Pharmacokinetics and Pharmacodynamics of Cannabis

กัญชาทางการแพทย์
Cannabis in Modern Medicine

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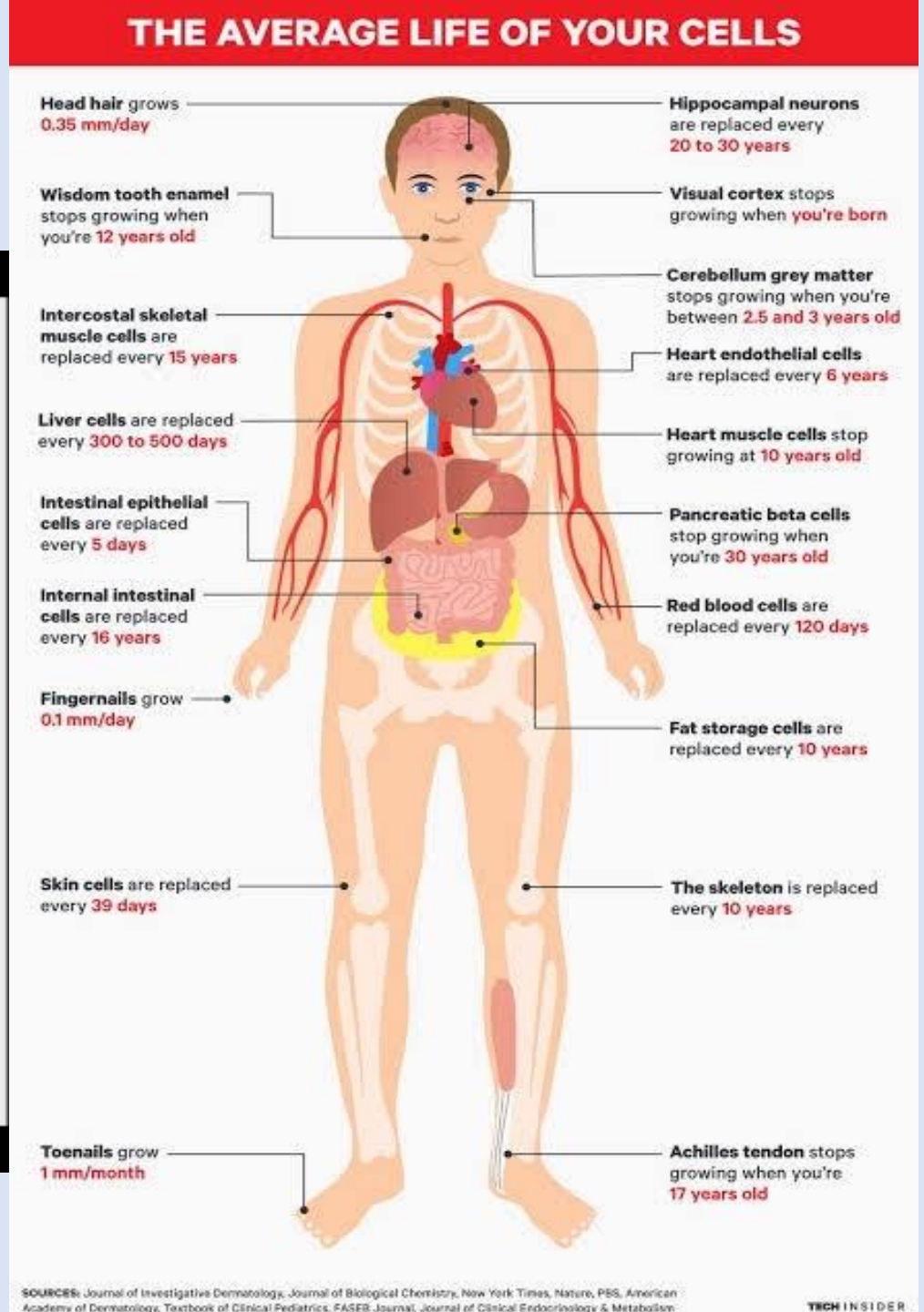
พบ.วทม. **FICS.FRCST. Dr.PH.**

Body regeneration schedule

Body Regeneration Schedule:

- Intestinal lining: **2-30** days
- Skin: **21-30** days
- Red Blood Cells: **90-120** days
- Pancreas: **5-12** months
- Liver: **6** weeks-**3** months
- Muscles: **6** months- **3** years
- Tissues: **1- 7** years
- Bones: **8** months – **4** years
- Hair: Grows 1mm every **3** days - renews every **6** yrs
- Mouth's Lining: Every few hours
- Bladder: About **49** days
- Lung's Surface: **2-3** weeks
- Heart: **3-4** times over a lifetime



พยาธิสรีรวิทยาที่สัมพันธ์กับระบบ ECS

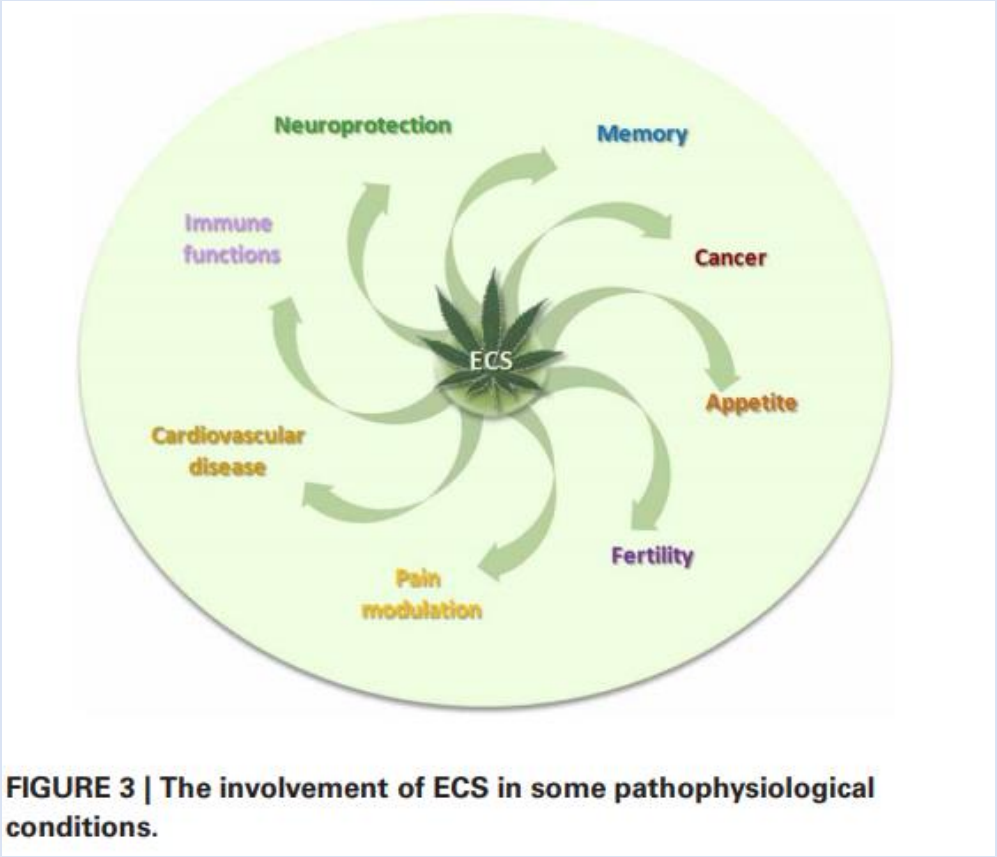


FIGURE 3 | The involvement of ECS in some pathophysiological conditions.

- ความผิดปกติของระบบเอนโดแคนนาบินอยด์มีส่วนเกี่ยวข้องกับการเกิดโรคหลากหลาย เช่น
- โรคมะเร็ง (cancer)
- ระบบความจำ (memory)
- โรคหัวใจ (cardiovascular disease)
- อาการความเจ็บปวด (pain modulation)
- ความอยากอาหาร (appetite) เป็นต้น

CB1 and CB2 pharmacology

- AEA กระตุ้น CB1 ทำให้กล้ามเนื้อเรียบของหลอดเลือดขยายตัว
- AEA กระตุ้น CB1 ทำให้กล้ามเนื้อกระเพาะอาหารคลายตัว
- 2-AG กระตุ้น CB1 เพิ่ม fatty acid synthase ทำให้เพิ่มระดับ triglyceride-rich apolipoproteins
- กระตุ้น CB1 เพิ่ม fat storage ในเซลล์ไขมัน adipocytes
- AEA เพิ่ม fibrogenesis ในเซลล์ตับ (ยับยั้งการเกิดตับแข็งด้วยสารยับยั้ง CB1 (CB1 antagonist)
- 2-AG กระตุ้น CB1 สังเคราะห์น้ำตาลที่ตับ (gluconeogenesis)

Function of Cannabis

- Cannabis consists of a large number of compounds, to date, 568 unique molecules have been identified in cannabis
- most of which are 60 pharmacologically active cannabinoids that act on receptors in the body's endocannabinoid system (ECS).[14]
- This system plays a key role in endogenous pain control.[14-17]
- the primary compounds found in the highest concentration are tetrahydrocannabinol (THC) and cannabidiol (CBD).
- THC contributes to the psychoactive effects of marijuana, including euphoria and psychosis.
- CBD is not psychoactive and is considered to have anti-anxiety and anti-psychoactive properties.[3]
- The therapeutic effects of medicinal cannabis depend on both the concentration of THC and the THC to CBD ratio.
- other cannabinoids, terpenes, and flavonoid compounds, are thought to exhibit synergistic effects that promote pain relief.[16,17]
- Recreational cannabis tends to contain a higher concentration of THC, whereas medicinal cannabis contains a higher concentration of CBD to limit the psychoactive effects of the drug.

Function of Cannabis

- There are two primary types of endocannabinoid receptors: cannabinoid receptors type 1 (CB1) and cannabinoid receptors type 2 (CB2).
- Both receptors are classified as G-protein coupled receptors.
- CB1 receptors are located in the central and peripheral nervous system, specifically in the centers of the brain involved in pain modulation, the nociceptive pathways of the spinal cord, and peripheral nerves.[4]
- CB2 receptors are primarily located in the periphery, such as in the immune and hematological systems, and aid in decreasing inflammation.
- THC is a partial agonist at both CB1 and CB2 receptors and inhibits the release of glutamate (GABA), 5-hydroxytryptamine(5HT), and alters dopaminergic function, thereby affecting pain pathways.[5]
- CBD is a negative allosteric modulator of CB1 receptors and also acts on serotonin, vanilloid, and other receptors.

Issues of Concern Acute adverse effects (negative theme)

- related to THC include anxiety, panic, disorientation, impaired attention, short-term memory, and driving performance.
- The most common acute side effect of CBD is diarrhea and has potential drug interactions with conventional pharmacotherapies as it interacts with cytochrome P450 (CYP 450) enzymes involved in drug metabolism.[8] Hence, it is prudent to avoid medicinal cannabis in patients with psychiatric illnesses, such as schizophrenia, as it may exacerbate the condition.
- Other negative themes associated with medicinal cannabis use amongst these patients were adverse effects of the medication and perceived bias against marijuana use.[11]
- the primary negative theme amongst these patients was the cost associated with medicinal cannabis.
- The average cost was about two thousand dollars per year, depending on the formulation and preferred route of administration.
- Unlike other medications, medicinal cannabis is not covered by insurance companies leading to increased costs.
- Regulations contributing to the difficulty in prescribing medicinal cannabis to patients suffering from chronic pain.
- Cannabis use continues to be a politically charged topic.

Phamacokinetics

Possible Routes of Administration

- Oral - absorbtion slow, variable
  - bioavailability usually < 15%
  - 1St pass metabolism (But product active) -

- Rectal - suppositories of hemisuccinate
  - good absorption
  - bioavailability 2 X as good
  - avoid 1st pass metabolism

- IV - very low water solubility, requires special formulation
  - rapid onset of action
  - dosage limitations → short duration of effect

- Smoking - rapid absorption (like IV)
  - bioavailability ดูด ซึม 18-50%
  - high variability due to smoking techniques

- Topical - very limited applicability

Methods of Administration

Inhalation

30 sec – 1 min.

Smoking/Vaping

Flower & concentrated oils

Easy titration

Ingestion

20 to 120 min.

Wide variety: Tincture, foods, beverages

Can be difficult to titrate

Topical

5 to 10 min

Can be helpful for neuropathic pain, psoriasis

No psychoactivity

GOVERNMENT OF THE DISTRICT OF COLUMBIA
DEPARTMENT OF HEALTH
Promote.Prevent. Protect.

Common Modes of
Administration and Formulations

Inhalation by smoking or vaporization

(herbal cannabis, resin, concentrates)

Oral

(prescription cannabinoids, edibles, tinctures)

Oro-mucosal or sublingual

(lollipops, lozenges, nabiximols)

Topical or Rectal

(herbal cannabis, resin, concentrates)

Metabolic Disposition

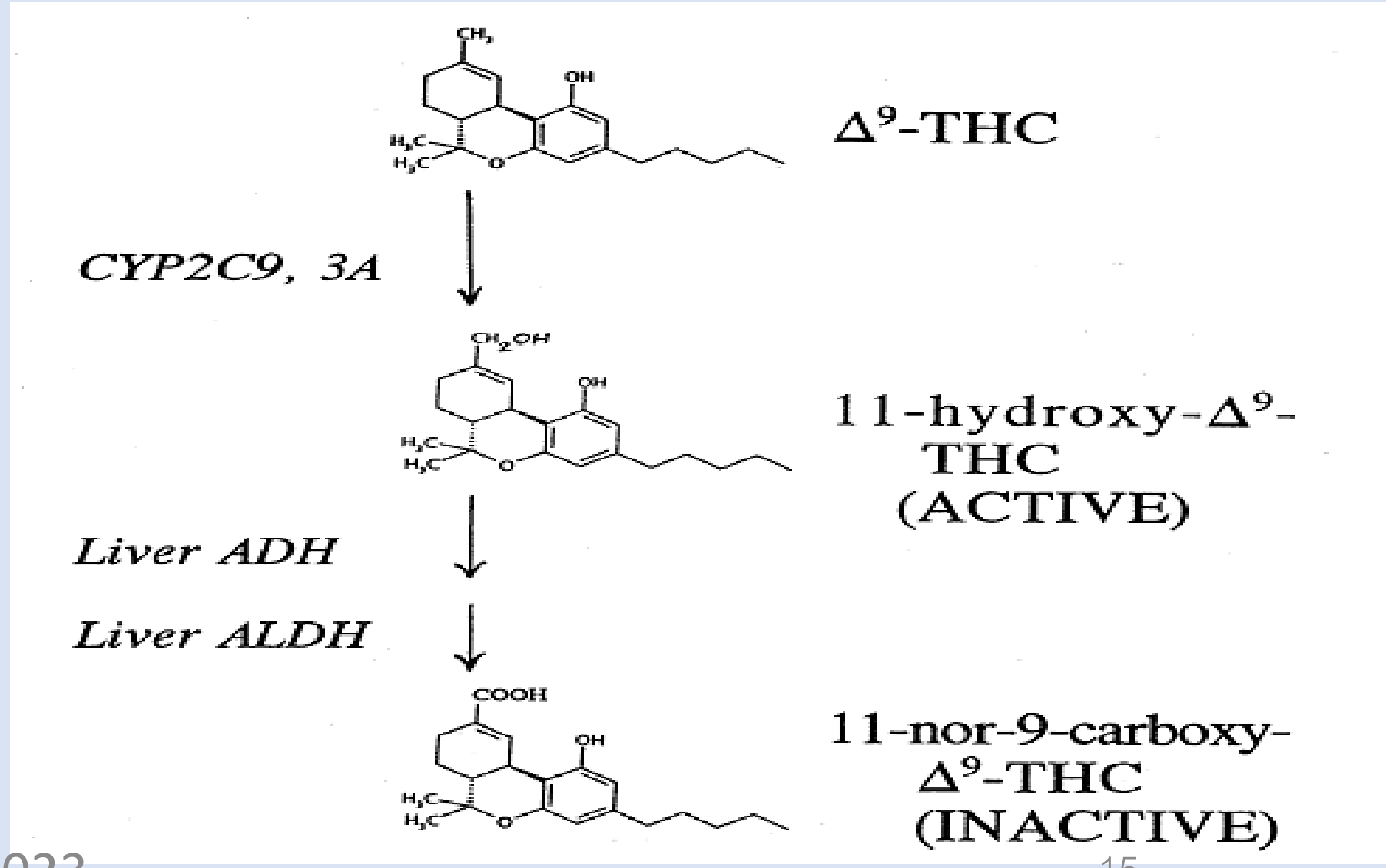
- Highly lipid-soluble, protein bound in plasma
- Enter tissue rapidly
- Plasma concentration curve after smoking is therefore triphasic:
  1 absorption phase with T50 = 50 sec
  2 distribution phase T50 = 40-50 min
  3 elimination phase T50 = 2-3 days

Metabolic Disposition (cont'd)

- No evidence for metabolic tolerance in chronic users
- i.e. little or no increase in rate of elimination
- Risk of cumulative build up of tissue concentration over time

- Many different final metabolites in both urine and feces,
  72 hour cumulative excretion in
  - urine - 13-17% of dose
  - Feces - 25-30% after IV
  - 48-53% after oral

Major Metabolic Pathway



Pharmacokinetics

- Cannabinoids are highly lipophilic.
- Rapidly absorbed into the blood from inhaled marijuana smoke, with plasma levels becoming detectable within seconds
- Peak plasma levels noted in fewer than 10 minutes.
- Bioavailability from smoking marijuana varies based on depth of inhalation, puff, and breath-holding duration.

Pharmacokinetics

- Smoking marijuana through a pipe instead of a cigarette can result in higher cannabinoid absorption because this results in less side stream smoke.
- Slow and erratic absorption orally resulting in irregular plasma levels, and reaching peak concentrations in 1-2 hours.
- Cannabinoids are acid-labile and degraded in the stomach thereby significantly reducing absorption.
- They also exhibit extensive first- pass effect.
- Crosses placenta and found in breast milk.

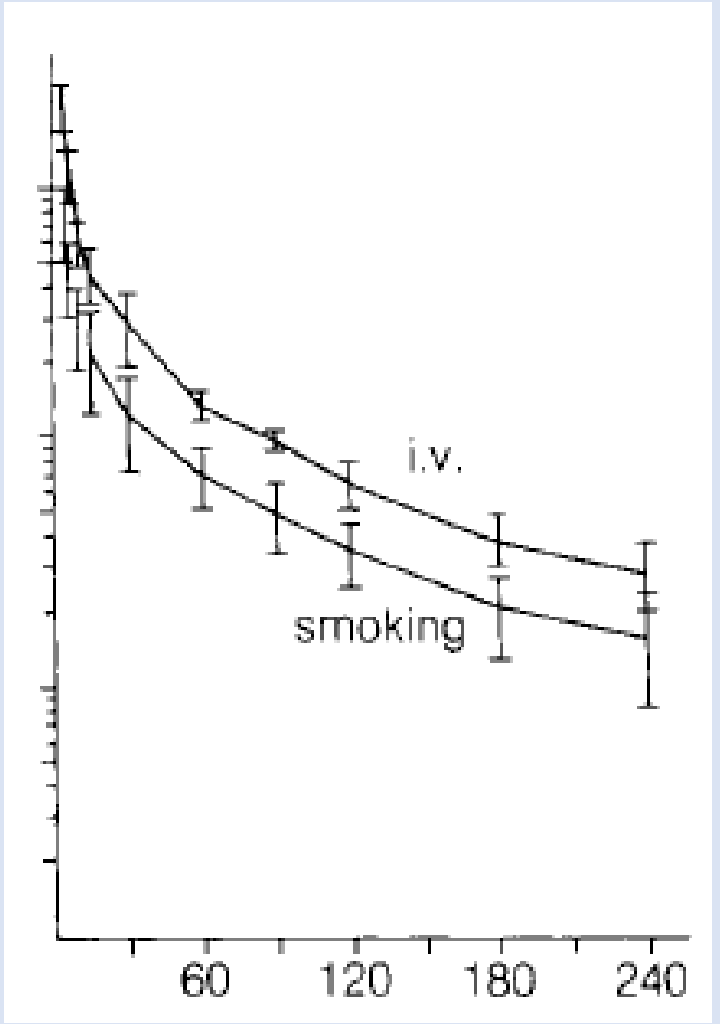
Pharmacokinetic profile of THC

Smoking

1 absorption phase with T50 = 1 minute

2 distribution phase T50 = 30 min

3 elimination phase T50 = 30 hrs



Smoking:

- Bioavailability: 10-25%

  50% of the THC content is delivered into smoke

  50% of smoke is exhaled again

  60% of inhaled smoke may be metabolized in the lung

Agurell S, 1986; Strougo A, 2005

Vaporization of medical cannabis

- Cannabinoids vaporize at a temp lower than combustion
- Increasingly popular
- Lower % of noxious chemicals

http://www.volcanovaporizer.com/products-page/complete-sets/ Accessed 08/31/2012

Pharmacokinetic profile of THC

Oral

Peak concentration are low and reach 1-3 hour

1 absorption phase with T50 = 0.8 hour

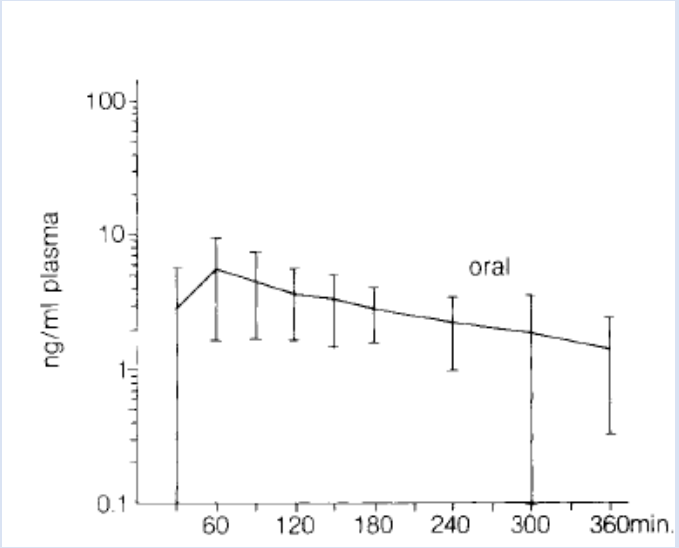
2 distribution phase T50 = 3.8 hour

3 elimination phase T50 = 25 hour

High intra-patient variability!

Oral:

- Bioavailability: 5-20%
- Often considered 1/3 that of smoked due to gastric degradation and extensive first-pass effects



Agurell S, 1984; Ohlsson A, 1980

THC is the most psychoactive component of cannabis

- Typical “effective” dosing of THC
- Low dose < 7 mg
- Medium dose = 7 – 18 mg
- High dose > 18 mg

GPO Standard Extraction	
CBD	100 mg/ml
THC	17 mg/ml
THC + CBD 1:1	THC 27mg + CBD 25 mg/ml

Zuurman L, Brit J Clin Pharm 2009

Labeling of product

- A net weight statement;
- THC potency and the potency of such other cannabinoids or other chemicals, including CBD,
- A serving size for edible retail marijuana products that does not contain more than ten milligrams of active THC,
- And limitations on the total amount of active THC in a package that is no more than one hundred milligrams of active THC;

The pharmacodynamics of THC

- Evaluated 165 studies to determine consistently found PD effects
  - Elevation in heart rate (average >19 bpm)
  - Increase in subjective feeling high
  - Decrease in subjective alertness
  - Increase in motor instability (body sway)

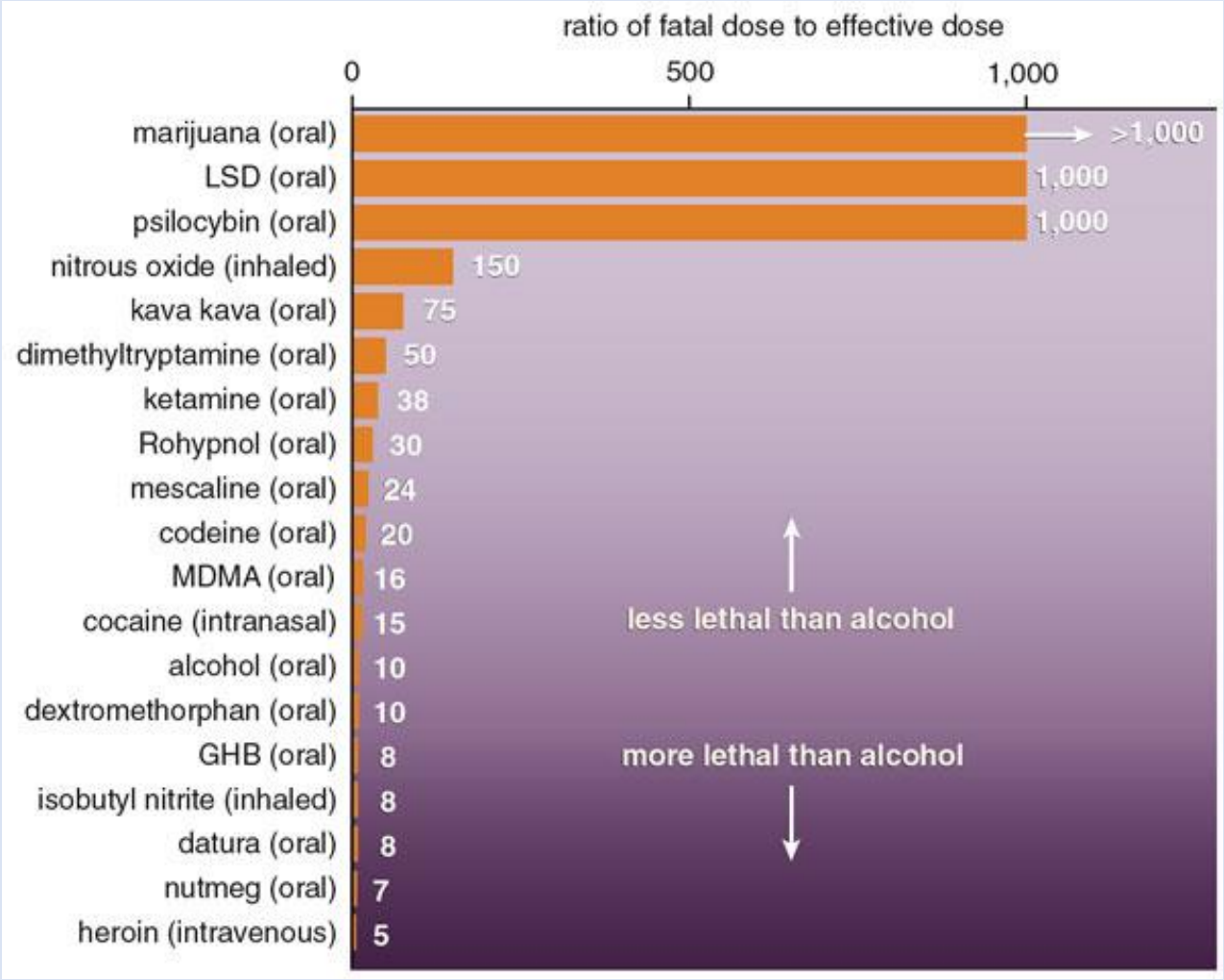
Zuurman L, Brit J Clin Pharm 2009

Population response to medical cannabis

- Hormones:
  - Males: decreased LH, FSH, prolactin, and GH levels
  - Females: more sensitive to THC effects (pain, behavior, reward) with higher estrogen levels
- Tobacco:
- greater increases in HR and carbon monoxide, despite lower THC
- concentrations
- MDMA: amphetamine or ecstasy
- synergistic impairment in working memory
- CV patients:
- ↑HR and ↓HRV with cannabis use

Acute toxicities

- Hallucinations
- Tachycardia
- Hypotension
- Dyspnea
- Drowsiness



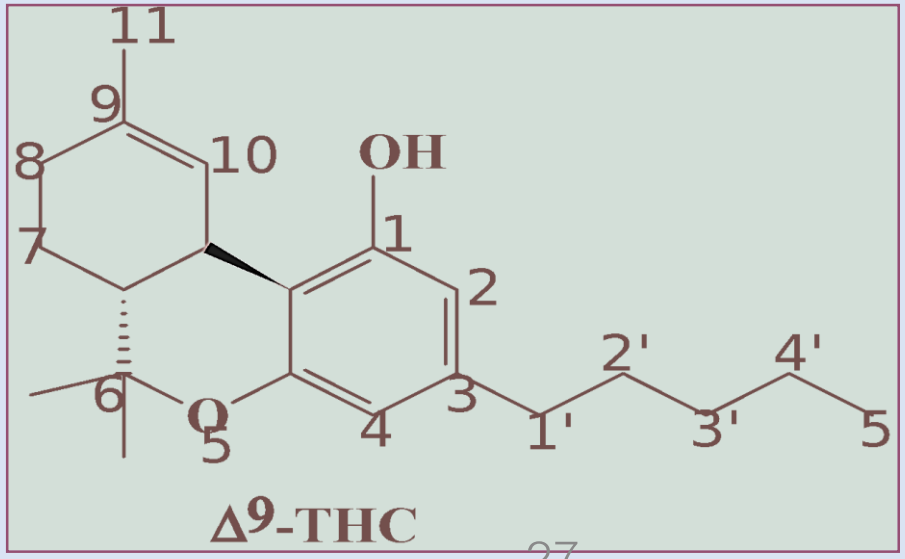
Wang GS JAMA Pediatrics, 2013

http://opiophilia.blogspot.com/2013_04_01_archive.html

The effect of the main substance of cannabis on the body

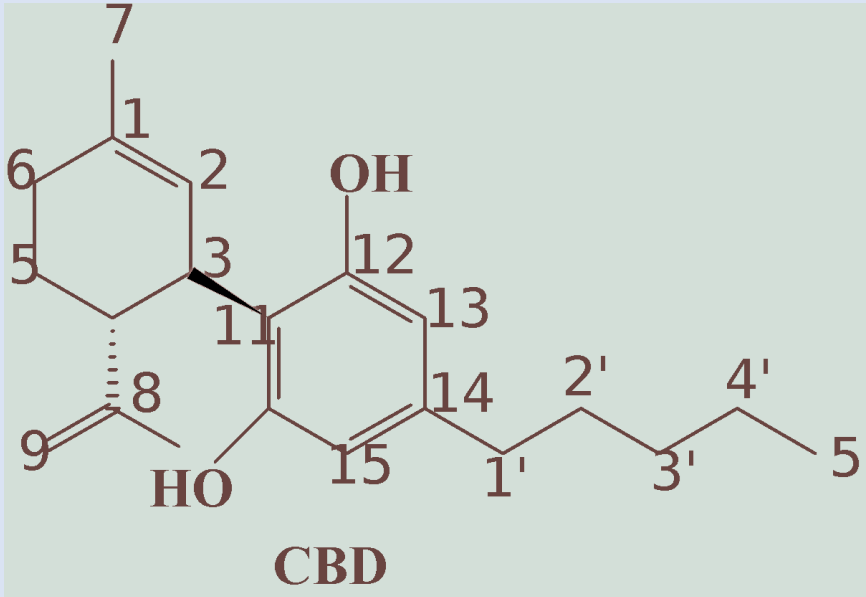
Pharmacological actions of THC

- Psychotropic
  - Initial euphoria and relaxation
  - Followed by a depressant period
  - Alterations memory and cognitive perceptual abilities
- Immuno-suppressive/ immuno-modulation
- Cardiovascular (tachycardia, orthostatic hypotension, peripheral vasodilation)
- Analgesic
- Anti-emetic
- Appetite stimulant



Pharmacological Effects of CBD

- Anticonvulsant
- Analgesic
- Anti-anxiety
- Anti-psychotic
- Anti-inflammatory
- Anti-arthritic
- Immunosuppressive



CBD

Pharmacological Effects

Acute Effects

- CNS depressant: drowsiness, ↓alertness, impairment of short term memory, slowed reactions, ↓accuracy of psychomotor task performance; ↓motor coordination and muscle tone

  - Low doses: mild euphoria, relaxation, ↑socialability, ↓anxiety

  - High doses: dysphoria, ↑anxiety and panic reactions (esp. inexperienced users) sensory distortions, hallucinations

Acute Effects

- Dry mouth
- Stimulated appetite (munchies)
- Antiemetic (low doses)
- Nausea and vomiting (high doses)
- Dilate blood vessels (red eyes)
- Increased heart rate
- Orthostatic hypotension
- Impaired:
  - Attention
  - Short term memory
  - Some complex cognitive processes,
  - Motor abilities
- Most effects are dose dependent and moderated by tolerance, comparable to those of moderate doses of alcohol (BAC approximately 0.05%)

Pharmacological Effects (cont'd)

Acute Effects

- Pain perception ↓ (exerted at CB_1 receptor)
- Antinauseant and antiemetic effects, ↑ appetite (CB_1 receptors)
- Anticonvulsant effects (not via CB_1 receptors)

Pharmacological Effects (cont'd)

Neuromuscular system

- Centrally and peripherally mediated antispasticity

Cardiovasular effects

- Tachycardia, ↑cardiac output, ↑myocardial oxygen need

Pharmacological Effects (cont'd)

Respiratory

- Bronchodilation → ↓ airway resistance (acute)
- Bronchial irritation → particulate fraction of cannabis smoke (chronic)
- Cannabis smoke similar to tobacco smoke

Eye

- ↓ IOP at doses that produce CNS effects

Immune System

- Effects unclear

Chronic Effects

- CNS
  - cognitive changes include poor memory, vagueness of thought, decreased verbal fluency, learning deficits
  - daily high doses can cause chronic intoxication syndrome (apathy), confusion, depression, paranoia
  - cannabis dependence (DSM-IV criteria)

Chronic Effects (cont'd)

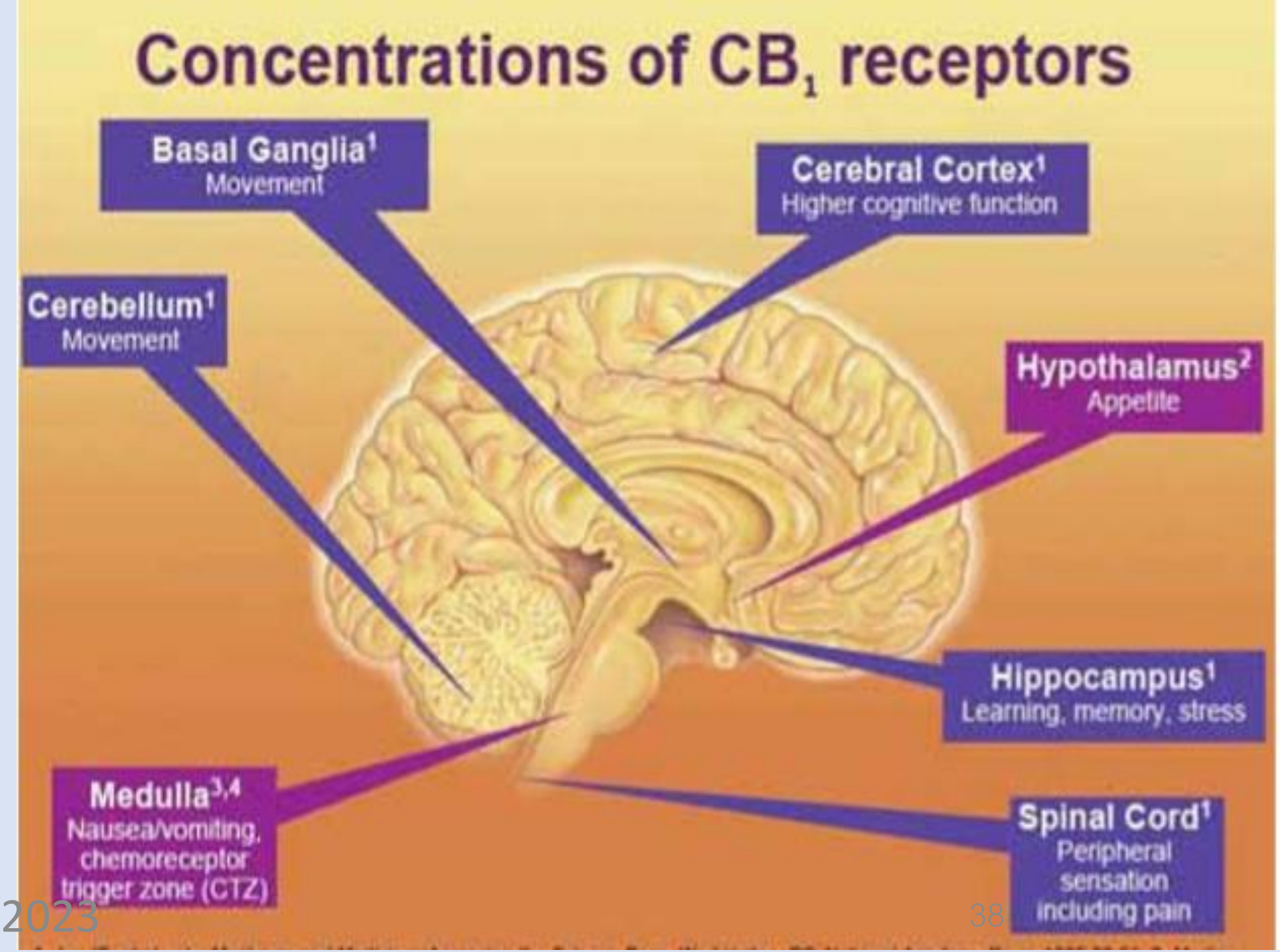
- Respiratory System
  - ↑ chronic inflammatory chest disease
  - precancerous changes

What Are the General Effects of Cannabis Use?

- Administration
  - Smoked (start 1-2 minutes -> ends 4 hours)
  - PO (start 30 minutes -> ends 6 hours)
- General effects of Cannabis use:
  - Potential Positives:
    - Euphoria, relaxation, laughing, >appreciation for music
  - Potential Negatives:
    - Anxiety, fear, paranoia, or panic
    - Hallucinations (rare)
    - Dissipate with time

Effects with Long Term Use

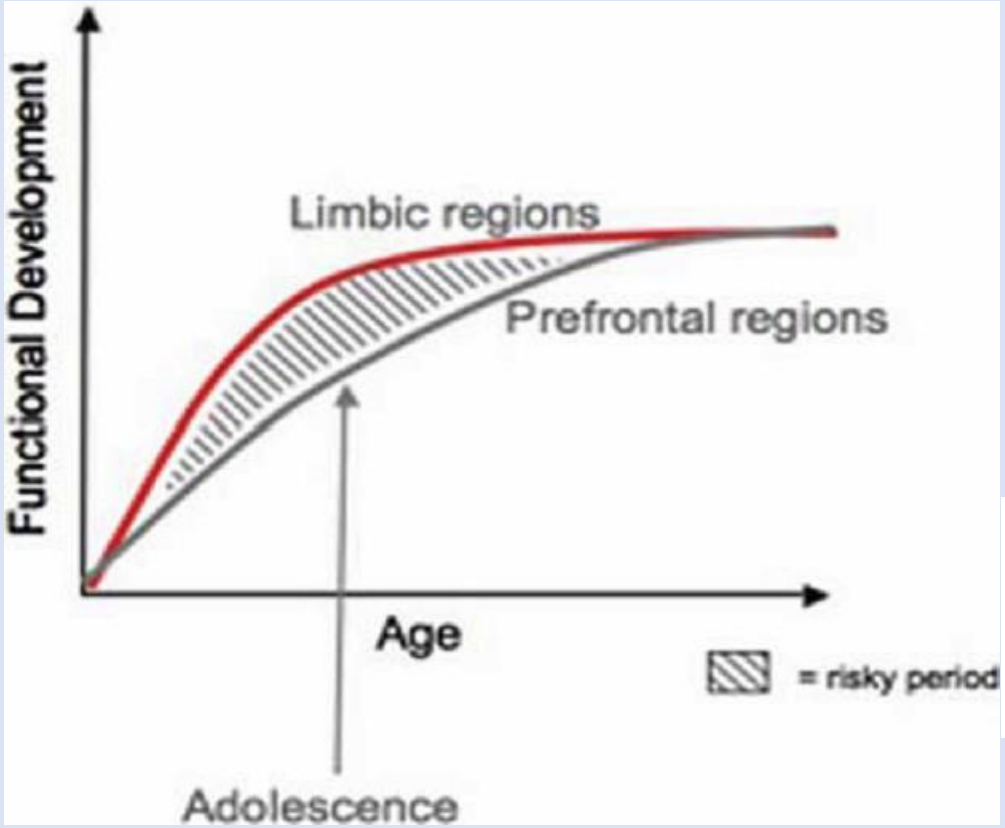
- Impaired cognition
  - Attention
  - Memory
  - Problem solving
  - Mental flexibility
- Altered brain function on neuroimaging:
  - Prefrontal cortex
  - Cerebellum
  - Hippocampus

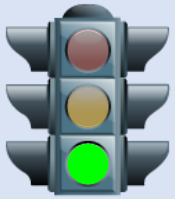

Concentrations of CB1 receptors
Basal Ganglia[1]
Movement
Cerebral Cortex[1]
Higher cognitive function
Cerebellum[1]
Movement
Hypothalamus[2]
Appetite
Hippocampus[1]
Learning, memory, stress
Medulla[3,4]
Nausea/vomiting, chemoreceptor trigger zone (CTZ)
Spinal Cord[1]
Peripheral sensation including pain

How Does Cannabis Interact with the Brain?

- Endogenous cannabinoid receptors (CB1, CB2) and 5 endogenous ligands
- CB1
  - Psychoactive and reinforcing effects
  - Highest concentrations
    - Basal ganglia (reward, learning, motor control)
    - Cerebellum (sensorimotor coordination)
    - Hippocampus (memory)
    - Cortex (planning, inhibition, higher-order cognition)
  - Dose and time dependent
  - Euphoria: increased dopamine in reward center

Brain development in adolescence





Accumbens
- Immediate rewards
- Impulsive behavior

Cortex
- Long term gain
- Thoughtful behavior

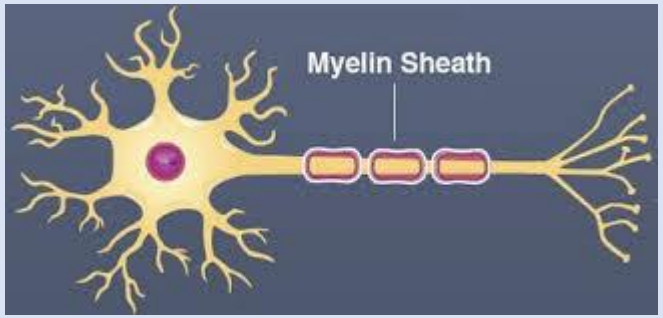
http://erichengelhardt.net/neuro-facts.html accessed 5/28/2013

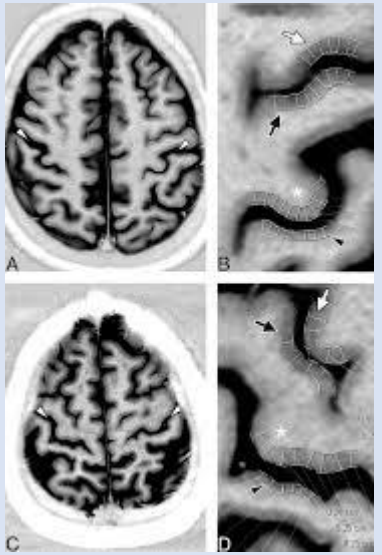
Amendment 64 prohibits the sale and use of cannabis products by those younger than 21 years. Why?

The adolescent brain is still developing. There is concern that the reward pathways and feedback loops may be altered if cannabis is used by those with still developing brains.

How Does Cannabis Interact with the Teen Brain?

- Chronic or frequent use
  - Impaired executive function
  - Impaired higher-level control of attention
  - Impaired working memory
  - Decreased cortical thickness
  - Possible decreased myelination





Behavioral, Medical, and Psychiatric Adverse Effects

- Adolescents with regular use:
  - Try other substances
  - Develop substance use disorders
  - Poor academic performance
  - Drop out of school
  - More delinquent behavior
  - Psychiatric problems
  - Emergency department visits
  - Risky behavior
    - Drugged driving
    - Sexually transmitted diseases

Cannabis and Schizophrenia

- Using Cannabis →psychotic disorders
  - Association repeatedly demonstrated
- Higher risk
  - Frequent use
  - Early onset
- Prior schizophrenia diagnosis
  - Negative effect on course and treatment
  - Possible positive effect on cognition

Cannabis Withdrawal

- Experienced by most heavy users
- Cannabinoid antagonist → withdrawal
- Resume THC and symptoms abate
- Cannabis withdrawal syndrome
  - Begins 1-2 days after stopping
  - Peaks in 2-4 days
  - Lasts for 1-3 weeks
  - No major medical/psychiatric consequences
  - More severe withdrawal=worse prognosis

Cannabis Withdrawal Symptoms

- Irritability/anger
- Nervousness/anxiety
- Sleep difficulty
- Decreased appetite
- Depressed mood
- Physical symptoms
  - Stomach pain
  - Tremor, headache
  - Fever, chills, sweating

Photo: Tony Fischer

Cannabis Use and Misuse

Risk Factors

- Genetic
- Environmental
  - *Availability*
  - Delinquent Behavior ผิดนัด
  - Chaotic Home วุ่นวาย
  - Low socio-economic status
  - Other psychopathology
  - Low perceived risk of harm
  - Peer/Family Use
  - Use of other substances
- Earlier initiation risk of CUD (cannabis use disorder)

Cannabis coffee shop in Amsterdam

Cannabis Side Effects

Cannabis has no known LD50

Euphoria
Motor coordination problems
Short term memory loss
Red eyes
Dry mouth
Low blood pressure
Heart Palpitation
Anxiety/panic/paranoid
Hallucination

No known negative drug interactions

Start Low Go Slow

Remember, while unpleasant, too much cannabis alone is not fatal.
Time, water, food, and a relaxing environment all help.

Common Adverse Effects

Anxiety

Reduced tear flow

Altered sense of time

Decreased eye blink rate

Bronchitis

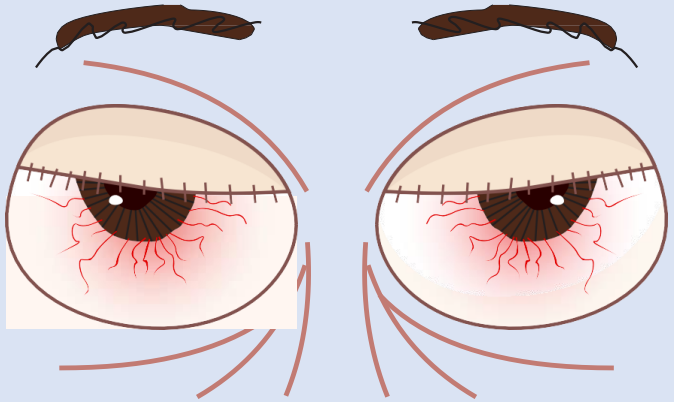
Dizziness

Reddened eyes

Changes in visual perceptions

Decreased sperm count

Dry mouth
(and possibly associated caries and periodontitis)



Slowed pupillary response to light

Sedation

Reduced coordination

Ataxia

Cough

Dysphoria

(Ashton 1999, Hall and Solowij 1998, Handbook on Cannabis 2015)