UNITED NATIONS
Office on Drugs and Crime

Perspectives in medical use of cannabis

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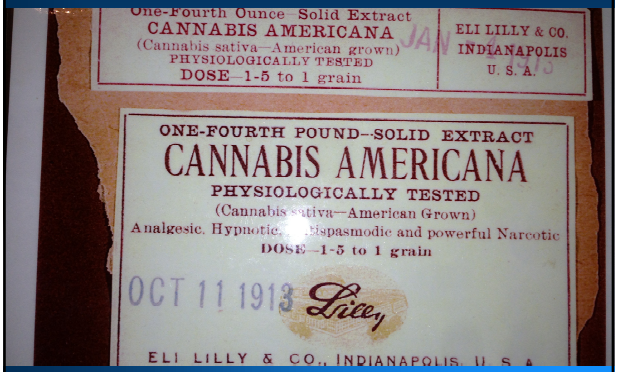
Cannabis: not a new medicine



Substances contained in cannabis

483 known compounds in the plant:

tetrahydrocannabinol (THC)

84 other cannabinoids:

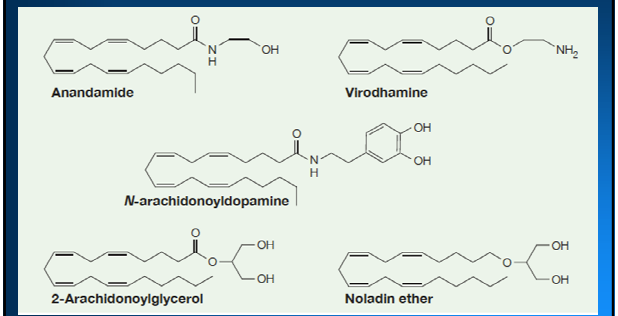
cannabidiol (CBD)
cannabinol (CBN)
tetrahydrocannabivarin (THCV)
cannabigerol (CBG)

Lots of media information

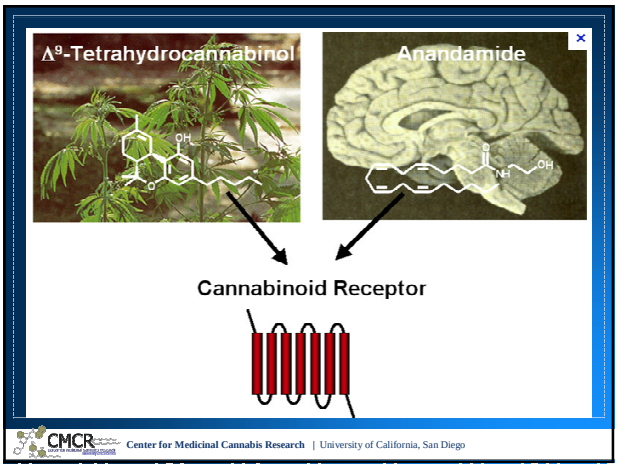
Lots of anecdotal information

Petition: allow veterans diagnosed with PTSD use of medicinal cannabis Nationwide.

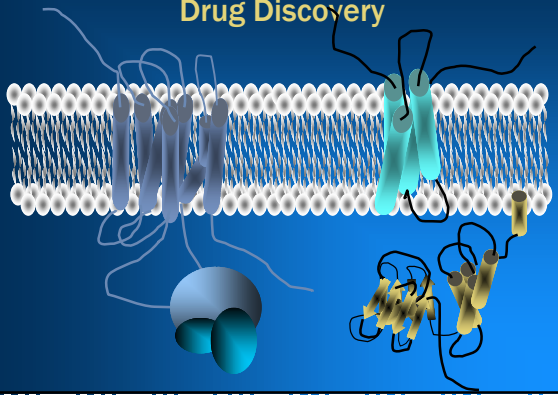
The endogenous cannabinoids



Piomelli, Nature Rev. Neurosci., 2003

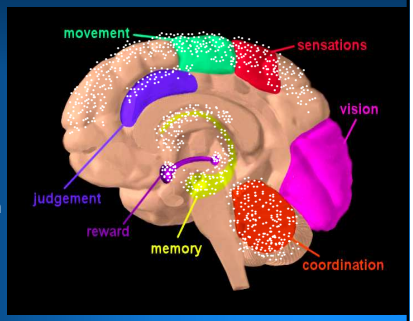


Cannabinoid Targets for Drug Discovery



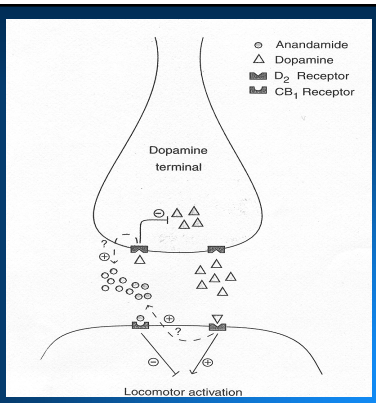
Cannabinoid Receptors Are Located Throughout the Brain and Regulate:

- Brain Development
- Memory and Cognition
- Motivational Systems & Reward
- Appetite
- Immunological Function
- Reproduction
- Movement Coordination
- Pain Regulation & Analgesia



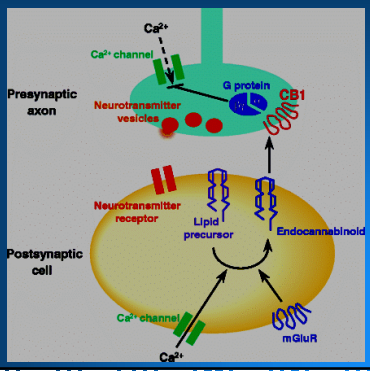
Distribution of Brain CB1 Receptors

- Hippocampus – Memory and Learning
- Amygdala – Novelty, Emotion, Appetitive Behaviour
- Basal Ganglia & Motor Cerebellum – Real Time Coordination, Selective Attention and Time Sense
- Nucleus Accumbens - Reward Mechanisms
- Cortex & Frontal Lobe - Executive Function, Judgment, Synthesis, Evaluation

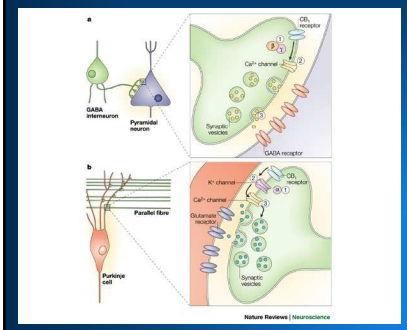


Nature Neuroscience, Vol. 2, 4, 304-5 (1999)

Retrograde Signaling & the Cannabinergic System



Pre-synaptically located CB1 cannabinoid receptors regulate GABA Release from Axon Terminals



Katona et al., 1999
Hájos et al., 2001
Piomelli et al., 2003

Example of findings regarding medicinal use of cannabis

- Cannabis reduces HIV Neuropathic Pain (*Abrams, D. I. et al. Neurology 2007;68:515-521; Ellis, et al. Neuropsychopharmacology 2009 Feb;34(3):672-80)*
- Cannabis Diminishes Mixed Ethiology Neuropathic Pain (*Wilsey, et al. 2008. Journal of Pain, 9 (6); 506-521)*
- Higher Concentration THC improves post surgical/traumatic neuropathic pain (*Ware, et al. 2010. CMAJ. 2010 Oct 5;182(14)*
- Cannabis improves MS spasticity in placebo controlled randomized study (*Corey-Bloom, et al. (2012) CMAJ 184(10); 1143-1150)*
- Dronabinol was found effective for appetite stimulation (*Beal, et al. (1995). Journal of Pain and Symptom Management. 10;2. 89-97)*

Medicinal Uses for Cannabinoids

Analgesic
Anticonvulsive
Sedative
Antidepressive
Hypnotic
Anti-asthmatic

Neuropathic Pain
Antiemetic
Antirheumatic
Antimigraine
Antineuralgic
Reduction of Fatigue

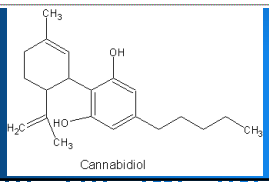
Immunomodulation
Memory Enhancing
Anesthetic
Appetite Stimulation
Antipyretic

Cannabis appears to have treatment value in patients with anxiety (social phobia)

Cannabidiol Reduces the Anxiety Induced by Simulated Public Speaking in Treatment-Naïve Social Phobia Patients

Mateus M Bergamaschi[1,2,3], Regina Helena Costa Queiroz[2,3], Marcos Hortes Nisihara Chagas[1,3], Danielle Chaves Gomes de Oliveira[1,3], Bruno Spinosa De Martinis[3,4], Flávio Kapczinski[3,5], João Quevedo[3,6], Rafael Roesler[3,7], Nadja Schröder[3,8], Antonio E Nardi[3,9], Rocio Martin-Santos[3,10], Jaime Eduardo Cecilio Hallak[1,3], Antonio Waldo Zuardi[1,3] and José Alexandre S Crippa*[,1,3]

Neuropsychopharmacology (2011), 1–8



Cannabidiol

Pharmacol Biochem Behav.
Antidepressant-like effect of delta9-tetrahydrocannabinol and other cannabinoids isolated from Cannabis sativa L.
El-Alfy et al., 2010

cannabigerol (CBG) and cannabinol (CBN)
no antidepressant-like action

cannabichromene (CBC) and cannabidiol (CBD)
significant antidepressant-like effect

Role for cannabinoids in schizophrenia treatment? Some evidence for cannabinoid involvement

- Heavy MJ use associated with increased risk of psychosis in some studies; THC itself can produce acute psychosis
- Human PET studies show increase in CB1 binding in various brain regions in untreated schizophrenia
- Serum/CSF anandamide increased during onset of psychotic symptoms, but not in heavy MJ users
- Higher CSF anandamide associated with less likely transition to psychosis in “high risk” cases
- In psychosis cases treated with cannabidiol, improvement in negative symptoms associated with greater anandamide rise

Leweke FM, Transl Psychiatry. 2012 Mar 20;2:e94.

Psychopharmacology (Berl)
Cannabinol and cannabidiol exert opposing effects on rat feeding patterns.
Farrimond et al., 2012.

Δ(9)-tetrahydrocannabinol-induced
- Increase in food consumption

Cannabinol
- increase in appetitive behavior and food intake

Cannabidiol
- reduction in food intake

an alternative to psychotropic Δ(9)-tetrahydrocannabinol-based medicines since cannabinol is considered to be non-psychotropic.

Treatment of refractory epilepsy-especially in children-using cannabidiol (CBD).

Little published evidence is available to prove or disprove the efficacy and safety of CBD in patients with epilepsy.

Clinical evidence suggesting efficacy in HIV-associated neuropathic pain

Efficacy in spasms associated with multiple sclerosis

Epilepsy Curr. 14(5):250-2.
Cannabidiol: promise and pitfalls.
Welty et al., 2014

PTSD treatment?

Amygdala FAAH and anandamide: mediating protection and recovery from stress.

A long-standing literature linking endo-cannabinoids to stress, fear, and anxiety has led to growing interest in developing novel anxiolytics targeting

Inhibition of FAAH (**Fatty acid amide hydrolase**) facilitates long-term fear extinction

Inhibiting FAAH as a mechanism to therapeutically mitigate the effects of traumatic stress.

Gunduz-Cinar et al., 2013

Neuro Endocrinol Lett.
Clinical endo-cannabinoid deficiency revisited: can this concept explain the therapeutic benefits of cannabis in migraine, fibromyalgia, irritable bowel syndrome?

underlying
endo-cannabinoid deficiencies
play a role
in migraine, fibromyalgia,
irritable bowel syndrome

Smith and Wagner, 2014

- Pre-clinical studies: cells, experimental animals

Clinical trials: in-human-studies

- Phase 0: Pharmacodynamics and Pharmacokinetics (15-20)

-Phase 1: Screening for safety, determine a safe dosage range, and identify side effects (80)

-Phase 2: Establishing the efficacy of the drug, usually against a placebo to see if it is effective (100–300)

- Phase 3: Final confirmation of safety and efficacy, to confirm its effectiveness, monitor side effects, compare it to commonly used treatments (1,000–3,000)

- Phase 4: Studies during sales (post marketing studies)

Medications approved by:

Court?

Referendum?

Acclamation?

Scientific trials?

No smoked medication is easy to manage in a clinical setting

(Kleber and DuPont, Am. J. Psychiatry, 2012)

Clinical trials should be prospective, organized, with systematic exposures of patients to an intervention.

Clinical trials need long term follow up

Clinical trials should be placebo-controlled randomized

(Feifel, 2009)

Biol Psychiatry.
Moderation of the effect of adolescent-onset cannabis use on adult psychosis by a functional polymorphism in the catechol-O-methyltransferase gene: longitudinal evidence of a gene X environment interaction.
Caspi et al., 2005

A functional polymorphism
in the catechol-O-methyltransferase (COMT) gene
moderated the influence of adolescent cannabis use
on developing adult psychosis

COMT valine158 allele
psychotic symptoms
if they used cannabis

COMT methionine allele
no such adverse influence

The epidemiological literature in the past 20 years shows that regular cannabis use induces:

- risk of accidents

- dependence

- poor psychosocial outcomes

- mental health problem in adulthood

Some researchers still argue that these relationships are explained by shared causes or risk factors

Hall, 2014

One in six teenagers who regularly smoke the drug become dependent on it

Cannabis doubles the risk of developing psychotic disorders (schizophrenia)

Cannabis users do worse at school

Heavy use in adolescence appears to impair intellectual development

One in ten adults who regularly smoke the drug become dependent on it

Cannabis users are more likely to go on to use harder drugs

Driving after smoking cannabis doubles the risk of a car crash

Smoking it while pregnant reduces the baby's birth weight

Hall, Addiction 2014

Adverse health effects of marijuana use.

Volkow et al., N. Engl J Med., 2014

Acute psychosis
Chronic psychosis
Depression
Anxiety
Suicidal thoughts
Personality disturbances
Lack of motivation

Eur Arch Psychiatry Clin Neurosci (2012) 262:47–57
DOI 10.1007/s00406-011-0223-5

ORIGINAL PAPER

Psychobiological responses to unpleasant emotions in cannabis users

Lorenzo Somaini · Matteo Manfredini · Mario Amore · Amir Zaimovic · Maria Augusta Raggi · Claudio Leonardi · Maria Lidia Gerra · Claudia Donnini · Gilberto Gerra

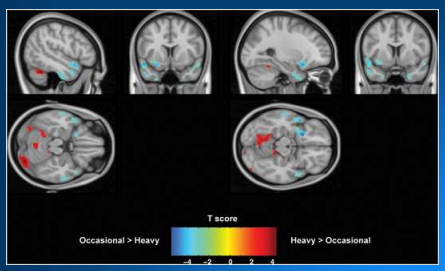
lower levels of arousal in response to negative emotions
compared to abstinent cannabis users and controls

a persistent hyperactivity of hypothalamus-pituitary-adrenal (HPA) axis

impaired hormonal reaction to negative emotions, in comparison with healthy subjects.

reduced sensitivity to negative emotions

Neuropsychopharmacology **39,** 2041–2048
Long-Term Effects of Cannabis on Brain Structure
Battistella et al., 2014



Cold color bar shows regions where gray matter volume is lower in regular smokers compared with occasional ones.

In conclusion

- Cannabinoids are very promising as medications.
- A rigorous approach will permit to recognize their value.
- The same approach that is applied to any other new medication
- The studies should target single cannabinoid substances
- Smoking as way of administration is inappropriate
- Undesirable side effects should be reported accurately in long term trials and considered before prescription