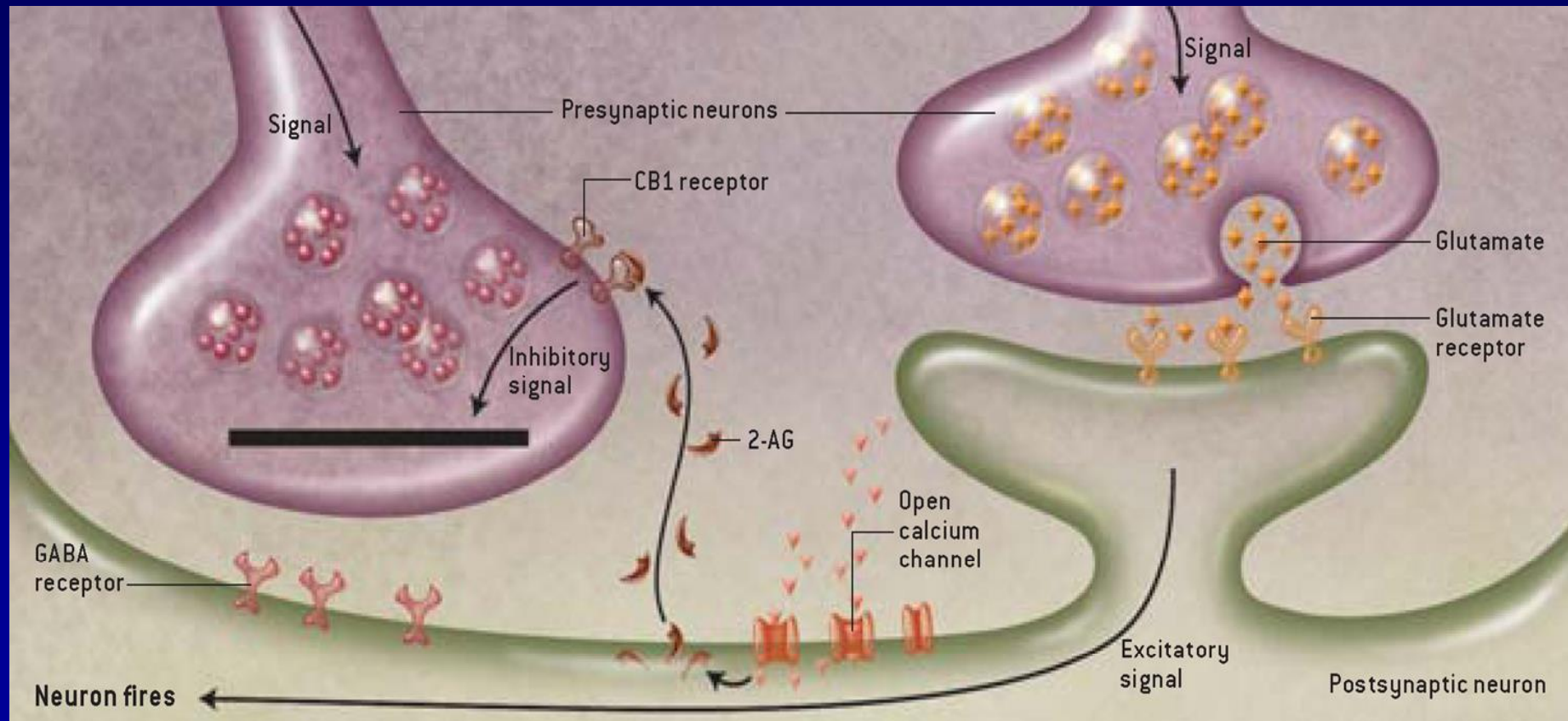
Moderate density: Amygdala, Spinal Cord, Brainstem



Nicoll & Alger, 2004

Depolarization-induced suppression of inhibition

POSTSYNAPTIC endocannabinoid release inhibits
PRESYNAPTIC GABA and glutamate release



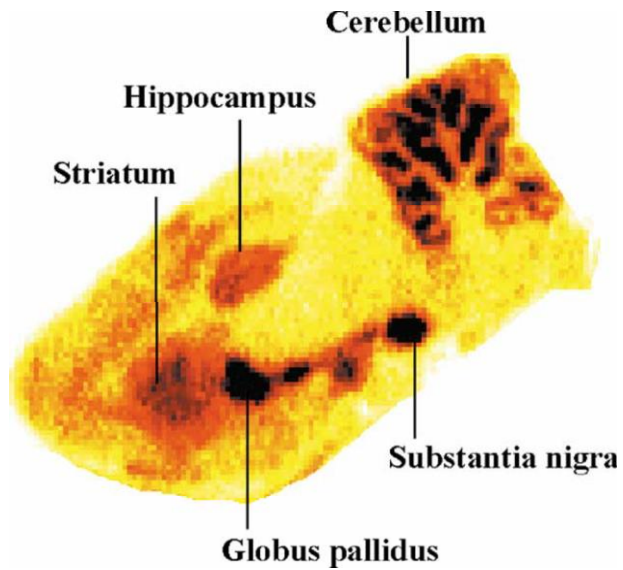
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Synthetic Cannabinoid Antagonists

SR 141716A (RIMONABANT, Phase 3 trials)

AM 281, AM 251 = CB1

SR 144528 = CB2



CB1 antagonists

Rimonabant

SPECT ligand

Obesity = Hyperactive endocannabinoid system?

Endocannabinoids and cannabis

- Induce appetite (orexigenesis)
- Reduce satiety
- Stimulate lipogenesis
- Reduce energy expenditure
- Increase hedonic reward value of palatable food

A CB1 antagonist should have opposite effects...

Treatment for Cannabis Dependence

- The demand for treatment at substance use disorder programs doubled between 1992 and 1998 in the United States.
- The percentage of illicit drug abuse treatment admissions for marijuana (23%) has approximated that for cocaine (27%) and heroin (23%) (1178).

Therapeutic potential of CB1 antagonists for substance abuse indications

- Blocks the direct reinforcing effects of some drugs of abuse and food
- Blocks the motivational effects (relapse prevention) of most drugs of abuse

Therapeutic potential of CB1 antagonists for substance abuse indications

- Preclinical:
 - SR141716 blocked conditioned place preference and reinstatement of drug seeking behavior to heroin and nicotine, but not cocaine (De Vries et al 2001)
- Clinical:
 - Rimonabant doubled smoking quit rates

Conclusions

- Marijuana delivery system (the “joint”) is more harmful than the substance itself (1999 IoM report)
- Relative to other illicit and legal psychoactive substances, the abuse and addictive potential of cannabinoids is modest

Conclusions

- Once separated from marijuana, cannabinoid agonists are a promising new class of compounds for a variety of non-psychiatric indications.
- Cannabinoid antagonists are a potentially important new class of compounds for the treatment of the disorders of motivation and reward system that include drug abuse and addiction.

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Pre-Lecture Exam

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 - b. Impaired memory
 - c. Weight gain
 - d. Altered perception
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Pre-Lecture Exam

2. Cannabis has been used as a therapeutic agent for the following conditions:
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Answers to Pre and Post Lecture Exams

1. C
2. E
3. C
4. C
5. A
6. E