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, bongs 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”

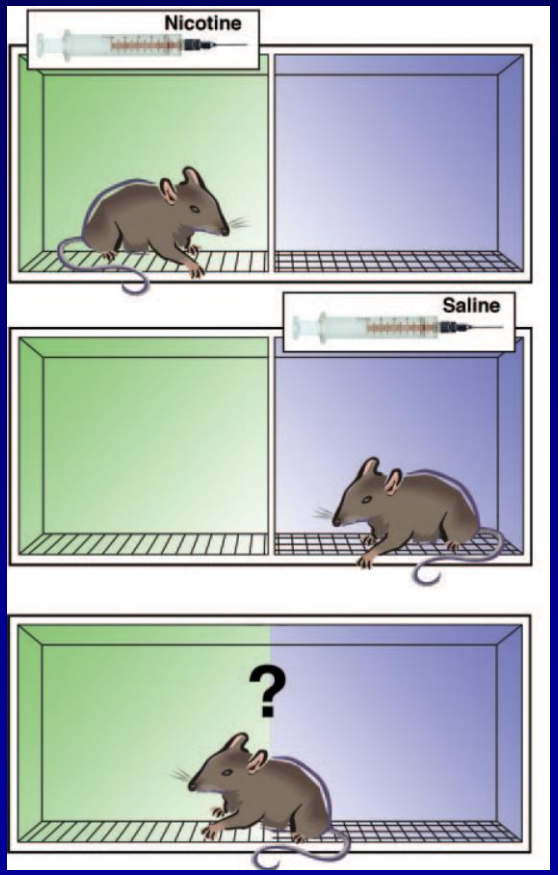
Toxic effects

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

Are canabinoids like other drugs of abuse?

Preclinical data: YES

- ✓ Is **self administered**
- ✓ **THC seeking** can be **reinstated** over delay
- ✓ **↑CRF & BSR ("brain stimulation reward")**
- ✓ **Dopamine**
- ✓ **P**roduces **Conditioned Place Preference (CPP)**



Clinical data: Equivocal

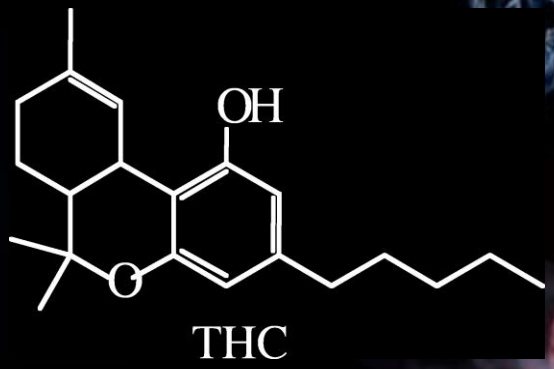
- Tolerance rapid on/off
- Withdrawal syndrome: atypical, mild
- Dependence: Only 9% of those who ever used

Le Foll & Goldberg 2005

Chemical constituents of Cannabis

Chemical classes

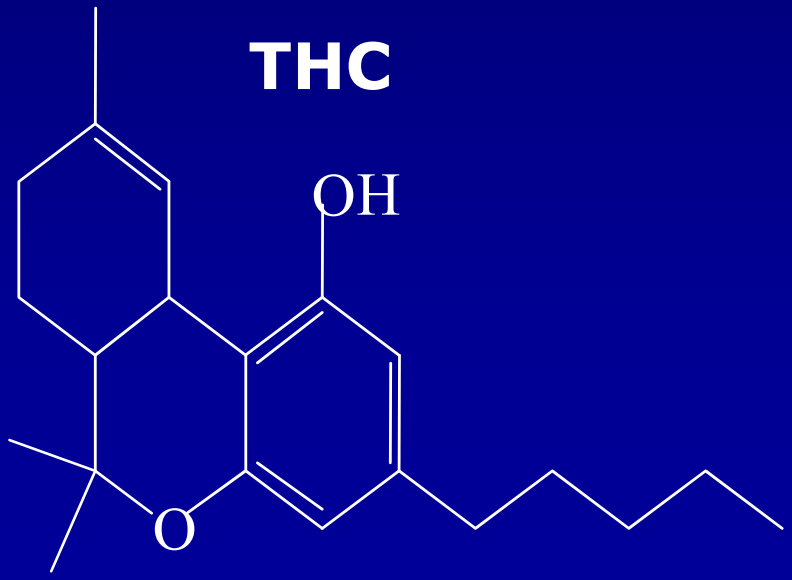
Cannabinoids (66)
Nitrogenous compounds (27)
Amino acids(18)
Proteins/ enzymes (11)
Sugars (34)
Hydrocarbons (50)
Simple alcohols (7)
Simple aldehydes (12)
Simple ketones (13)
Simple acids (21)
Fatty acids (22)
Simple esters/lactones (13)
Steroids (11)
Terpenes (20)
Non-cannabinoid phenols (25)
Flavoroids (21)
Vitamins (1)
Pigments (2)
Elements (9)
Total known compounds (483)

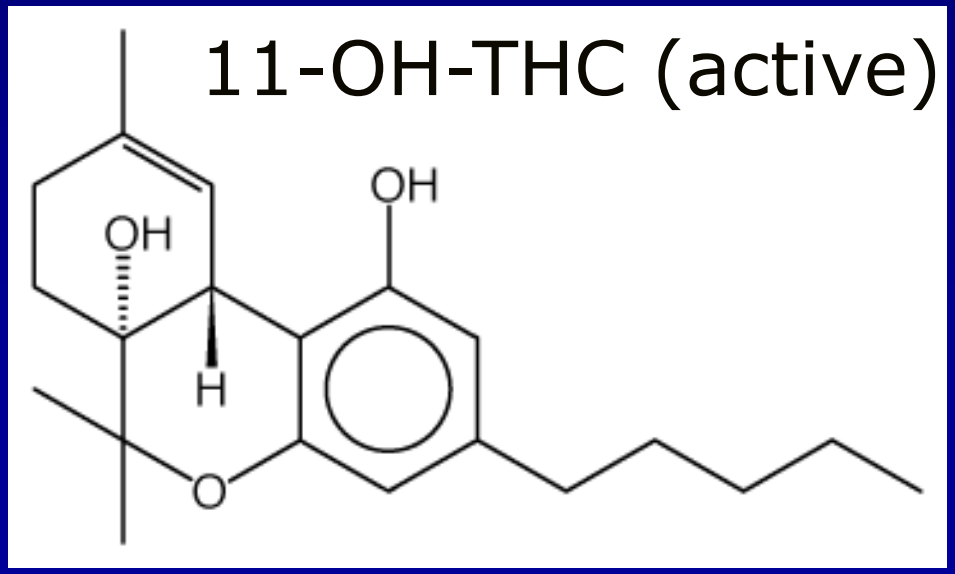


- Delta-9-tetrahydrocannabinol (THC) is the active ingredient of marijuana

- 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





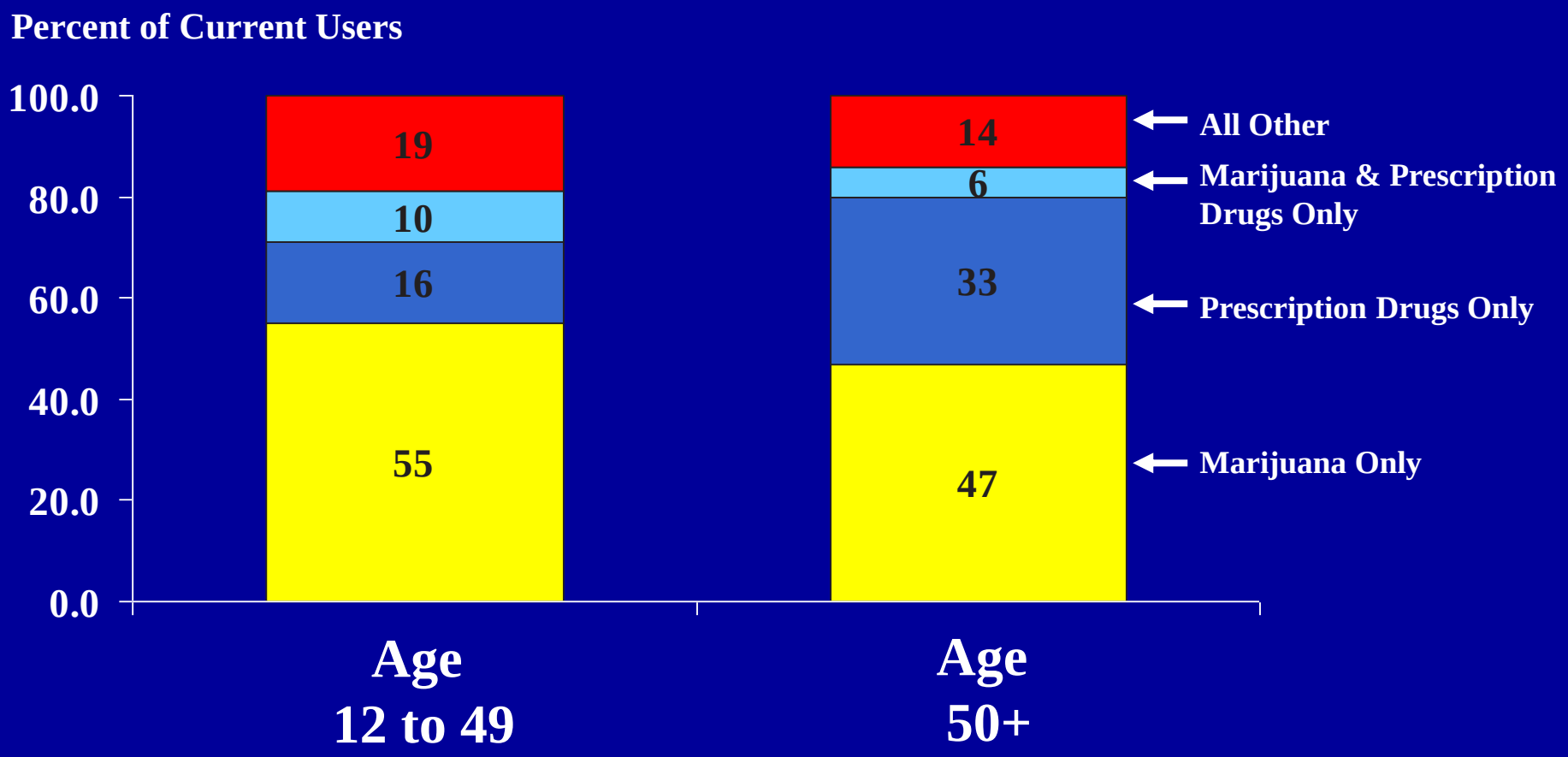
Epidemiology: *The Demand*

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

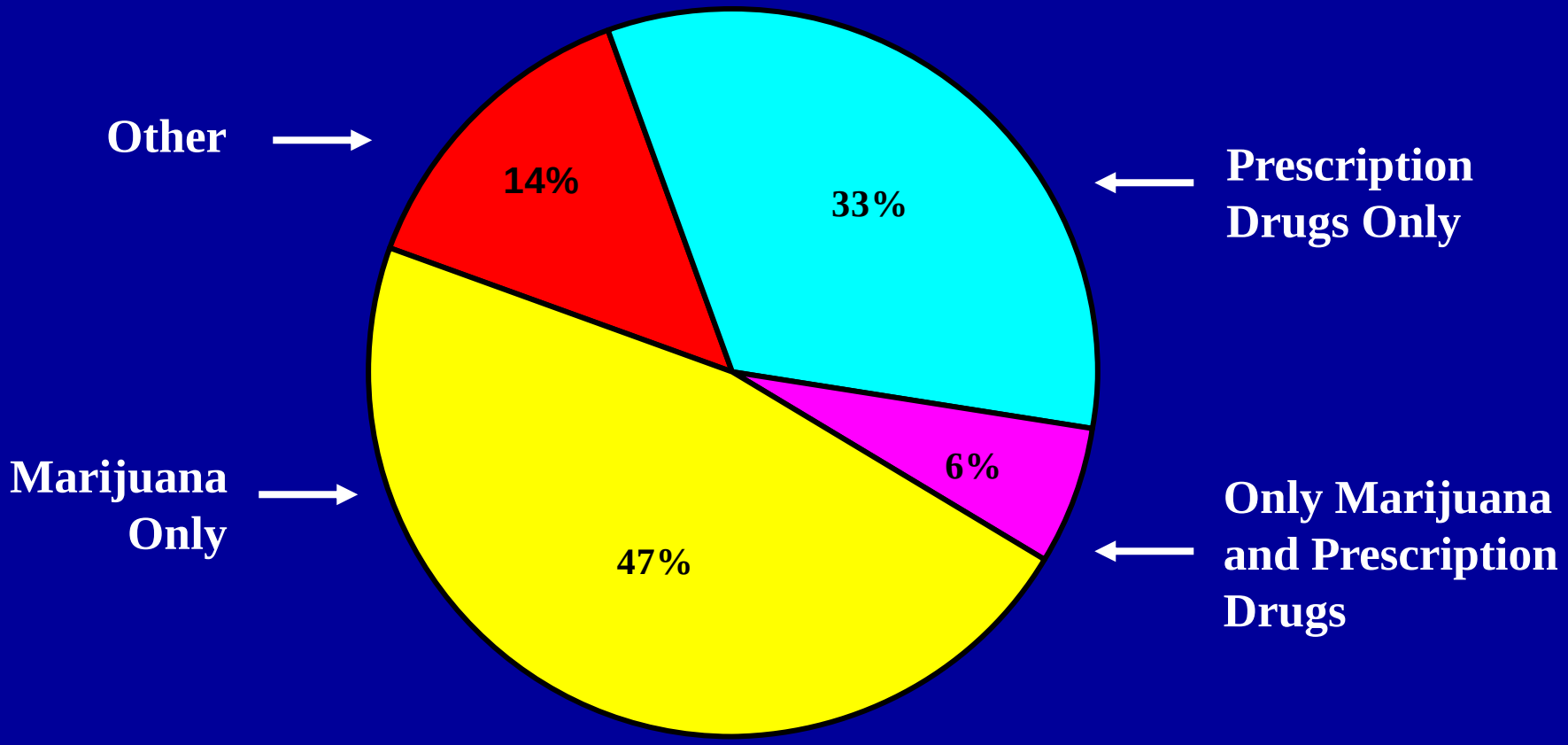
(National Survey on Drug Use and Health, 2003)

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



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

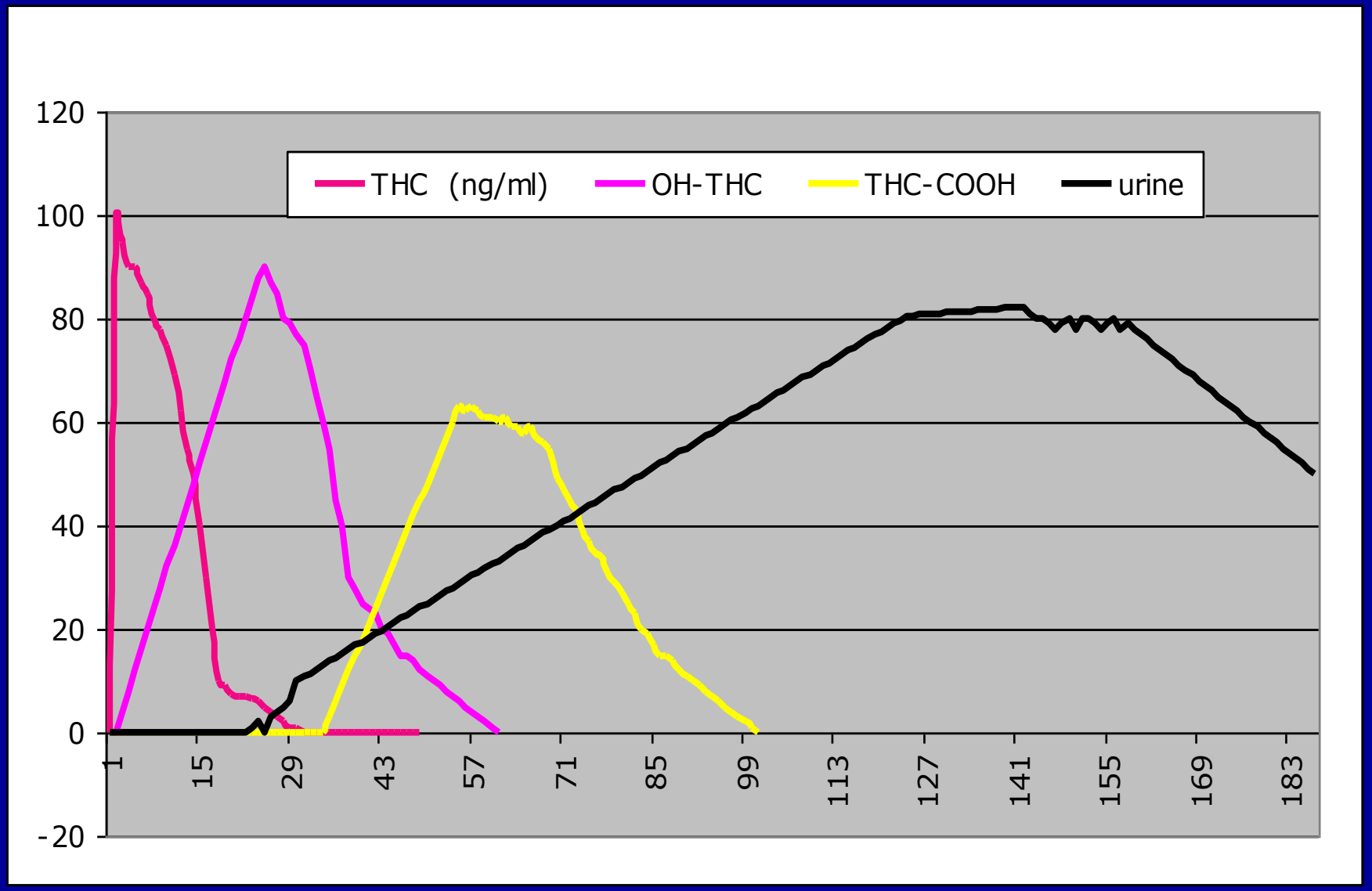
- Liver - CYT P450
- Lipophilic: redistributed in fatty tissues and could be released back into circulation
- Elimination: 35% urine, 65% feces

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

MMWR Weekly September 16, 1983 / 32(36);469-71
NHTSA Fact sheet 2002

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 <u>with medical recommendation</u>: 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 > CB 2*

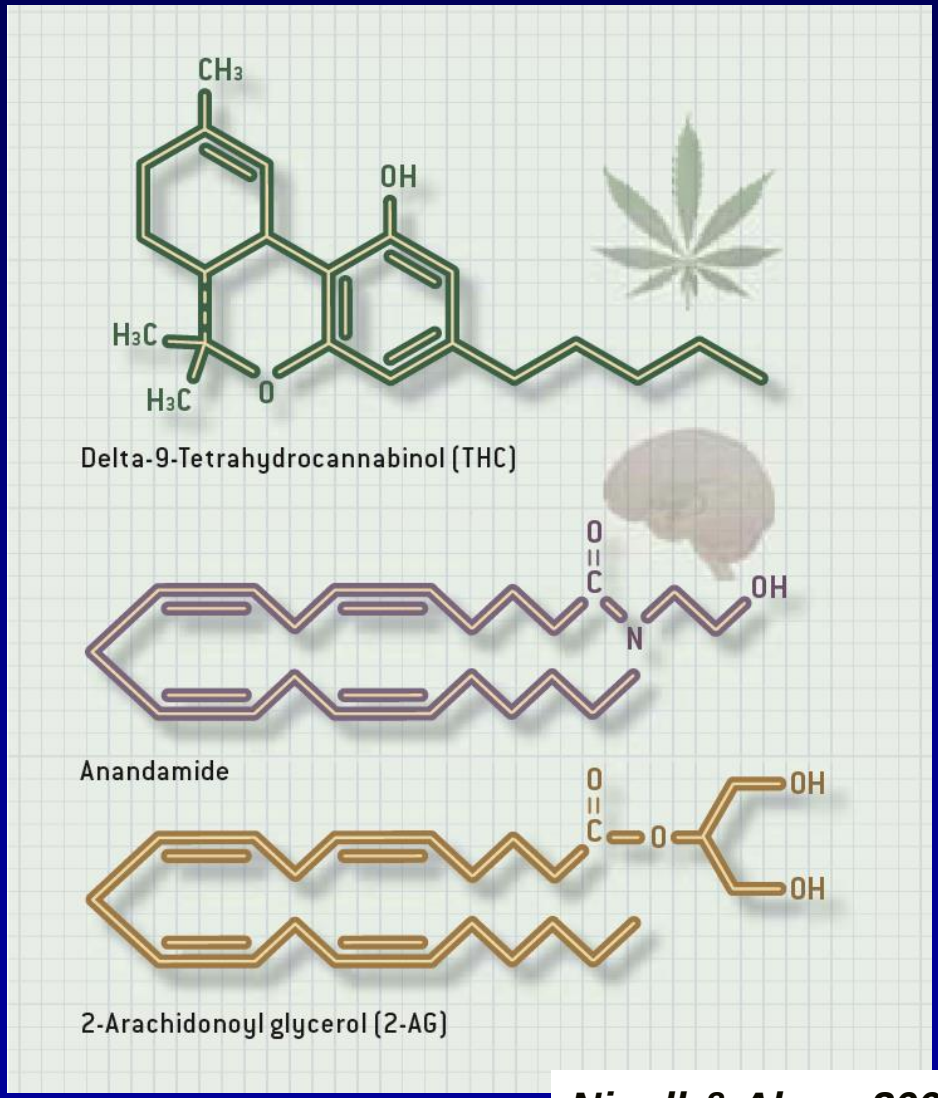
structure, related to prostaglandins

- Annandamide

(arachidonyl-ethanolamid)

- 2-Arachidonoyl - glycerol (2-AG)

more abundant, less potent

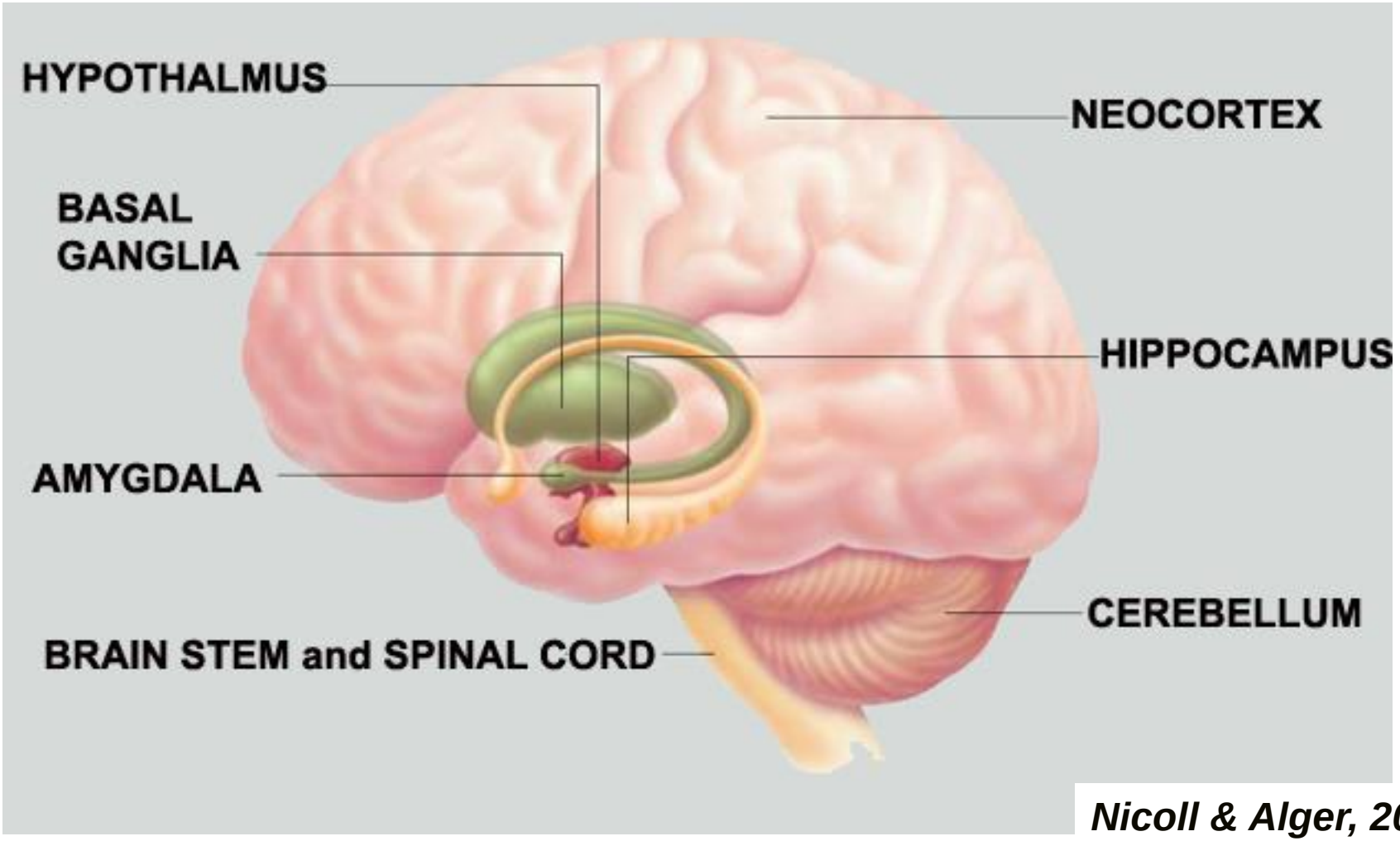


Nicoll & Alger, 2004

CB1 receptor density in the brain

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

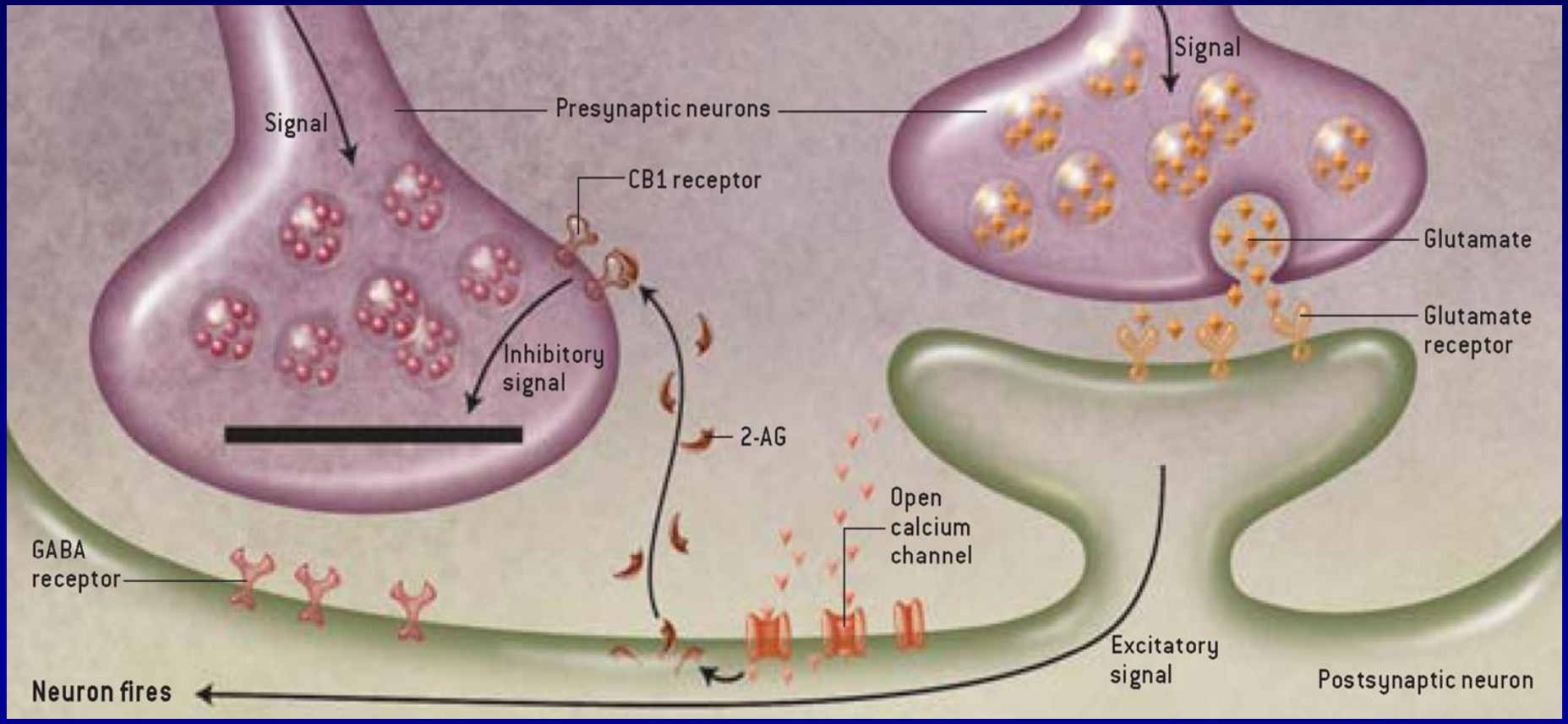
Moderate density: Amygdala, Spinal Cord, Brainstem



Nicoll & Alger, 2004

Depolarization-induced suppression of inhibition

POSTSYNAPTIC endocannabinoid release inhibits PRESYNAPTIC GABA and glutamate release



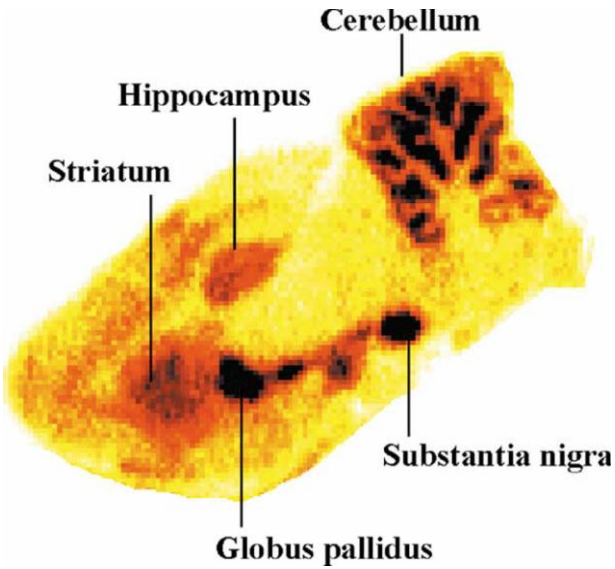
Nicoll & Alger, 2004

Synthetic Cannabinoid Antagonists

SR 141716A (RIMONABANT, Phase 3 trials)

AM 281, AM 251 = CB1

SR 144528 = CB2



CB1 antagonists

Rimonabant

SPECT ligand

Gifford AN, Makriyannis A, Volkow ND, Gatley SJ. In vivo imaging of the brain cannabinoid receptor. Chem Phys Lipids. 2002 Dec 31;121(1-2):65-72.

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

1. Cannabis use can lead to all except:
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   d. The most common adverse effects marijuana are anxiety, panic reactions, and psychosis.
   e. All of the above.

Answers to Pre and Post Lecture Exams

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