Comparative Neurology in Cannabinoid Medicine

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McPartland, J.M. et al., 2019. *Cannabis* in Asia: Its center of origin and early cultivation, based on a synthesis of subfossil pollen and archaeobotanical studies. *Vegetation History and Archaeobotany*.

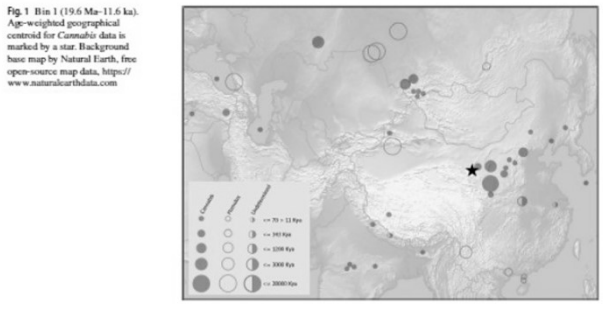


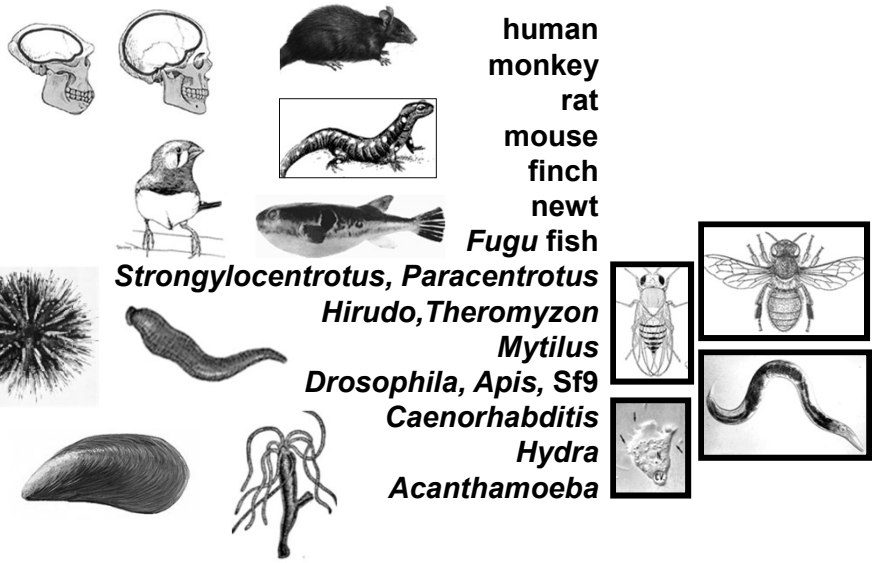
Fig. 1 Bin 1 (19.6 Ma–11.6 ka). Age-weighted geographical centroid for *Cannabis* data is marked by a star. Background base map by Natural Earth, free open-source map data, https://www.naturalearthdata.com

- Based on pollen analyses, *Cannabis* is about 27.8 million years old, diverging at that time from *Humulus,* and originated in the Tibetan Plateau.

Gene homologs of human CB1

species	Percentage identity with human CB1 sequence
Monkey (*Macaca mulatta*)	**100**% of 472 amino acids
Rat (*Rattus norvegicus*)	**97**% of 473 amino acids
Mouse (*Mus musculus*)	**97**% of 473 amino acids
Finch (*Taeniopygia guttata*)	**91**% of 473 amino acids
Newt (*Taricha granulosa*)	**83**% of 473 amino acids
Puffer fish (*Fugu rubripes*) A	**72**% of 468 amino acids
Puffer fish (*Fugu rubripes*) B	**59**% of 470 amino acids
Leech (*Hirudo medicinalis*)	**58**% of 153 (fragment)

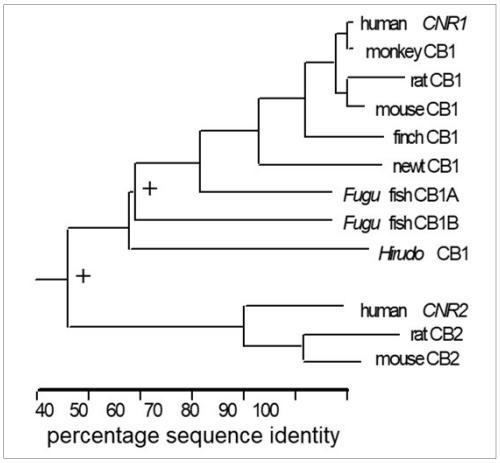
Binding studies with [^{3}H] cannabinoids



human
monkey
rat
mouse
finch
newt
***Fugu* fish**
Strongylocentrotus, Paracentrotus
Hirudo,Theromyzon
Mytilus
***Drosophila, Apis,* Sf9**
Caenorhabditis
Hydra
Acanthamoeba

CB receptor gene tree

based on percentage sequence identity

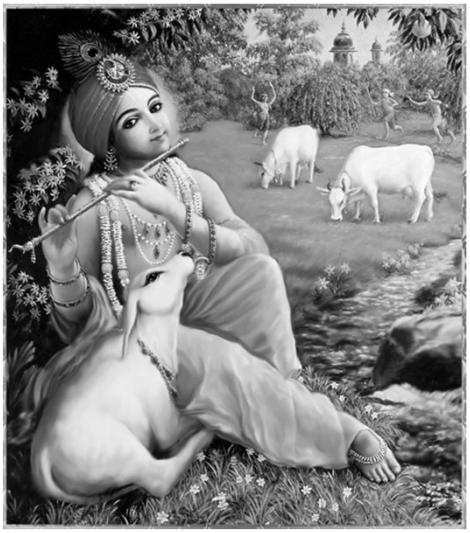


CB receptors are at least 600 million years old

Insects Have No Endocannabinoid System!

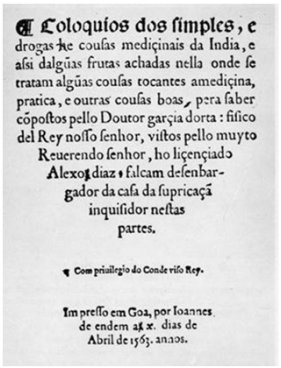
Larva feeding on cannabis flower, Rif Mountains, Morocco

Cannabis in India



- Used in veterinary medicine from at least the 12th century (Dwarakanath 1965).
- Still utilized for diarrhea in livestock, anti-helminthic, for "footsore disease, increasing milk-flow in cows, and pacifying them, but also was administered to bullocks as a tonic, to relieve fatigue and impart staying power." (Chopra 1957, p. 9)

Garcia da Orta, 1563.



Colloquios dos ſimples, e drogas he couſas mediçinais da India, e aſsi dalgũas frutas achadas nella onde ſe tratam algũas couſas tocantes amediçina, pratica, e outras couſas boas, pera ſaber cõpoſtos pello Doutor garçia dorta: fiſico del Rey noſſo ſenhor, viſtos pello muyto Reuerendo ſenhor, ho liçençiado Alexo diaz, falcam deſembargador da caſa da ſupricaçã inquiſidor neſtas partes.

¶ Com priuilegio do Conde viſo Rey.

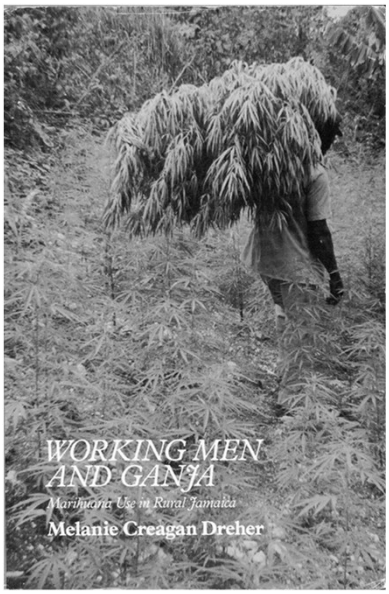
Im preſſo em Goa, por Ioannes de endem aſ x. dias de Abril de 1563. annos.

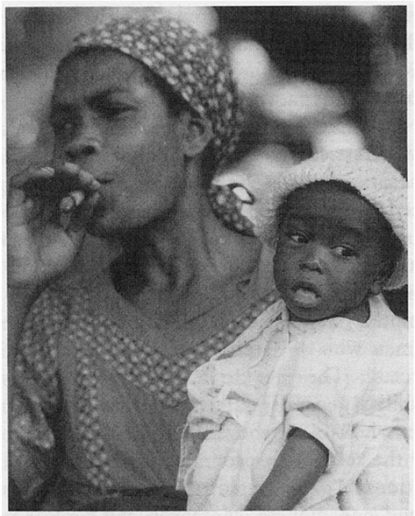
EBR

"The profit from its use is for the man to be beside himself, and to be raised above all cares and anxieties, and it makes some break into a foolish laugh."

"Those of my servants who took it, unknown to me, said that it made them so as not to feel work, to be very happy, and to have a craving for food."

Jamaica 1982/1997





"Roots daughter" smoking ganja. Photo supplied by Melanie Dreher.

Pliny the Elder, 1st Century

"The virtues of **hemp**, it is said, are so great, that an **infusion of it in water** will cause it to coagulate: hence, it is, if taken in water, it **will arrest looseness in beasts of burden.**"

Natural History (Pliny 1951)
(Book XX, Ch. 97, p.298)

François Rabelais, 1546

I won't stop to tell you that the juice of this marvelous herb, squeezed out and then placed in the ears, kills every manner of putrefied vermin that could possibly have bred in there, as well as all other creatures that might have crawled in. Put this juice in a small pail of water and you'll see the water suddenly coagulate like clotted milk- that's how powerful it is**. And this coagulated water is a sovereign remedy for colicky horses and also those with short breath.**

RABELAIS, F. 1990. Gargantua and Pantagruel, New York, Norton. Book III, Chapter 51, page 371

O'Shaughnessy, W.B. (1838-1840). On the preparations of the Indian hemp, or gunjah *(Cannabis indica)*. *Transactions of the Medical and Physical Society of Bengal***,** 71-102, 421-461.

He noted the narcotic effect of the electuary form of cannabis called majoon as reported by his informants, and then proceeded to experiment on dogs and an expanded menagerie of other creatures to differentiate their reactions. The results affirmed both sedative and appetite-stimulation effects of cannabis, along with static ataxia at higher doses (*vide infra*), all of which passed without notable sequelae after a few hours. **He observed, "---while carnivorous animals and fish, dogs, cats swine, vultures, crow and adjutants [military administrators], invariably exhibited the intoxicating influence of the drug, the graminivorous [grass eaters], such as the horse, deer, monkey, goat, sheep, and cow, experience but trivial effects from any dose we administered."** (O'Shaughnessy 1838-1840) (p. 363).

Table of 19th Century Veterinary Uses of Cannabis

Author/Year	Country	Indications
O'Shaughnessy/1838	India	Sedative, appetite stimulant, muscle relaxant in tetanus, anticonvulsant, anti-rheumatic
Ley/1843	England	Equine tetanus, antidote to strychnine poisoning
Tabourin/1875	France	Chancres in dog ears, purgative in cattle
Chiappero & Bassi/1879	Italy	Colic and urinary pain
Dun/1880	Scotland	Analgesic, hypnotic and antispasmodic equal to opium
Gresswell/1886	South Africa	Bowel inflammation, equine cough and canine chorea
Banham/1887	England	Asthma, convulsions, cough, cystitis and tetanus
Hassloch/1896	USA	Tetanus, cystitis, excitement in azoturia (equine exertional rhabdomyolysis)

Table of 20th Century Veterinary Uses of Cannabis

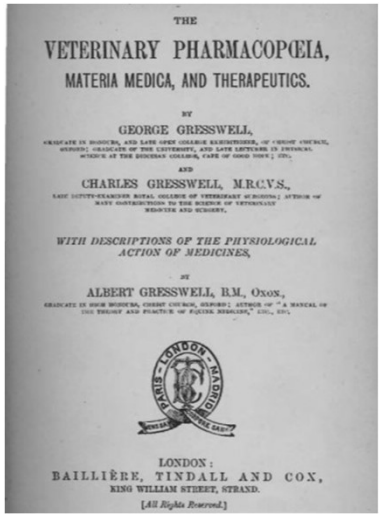
Author/Year	Country	Indications
Muir/1900	USA	Equine sedative
Muir/1904	USA	Equine analgesic, antispasmodic and hypnotic
Winslow/1901	USA	50% survival in tetanus
Sayre/1907	USA	Narcotic without constipation
Quitman/1912	USA	Equine melancholia with pneumonia
Brumley & Snook/1913	USA	Liniment
Milks/1917	USA	Spasms, irritability and narcotic for equine operations
Udall/1917	USA	Hobbling horses
Winslow & Eichorn/1919	USA	Delirium with parturient apoplexy
Greig/1939	Scotland	Volvulus and enteritis

Dominic Corrigan, 1802-1880

After a colorful early career that included a stint as a grave-robber supplying medical school anatomy laboratories, he is best known for his work on aortic valvular disease ("Corrigan's pulse") (Coakley 1988). He **described successful treatment of several cases of Sydenham's chorea in children with cannabis over the course of 5-6 weeks.**

CORRIGAN, O. 1845. Treatment of chorea by the use of Cannabis indica. *Medical Times* 12:291-292.

Gresswell, G., Gresswell, C., and Gresswell, A. 1886. *The veterinary pharmacopoeia, materia medica, and therapeutics.* London: Baillière, Tindall and Cox.


THE

VETERINARY PHARMACOPŒIA,

MATERIA MEDICA, AND THERAPEUTICS.

BY

GEORGE GRESSWELL,

AND

CHARLES GRESSWELL, M.R.C.V.S.,

WITH DESCRIPTIONS OF THE PHYSIOLOGICAL ACTION OF MEDICINES,

BY

ALBERT GRESSWELL, B.M., Oxon.,

LONDON:
BAILLIÈRE, TINDALL AND COX,
KING WILLIAM STREET, STRAND.

[All Rights Reserved.]

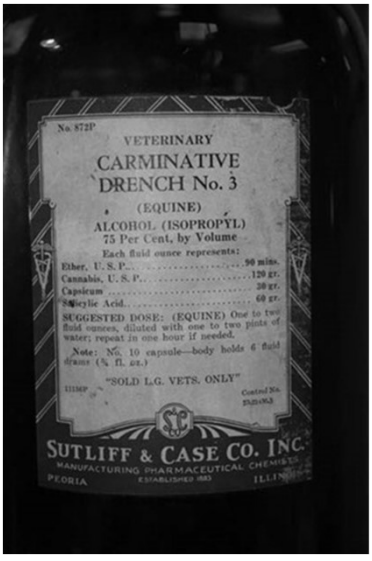
"In chorea, in dogs, the tincture or the extract is useful in allaying the spasms." (p. 123).

Muir, E.S. 1904. *Manual of materia medica and pharmacy.* Philadelphia: F.A. Davis


EDWIN S. MUIR, V. M. D., Instructor in Veterinary Materia Medica and Pharmacy

- Performed extensive experiments with cannabis in horses noting safe sedation, analgesia and hypothermia.
- Established dose ranges in horse and dog.

Carminative Drench No. 3



Sloan's Anti-Colic

Colic and Bloat

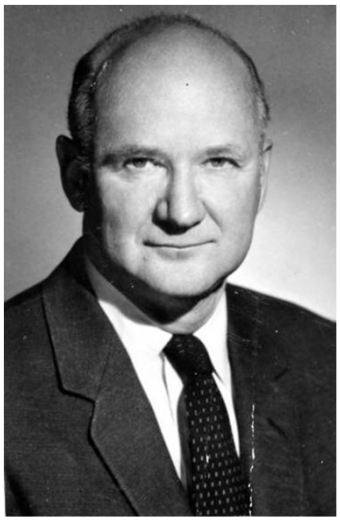
Wirtshafter, D. 2016. Compendium: The Cannabis Museum: Collection of Cannabis Artifacts." CannabisMuseum.com. 1st ed. (Athens, OH: www.cannabismuseum.com).

Patent medicines also existed for dogs, including "Security Cough, Cold and Distemper Remedy" which cost $1 in 1906 (equivalent to $28 today) containing *Cannabis indica*: "Will relieve the worst cough, chill or fever, Influenza or mucous membranes affections of the animal's throat, nose eyes, mouth or air passages."(Wirtshafter 2016)(p.26). (E. Russo, Foreword)

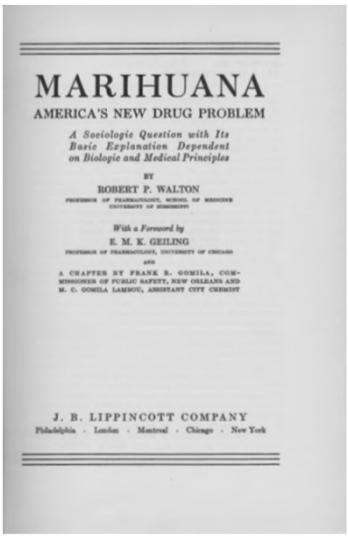
Hemp Seed Fish Bait

Robert P. Walton, MD, PhD (1905-1971)

Professor and Chairman of MUSC Department of Pharmacology from 1942

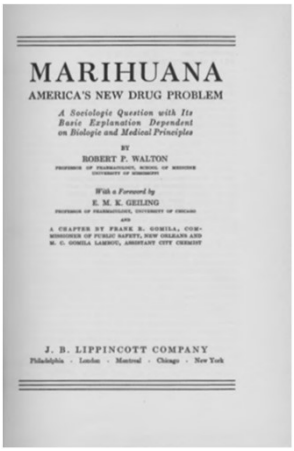


Courtesy of Jane Brown, Waring Library, 2003



Published in 1938, Walton's tome was the premier publication on cannabis for the first half of the 20th century.

Walton, R.P. 1938. *Marihuana, America's new drug problem.* Philadelphia: J.B. Lippincott.



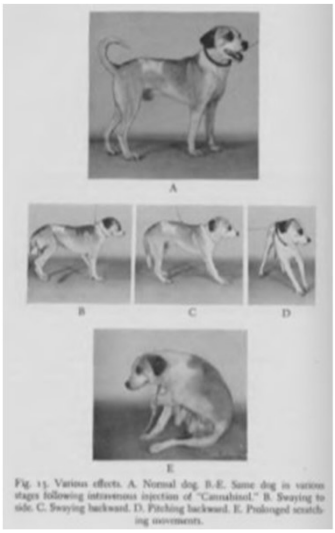


Fig. 13. Various effects. A. Normal dog. B-E. Same dog in various stages following intravenous injection of "Cannabinol." B. Swaying to side. C. Swaying backward. D. Pitching backward. E. Prolonged scratching movements.

- Noted various effects in dogs:

A: Normal

B. Progressive ataxia stages

C: Swaying backward

D: Pitching backward

E: Scratching movements.

Herkenham, M., et al. 1990. Cannabinoid receptor localization in brain. *Proc Natl Acad Sci U S A* 87(5), 1932-1936.

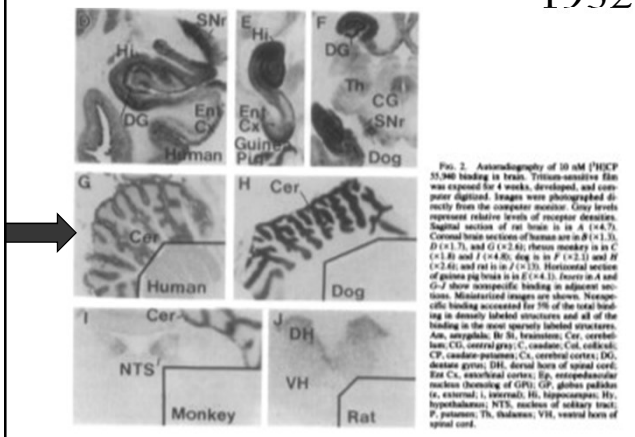


FIG. 2. Autoradiography of 10 nM [^{3}H]CP 55,940 binding in brain. Tritium-sensitive film was exposed for 4 weeks, developed, and computer digitized. Images were photographed directly from the computer monitor. Gray levels represent relative levels of receptor densities. Sagittal section of rat brain is in *A* (×4.7). Coronal brain sections of human are in *B* (×1.3), *D* (×1.7), and *G* (×2.6); rhesus monkey is in *C* (×1.8) and *I* (×4.8); dog is in *F* (×2.1) and *H* (×2.6); and rat is in *J* (×13). Horizontal section of guinea pig brain is in *E* (×4.1). *Insets* in *A* and *G–J* show nonspecific binding in adjacent sections. Miniaturized images are shown. Nonspecific binding accounted for 5% of the total binding in densely labeled structures and all of the binding in the most sparsely labeled structures. Am, amygdala; Br St, brainstem; Cer, cerebellum; CG, central gray; C, caudate; Col, colliculi; CP, caudate–putamen; Cx, cerebral cortex; DG, dentate gyrus; DH, dorsal horn of spinal cord; Ent Cx, entorhinal cortex; Ep, entopeduncular nucleus (homolog of GPi); GP, globus pallidus (e, external; i, internal); Hi, hippocampus; Hy, hypothalamus; NTS, nucleus of solitary tract; P, putamen; Th, thalamus; VH, ventral horn of spinal cord.

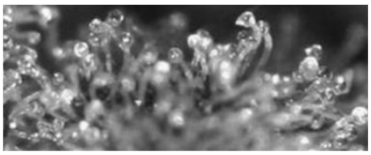
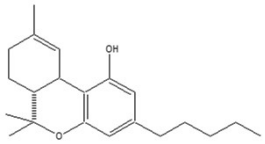
- Used tritiated CP55,940 to map CB_1 receptor density in the brains of various species.
- The CB_1 density in the cerebellum of dogs (H) was much greater than that of humans (G).

Raphael Mechoulam & Me

Discovered THC 1964

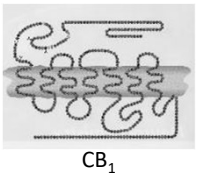
Discovered THC 1970

Cannabis sativa and the Endocannabinoid System

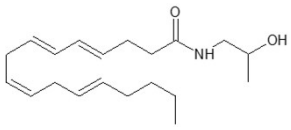




delta-9-tetrahydrocannabinol (THC)

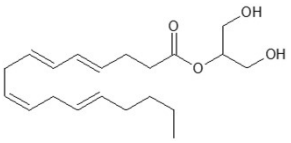
- It began with a plant called cannabis----
- Cannabis makes glandular trichomes, that in turn produce THC



CB_1



anandamide



2-arachidonylglycerol

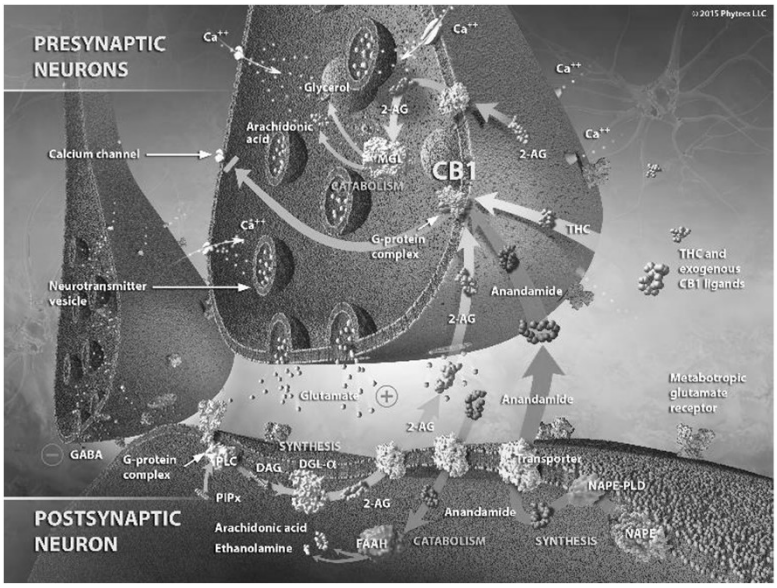
- THC binds to a receptor, CB_1 that also binds endogenous cannabinoids, the "endocannabinoids," anandamide and 2-arachidonylglycerol.
- **Endocannabinoid tone** is a function of endocannabinoid levels, the status of the receptors and enzymes

Cannabinoids: 3 Varieties

- **Phytocannabinoids** (Pate 1994): terpenophenolic 21-C compounds found in the genus *Cannabis* (e.g., THC, CBD)
- **Endocannabinoids** (Di Marzo 1998): natural endogenous compounds binding cannabinoid receptors (e.g., anandamide) whose functions are: **"relax, eat, sleep, forget and protect"**
- **Synthetic cannabinoids** (e.g., ajulemic acid) that also affect cannabinoid receptors

Russo, E.B. 2008. Cannabinoids in management of difficult to control pain. *Therapeutics & Clinical Risk Management* 4(1):245-259.

CB_1 Activation, Synthesis, Catabolism



An internal homeostatic regulatory system of 3 components:

Endocannabinoids (anandamide, 2-AG)

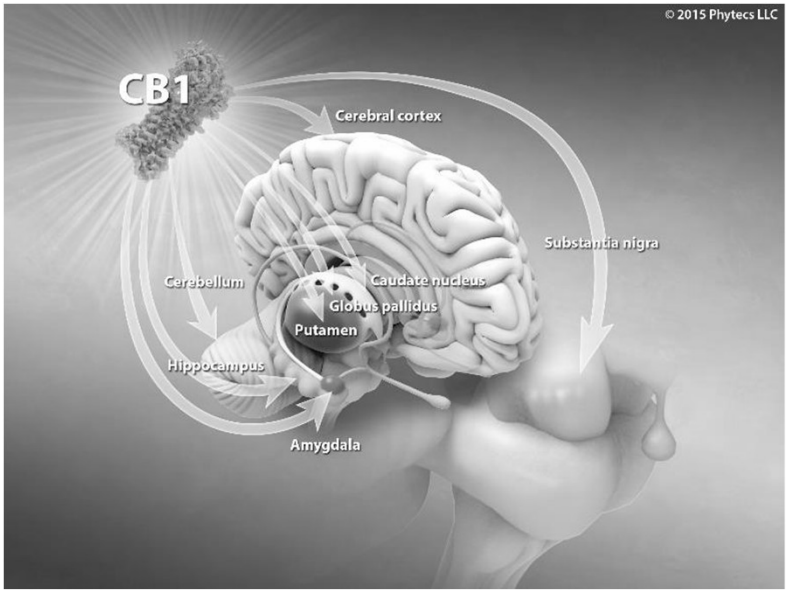
CB_1 and CB_2 receptors

Their regulatory enzymes

Endocannabinoids are produced on demand, travel in retrograde fashion to inhibit neurotransmitter release.

Active and "inactive" components work together in an "Entourage Effect."

CB_1 Expression in Brain

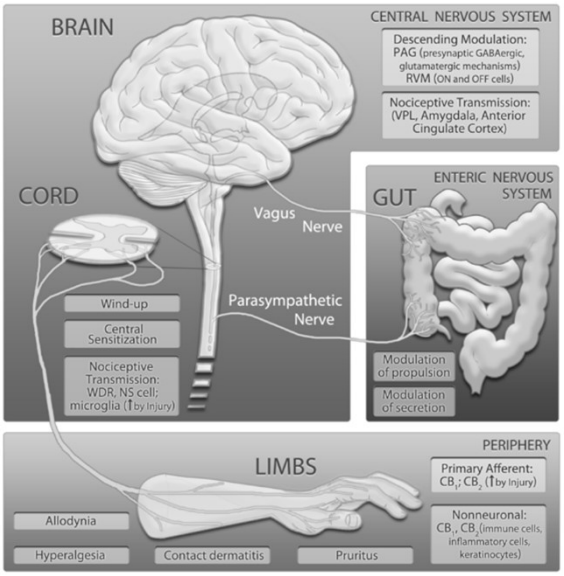


CB_1 is highly expressed in nociceptive areas, cerebellum, limbic system, basal ganglia and reward pathways.

Although prominent in the substantia nigra and periacqueductal grey matter, it is distributed in a limited fashion otherwise in the brainstem, and not in medullary respiratory centers.

The Endocannabinoid System (continued)

Russo EB, Hohmann AG. Role of cannabinoids in pain management. In: Deer T, Gordin V, editors. *Comprehensive Treatment of Chronic Pain by Medical, Interventional and Behavioral Approaches.* New York: Springer; 2013, pp. 181-197.



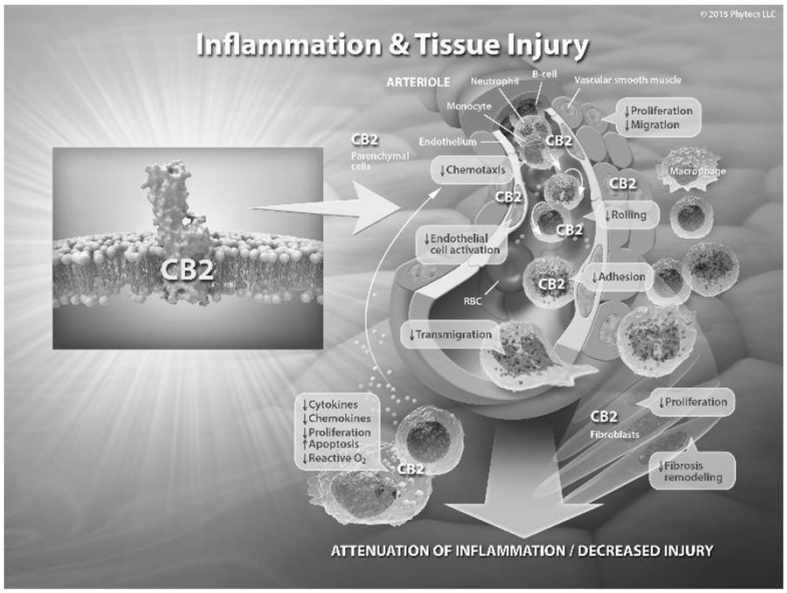
James Brodie, 2012

CB_1 is the most abundant G-protein-coupled receptor in the brain, with a major neuromodulatory function.

Role characterized as, “relax, eat, sleep, forget and protect.” (Di Marzo, 1998)

Modulates pain, movement, emotion, emesis, seizure threshold, GI motility/secretion, et al.

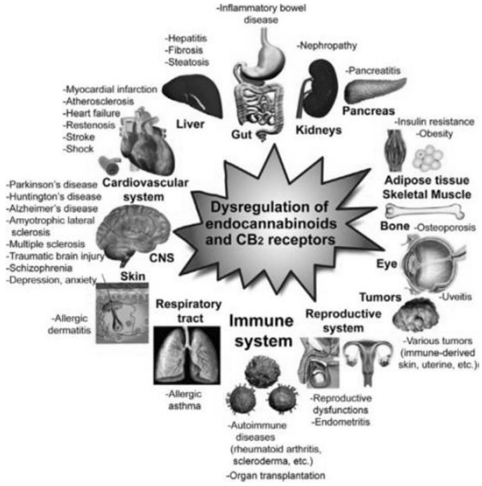
CB_2 and Inflammation

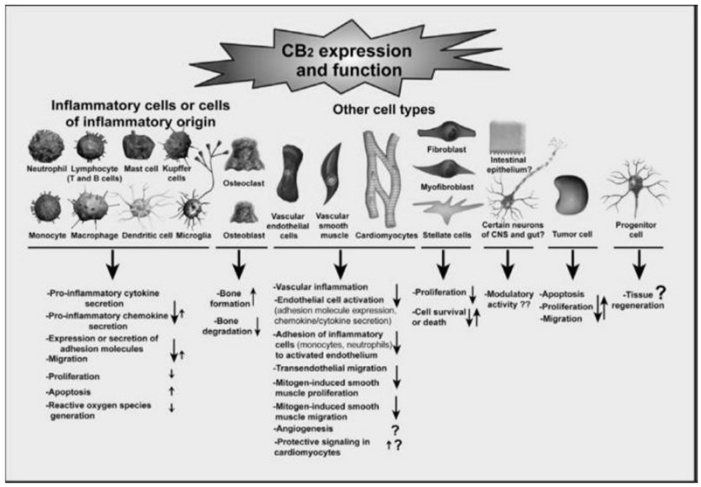


CB_2 is a mainly peripheral, immunomodulatory receptor with an important role in pain and inflammation.

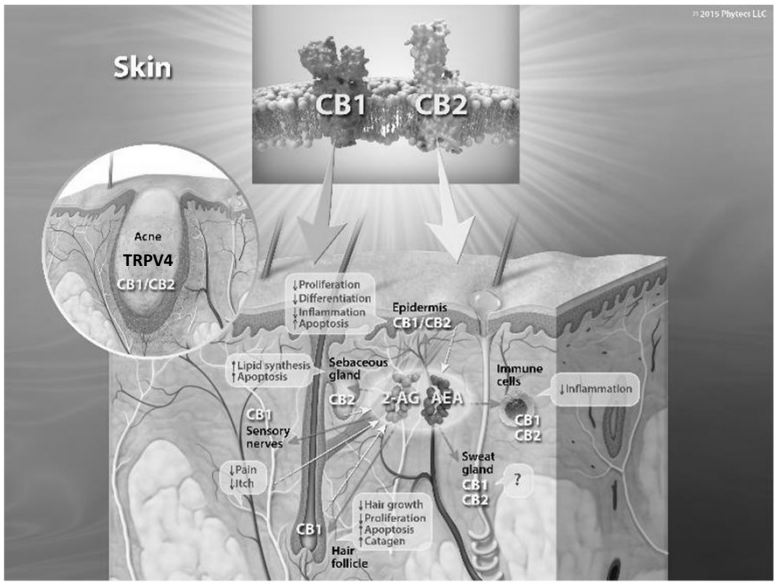
CB_2 agonists also hold great promise in treatment of hepatic fibrosis and related conditions.

Pacher P, Mechoulam R. Is lipid signaling through cannabinoid 2 receptors part of a protective system? *Prog Lipid Res* 2011.



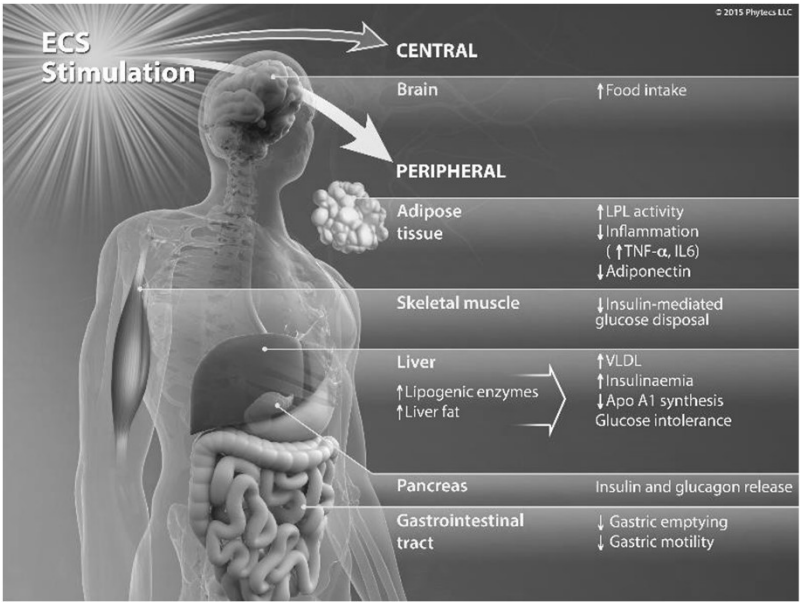


CB_1 and CB_2 in Skin



In addition to its anti-inflammatory and bacteriostatic effects, cannabidiol is a TRPV4 agonist that works as a sebostatic agent in acne.

ECS Stimulation



In addition to these systems, the ECS is active in cardiac and bone physiology.

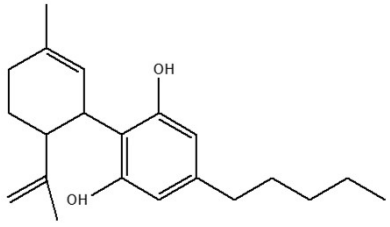
Cannabidiol was recently demonstrated to stimulate bone fracture healing (Kogan et al. 2015)

Cannabis sativa L.

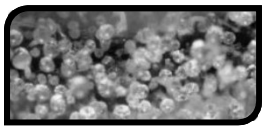
- Food (seed)
- Fuel (seed oil)
- Fiber (stalks)
- Farmacy (unfertilized female flowering tops)

Photo EBR, with permission, Hash, Marijuana and Hemp Museum, Amsterdam, June 2001

Misconceptions about Cannabidiol (CBD)



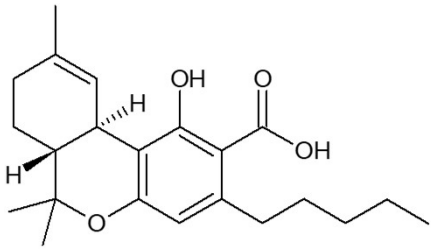
cannabidiol



G5 CBD trichomes
Photo DJP

- A tiny amount is enough **(actually more is better)**
- It is a sedative (**Alerting vs. THC in clinic (Nicholson 2004), and sedation may be operative with high doses, drug-drug interactions or terpenoid effects, i.e., myrcene)**
- **It turns into THC in the body (actually upregulates anandamide/ECS)**

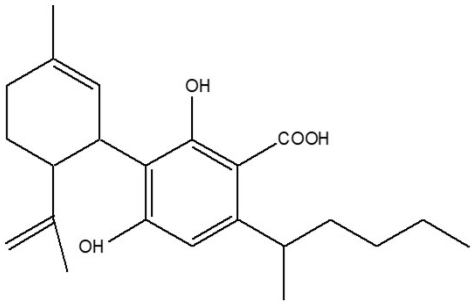
Tetrahydrocannabinolic Acid (THCA)



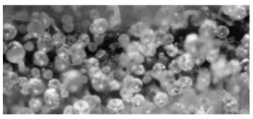
delta-9-tetrahydrocannabinolic acid

- THC form in fresh, unheated cannabis flowers
- Insecticidal (Sirikantaramas 2005)
- **Anti-inflammatory/anti-TNF-alpha (Verhoeckx 2006)**
- Anticonvulsant in mice only at 200 mg/kg (Karler 1978), but clinical reports in epilepsy (Sulak/Goldstein) indicate efficacy at much lower dosages (Russo 2016)
- Has high affinity for CB_1 (Rock 2013), but is unable to cross the BBB (Moreno-Sanz 2016)
- Increased cell survival and neurite morphology in PD model (Moldzio 2012)
- Reduced N&V reactions in rodents (Rock 2013)
- **Recently shown to be PPARγ agonist**, and possibly useful in Huntington disease (Nadal 2017)

Cannabidiolic Acid (CBDA)



cannabidiolic acid



G5 CBD trichomes
Photo DJP

- Predominant phytocannabinoid in fresh hemp
- Natural herbicide (Shoyama 2008), as long known in retting pond usage
- Produces COX-inhibition at high doses (Takeda 2008)
- **Powerful anti-emetic via 5-HT_{1A} stimulation (Bolognini 2013; Rock 2013)**
- Promising for treating tumors (historical data)

Randomized Controlled Trials of nabiximols in Pain

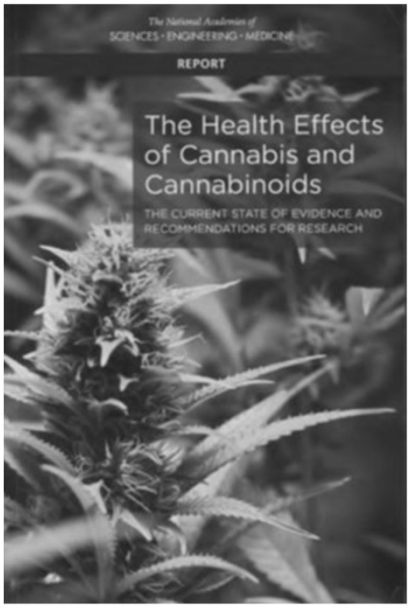
N=	Indication	Duration/Type	Outcome/References
20	Neurogenic pain	Series of 2-week N-of-1 crossover blocks	Improvement with high-THC extract and nabiximols on VAS pain vs. placebo (p<0.05), symptom control best with nabiximols (p<0.0001) [Wade et al. 2003]
24	Chronic intractable pain	12 weeks, series of N-of-1 crossover blocks	VAS pain improved over placebo (p<0.001) especially in MS (p<0.0042) [Notcutt et al. 2004]
48	Brachial Plexus Avulsion	6 weeks in 3 two-week crossover blocks	Benefits noted in Box Scale-11 pain scores with high-THC extract (p=0.002) and nabiximols (p=0.005) over placebo [Berman et al. 2004]
66	Central Neuropathic Pain in MS	5 weeks	Numerical Rating Scale (NRS) analgesia improved over placebo (p=0.009) [Rog et al. 2005]
125	Peripheral Neuropathic Pain	5 weeks	Improvements in NRS pain levels (p=0.004), dynamic allodynia (p=0.042), and punctuate allodynia (p=0.021) vs. placebo [Nurmikko et al. 2007]
56	Rheumatoid Arthritis	Nocturnal dosing for 5 weeks	Improvements over placebo morning pain on movement (p=0.044), morning pain at rest (p=0.018), DAS-28 (p=0.002), and SF-MPQ pain at present (p=0.016) [Blake et al. 2006]
117	Pain after spinal injury	10 days	NSD in NRS pain scores, but improved Brief Pain Inventory (p=0.032), and Patients Global Impression of Change (p=0.001) (unpublished)
177	Intractable cancer pain	2 weeks	Improvements in NRS analgesia vs placebo (p=0.0142), Tetranabinex NSD [Johnson, 2010 #6899]
135	Intractable lower urinary tract symptoms in MS	8 weeks	Improved bladder severity symptoms including pain over placebo (p=0.001) (unpublished)
360	Intractable cancer pain	5 weeks/DB	CRA of lower and middle dose cohorts improved over placebo (p=0.006)/GWCA0701)/ unpublished

Smoked cannabis RCTs in pain total 3 patient-years

Nabiximols RCTs and other monitoring total >6000 patient-years

Adapted from: Russo EB, Hohmann AG. Role of cannabinoids in pain management. In: Deer T, Gordin V, editors. Comprehensive Treatment of Chronic Pain by Medical, Interventional and Behavioral Approaches. New York: Springer. 2013:181-197.

National Academies: The Health Effects of Cannabis



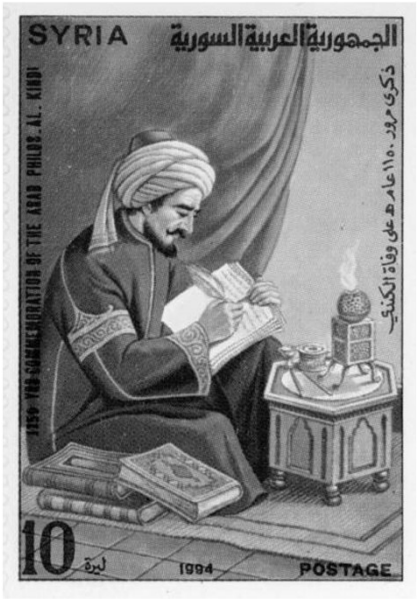
- Released in January 2017
- Data cut-off August 1, 2016
- Lacked recent data on cannabidiol and epilepsy

Cannabis and Tetanus

In the 19th century, there was no immunization for *Clostridium tetani,* and it was uniformly fatal.

"Opisthotonus in a patient suffering from tetanus - Painting by Sir Charles Bell - 1809"
http://www.anatomyacts.co.uk/exhibition/object.asp?objectnum=62

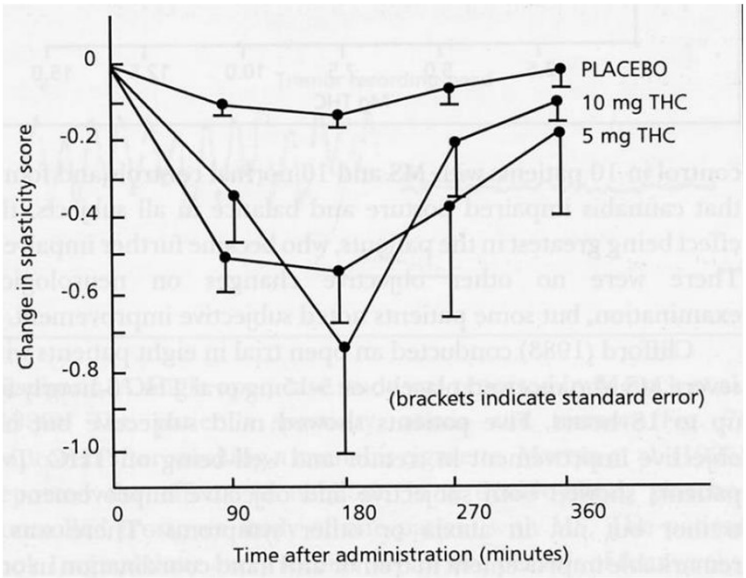
Abu Yousuf Yaqub ibn Ishaq al-Kindi, 9th century



"hasheesh---eases the muscles of the limbs and what flows"

al-Kindi, Levey M. The medical formulary, or Aqrabadhin of al-Kindi. Madison,: University of Wisconsin Press; 1966, p. 194.

Spasticity Scores (Petro & Ellenberger 1981)



Petro DJ, Ellenberger C (1981). Treatment of human spasticity with delta9-tetrahydrocannabinol. *J Clin Pharmacol* 21: 413S-416S.

Metz, L., and S. Page. 2003. Oral cannabinoids for spasticity in multiple sclerosis: will attitude continue to limit use? *Lancet* 362 (9395):1513.

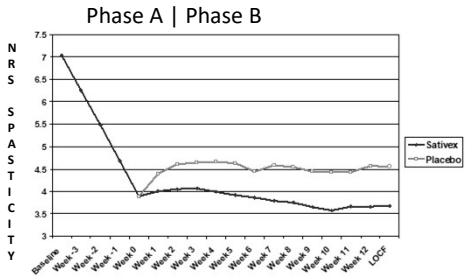
After the CAMS Study (Zajicek et al. 2003):

"We now have as much evidence to support the use of the oral cannabinoids for spasticity in ambulatory people with multiple sclerosis as we do for many standard therapies for spasticity, including baclofen."

Sativex Efficacy –N Multiple Sclerosis Clinical Studies
Nabiximols Efficacy: Multiple Sclerosis Clinical Trials

Study Code	Study Details	Key Efficacy Result	P-value	Reference
Phase II *(Randomised, Double-Blind, Placebo Controlled Studies)*				
GWN19902	Symptoms of MS and other nervous system conditions (n=25)	Improvement in Spasticity (VAS)	<0.05	Wade DT et al. Clin Rehab. 2003
GWMS0001	MS Symptoms (n=160)	Improvement in Spasticity (VAS)	0.001	Wade DT et al. Multiple Sclerosis 2004
Phase III *(Randomised, Double-Blind, Placebo Controlled Studies)*				
GWCL0403	MS, Spasticity (n=337)	Improvement in Spasticity (NRS)	0.22 0.035 (PP)	Collin C et al. Neurol Res. 2010
GWMS0106	MS, Spasticity (n=189)	Improvement in Spasticity (NRS)	0.048	Collin C et al. Eur J Neurol. 2007
GWSP0604	MS, Spasticity (n= (A) -572, (B) -241)	Improvement in Spasticity (NRS)	p=0.0002	Novotna J et al. Eur J Neurol 2011
GWSP0702	MS, Spasticity (n=36) *Randomised Withdrawal Study Design*	Time to treatment failure (NRS)	p=0.013	Notcutt W et al. Multiple Sclerosis 2011
GWSP1172	MS Spasticity (n=121) 12 month RCT	GIC	P<0.0001	ECTRIMS 2013
Long Term Extension Studies (Open Label)				
GWMS0001	Open label extension study (n=137)	Long term efficacy(NRS)	N/A	Wade DT et al. Mult Scler 2007
GWEXT0102	Open label extension study (n=507)	Long term efficacy(NRS)	N/A	

Cannabis and Spasticity



Mean 48% improvement in spasticity on nabiximols over 16 weeks

Novotna J et al. Eur J Neurol 2011

- Muscle tone is under tonic control of the ECS
- CB_1 agonists reduce spasticity, while antagonists such as SR141716A (Rimonabant) exacerbate it (Baker et al. 2000).
- CB_1 receptors are densely represented in cortical and basal ganglia areas sub-serving motor control and their corresponding cerebellar counterparts (Glass et al. 1997).
- Endocannabinoid functions are also prominent in interneurons of the spinal cord (Farquhar-Smith et al 2000) and neocortex (Bacci et al. 2004) that may relate to pathophysiological mechanisms of spasticity.
- Cannabis-based medicines are clinically effective treatments for spasticity in multiple sclerosis (Novotna et al. 2011, and many others).

Koehler J (2014). Who benefits most from THC:CBD spray? Learning from clinical experience. *European Neurology* 71 Suppl 1: 10-15.

"Perhaps the most important finding is the possibility of obtaining relevant Improvements in QoL/ADL in some patients with resistant MD spasticity, allowing them to engage back in physical and social activities." (p.10)

"For some patients the dosage of existing therapies might be reduced and this can help minimise the impact of weakness---" (p. 14)

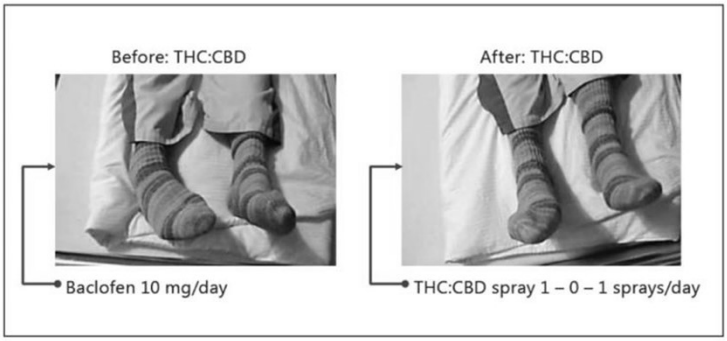


Fig. 3. Case 2: Recurrent equinovarus position of the right foot at rest before and after treatment with THC:CBD oromucosal spray.

(p. 13)

Rekand T (2014). THC:CBD spray and MS spasticity symptoms: data from latest studies. *European Neurology* 71 Suppl 1: 4-9.

- Examined 150 patients in clinical studies and 900 in post-marketing
- "---in practice average doses used by patients tended to be lower than those reported in clinical studies (5-6.4 vs. >8 sprays/day), and effectiveness was maintained in the majority of patients---." (p. 4)
- 33 patients were specifically examined: "The mean spasticity 0-10 NRS score decreased from 6.0 (±1.76) at baseline to 3.6 (±1.73) at final visit ($p<0.0001$)" (p. 6)
- "There was one case of suicidal ideation, in a subject taking placebo." (p. 7)
- "---long-term treatment with THC:CBD spray was not associated with cognitive decline, depression or significant changed in mood." (p. 7)
- "At 6 months 69% of the initial patients were continuing with THC:CBD oromucosal spray and the equivalent number was 66% at 1-year." (p. 8)

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Rekand T (2014). THC:CBD spray and MS spasticity symptoms: data from latest studies. *European Neurology* 71 Suppl 1: 4-9.

Driving skills

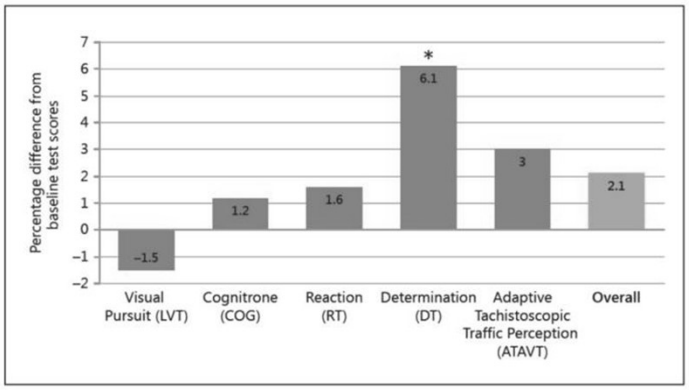

Fig. 1. Effect of THC:CBD oromucosal spray on 5 specific driving-related ability dimensions in patients with moderate to severe resistant MS-related spasticity. * $p = 0.0255$ versus baseline.

Rekand T (2014). THC:CBD spray and MS spasticity symptoms: data from latest studies. *European Neurology* 71 Suppl 1: 4-9.

No cognitive sequelae but Clear improvement in functional status

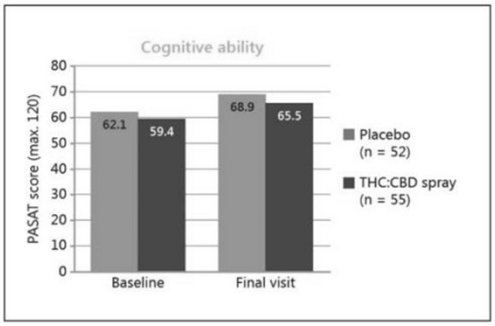

Fig. 2. Effects of THC:CBD oromucosal spray and placebo on cognitive ability of MS patients with spasticity treated for 50 weeks.

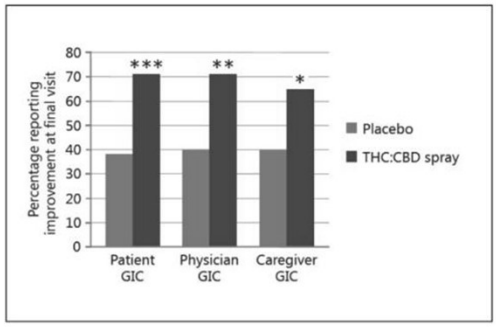

Fig. 3. Effects of THC:CBD oromucosal spray and placebo on patient, physician and caregiver Global Impression of Change (GIC) in MS patients with spasticity treated for 50 weeks. * p = 0.0042; ** p = 0.0014; *** p < 0.001.

1

Rekand T (2014). THC:CBD spray and MS spasticity symptoms: data from latest studies. *European Neurology* 71 Suppl 1: 4-9.

Table 1. Tolerability of THC:CBD oromucosal spray and placebo in MS patients with spasticity treated for 50 weeks

	THC:CBD spray (n = 62)	Placebo (n = 59)
Any AE	39 (63%)	19 (32%)
Treatment-related	25 (40.3%)	5 (8.5%)
Vertigo	6 (9.7%)	0
Dizziness	5 (8.1%)	0
Fatigue	5 (8.1%)	1 (1.7%)
Muscle spasticity	5 (8.1%)	2 (3.4%)
Respiratory tract infection	0	3 (5%)
Withdrawals from study	12 (19%)	11 (19%)
AE	8	2
Withdrew consent	4	7
Lost to follow-up	0	1
Investigator decision	0	1

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Rekand T (2014). THC:CBD spray and MS spasticity symptoms: data from latest studies. *European Neurology* 71 Suppl 1: 4-9.

Table 2. Safety findings of special interest from the UK/German registry (n = 687)

	Incidence (n = 687)
Any AE, % (n)	27.7 (190)
	10.5 (72) treatment-related
Falls	4.9 (34)
Depression	3.3 (23)
Multiple sclerosis	1.9 (13)
Dizziness	1.9 (13)
Urinary tract infection	1.5 (10)
SAEs, % (n)	11.5 (79)
	2.3 (16) treatment-related

Treating physicians rated 84% of patients as gaining worthwhile benefit from THC:CBD spray.

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Rekand T (2014). THC:CBD spray and MS spasticity symptoms: data from latest studies. *European Neurology* 71 Suppl 1: 4-9.

Table 3. Safety findings of special interest from the Spanish registry

Tolerability	Incidence (n = 196)
Any AE, % (n)	19.9% (39)
Significant psychiatric or psychotic event	2.4% (5)
Reduced driving ability	0.5% (1)
Fall requiring medical attention	0% (0)
Suicidal thoughts/attempted suicide	0% (0)
Abuse/misuse	0% (0)
Other	16.8% (33)

More than two-thirds of patients reported deriving benefit from THC:CBD spray, despite having spasticity resistant to treatment with current oral antispasticity agents.

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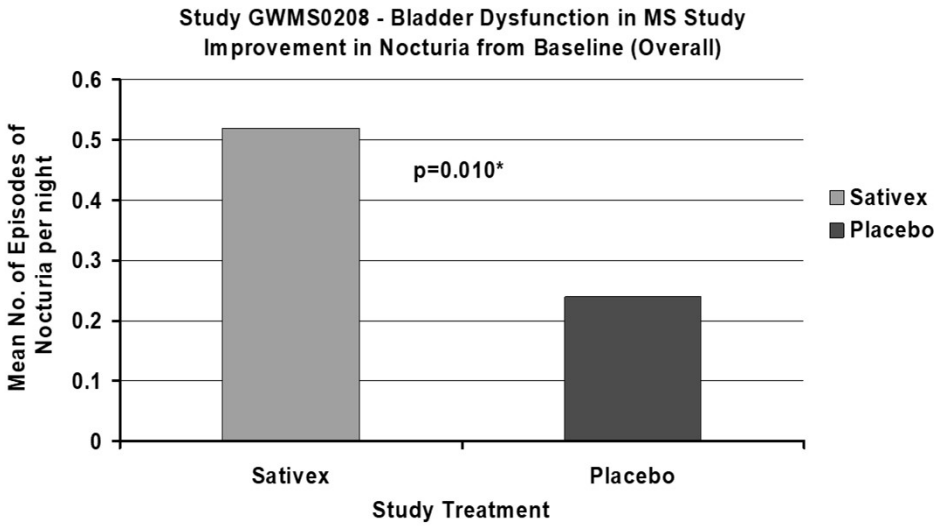
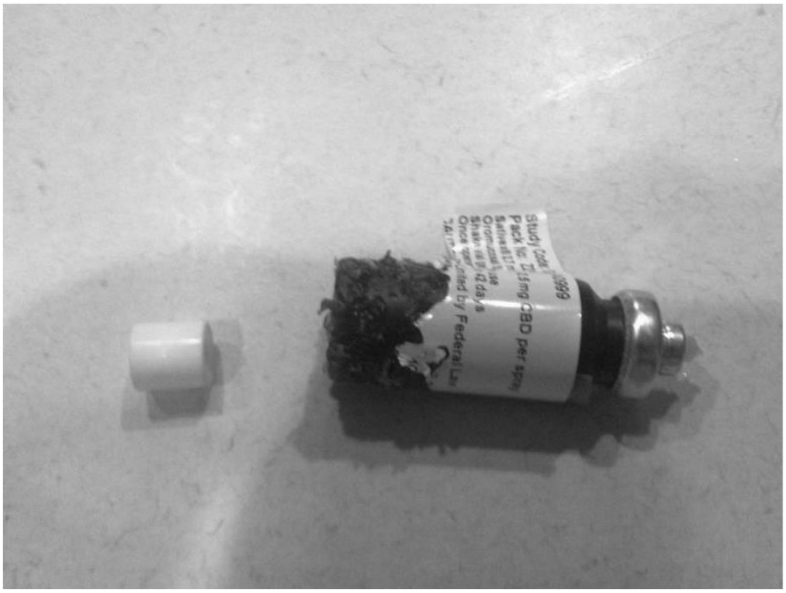
Bladder Dysfunction in MS Study (Fowler, C. et al.) (N=135)



Nabiximols Abuse and Attempted Diversion



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The Perpetrator---

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Cannabis and the Future of Neurology

Ethan Russo, MD

ethanrusso@comcast.net

Sumeria, 2200 BCE

"A.ZAL.LA U.HI.A sindi sa qat etemmi" and translated (p. 21), "Root of caper which is on a grave, root of acacia, right horn of an ox, left(?) horn of a kid that has been covered, seed of tamarisk, seed of laurel, ***Cannabis; these seven drugs are a cataplasm for the hand of a ghost, with which to bind his temples.***" Thompson, R.C. (1930b): Assyrian prescriptions for treating bruises or swellings. *American Journal of Semitic Languages and Literatures* 47(1): 1-25.

"Hand of ghost" was identified as nocturnal epilepsy.

Wilson, J. V. & Reynolds, E. H. (1990). Texts and documents. Translation and analysis of a cuneiform text forming part of a Babylonian treatise on epilepsy. *Med Hist,* 34, 185-98.

Russo EB (2007). History of cannabis and its preparations in saga, science and sobriquet. *Chemistry & Biodiversity* 4(8): 2624-2648.

al-Mayusi, circa 1100 CE

Described the intranasal administration of cannabis leaf juice to treat epilepsy.

Lozano, I. (2001). The therapeutic use of *Cannabis sativa* L. in Arabic medicine. *Journal of Cannabis Therapeutics,* 1, 63-70.

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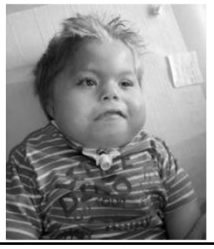
Wallace, M. J. et al. 2003. The endogenous cannabinoid system regulates seizure frequency and duration in a model of temporal lobe epilepsy. *J Pharmacol Exp Ther* 307 (1):129-37.

- **Seizure threshold is mediated by endocannabinoid mechanisms.**
- **In rats, THC produced a 100% reduction in seizures, whereas phenobarbital and diphenylhydantoin did not.**
- Animals demonstrated both acute increases in endocannabinoid production and a long-term up-regulation of CB_1 production as apparent compensatory effects counteracting glutamate excitotoxicity.
- **The anticonvulsant effect was present at sub-sedating levels.**

Gottschling, S. 2001. Cannabinoide bei Kindern Gute Erahrungen bei Schmerzen, Spastik und in der Onkologie. *Angewandte Schmerztherapei und Palliativmedizin*, 55-57.

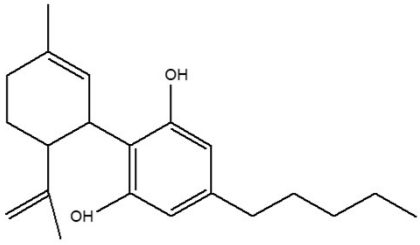


Dronabinol (average dose 0.2 mg/kg/d) was similarly administered to 13 severely neurologically impaired children, aged 7 months-17 years with uniform benefit on spasticity and pain, improved sleep in 10. The longest treatment duration was five years, and no tolerance or dose escalation was apparent. Similarly, more than 50 patients from the age of three months were treated for nausea and inanition from chemotherapy. Marked benefit was noted with no serious side effects aside from one self-limited case of 10-fold accidental overdose, and no withdrawal effects were seen even after abrupt withdrawal after months of therapy.

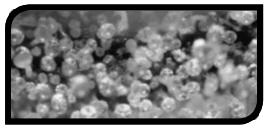
Lorenz, R. 2004. On the application of cannabis in paediatrics and epileptology. *Neuroendocrinol Lett* 25 (1-2):40-44.

- Use of Marinol® in 8 severely affected children with degenerative diseases, post-traumatic syndrome, epilepsy, hypoxic encephalopathy.
- Doses 0.04-0.12 mg/kg/d.
- Prominent positive changes noted in seizures, spasms, social interaction, with prominent palliation in fatal diseases.

Cannabidiol (CBD) and Epilepsy I (Russo)



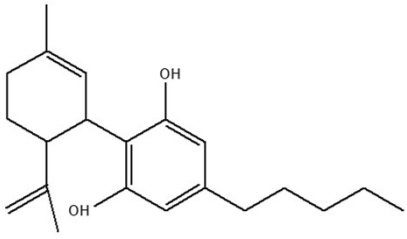
cannabidiol



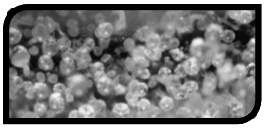
G5 CBD trichomes
Photo DJP

- Isolated 1940 (Adams), but identified positively in 1963 (Mechoulam & Shvo)
- CBD hardly binds to cannabinoid receptors (Thomas 2007)
- **Neuroprotective AO, strongly inhibits glutamate excitotoxicity, also anti-oxidant > Vitamins C and E (Hampson et al. 1998)**
- **Now known to be a $TRPV_1$ agonist with EC_{50} 3.2-3.5 µM (Bisogno et al. 2001), possibly an anticonvulsant mechanism (Shu 2013; Iannotti 2014)**
- **Inhibits uptake of the anandamide (AEA, the endocannabinoid) and weakly inhibits its hydrolysis (Bisogno et al. 2001)**
- Alerting vs. THC in clinic (Nicholson 2004)

Cannabidiol (CBD) and Epilepsy II (Russo)



cannabidiol



GS CBD trichomes
Photo DJP

- **Antagonizes tumor necrosis factor alpha (TNF-α) in rodent rheumatoid arthritis (Malfait 2000), an anti-inflammatory effect.**
- Not COX-1 or COX-2 inhibitor (Stott 2005)
- **Displays agonistic activity at 5-HT_{1A} receptor (Russo-Parker 2005), possible basis for** observed anxiolysis (Resstel 2009; Soares 2010), CVA reduction (Mishima 2005), nausea (Limebeer 2009), improvement of cognition in hepatic encephalopathy (Magen 2009), **and anticonvulsant activity (Henry 2013)**
- **Voltage-gate Na+ channel blockade is not the anticonvulsant mechanism (Hill 2014)**
- **Enhances adenosine receptor A2A signaling** via inhibition of an adenosine transporter (Carrier 2006), suggesting an important therapeutic role in various inflammatory and chronic pain states

Porter, B. E. & Jacobson, C. (2013). Report of a parent survey of cannabidiol-enriched cannabis use in pediatric treatment-resistant epilepsy. *Epilepsy Behav,* 29, 574-7.

- Solicited data from an online Facebook survey of 150 families whose children were using cannabidiol-enriched cannabis to treat drug resistant seizures
- 19 responses (12.7%): 13 Dravet syndrome, 4 Doose syndrome, 1 Lennox-Gastaut syndrome, 1 idiopathic epilepsy
- These children had used an average of 12 ACDs previously!

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Porter, B. E. & Jacobson, C. (2013). Report of a parent survey of cannabidiol-enriched cannabis use in pediatric treatment-resistant epilepsy. *Epilepsy Behav,* 29, 574-7.

Overall, 84% noted decreased seizure frequency on CBD:

- 2 (11%) had complete remission
- 8 (42%) had >80% reduction in seizure frequency
- 6 (32%) had 25-60% reduction

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Porter, B. E. & Jacobson, C. (2013). Report of a parent survey of cannabidiol-enriched cannabis use in pediatric treatment-resistant epilepsy. *Epilepsy Behav,* 29, 574-7.

Cannabidiol was associated with adverse events:
- Drowsiness: 37%
- Fatigue: 16%

With some side benefits:
- Better mood: 79%
- Increased alertness: 74%
- Better sleep: 68%

Study Limitations:
- A preliminary survey of limited duration
- A self-selected population with low response rate
- No control group

68

Press CA, et al. Parental reporting of response to oral cannabis extracts for treatment of refractory epilepsy. *Epilepsy & behavior.* 2015;45:49-52.

Table 2
Epilepsy characteristics and response rate.

Seizure type	N	Responders	% Responders
Generalized tonic–clonic	30	9	30%
Focal	21	8	38%
Absence	18	5	28%
Myoclonic	15	3	20%
Epileptic spasms	14	5	36%
Tonic	12	2	17%
Atonic	9	4	44%
Syndrome type	**N**	**Responders**	**% Responders**
Doose syndrome	3	0	0%
Dravet syndrome	13	3	23%
Lennox–Gastaut syndrome	9	8	89%*

Responders reported >50% decrease in seizures.
* $p < 0.05$ Fisher's exact.

Table 3
OCE type and response.

OCE type	N	Responders
CBD only	52	18 (35%)
CBD + other OCE	8	5 (63%)
THCA only	5	0 (0%)
Other	10	2 (20%)

CBD = Cannabidiol, THCA = Tetrahydrocannabinolic acid.

Table 4
Reported improvements.

Additional improvements (56% of all patients)	Frequency	Percent
Alertness/behavior	25	33%
Language	8	11%
Motor skills	8	11%
Sleep	5	7%

75 pts. in Colorado identified using cannabis extracts for intractable seizures.

57% reported improvement; 33% a >50% improvement

There was NSD in response rates by seizure type.

There was no difference in response rate of CBD strains vs. mixed strains, but no improvement in 5 pts. receiving THCA only

Response rate for families moving to CO for Tx. was 47% vs. only 22% for those already there, and 3X as great for those reporting >50% response!

Improvements also noted in functional status

Devinsky O, et al. Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial. *Lancet Neurol.* 2016;15(3):270-8.

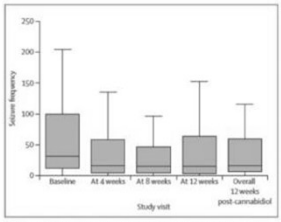


Figure 2: **Monthly frequency of motor seizures in patients in the efficacy analysis group (n=137)**
Boxplots show median values, with 25th and 75th percentiles. The whiskers denote the 25th percentile − 1·5 × IQR and the 75th percentile + 1·5 × IQR.

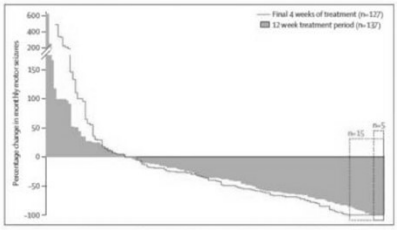


Figure 3: **Percentage change in monthly frequency of motor seizures in patients in the efficacy analysis group (n=137)**
Percentage changes for each patient are ordered from greatest increase to greatest decrease. The dashed boxes indicate patients who became free of that seizure type during the 12 week treatment period (blue) or the last 4 weeks of treatment (red).

- 162/214 pts. observed over 12 w., starting CBD 2-5 mg/kg/d titrating to 25-50 (mean dose 22.7-22.9 mg/kg/d)
- AE: somnolence 25%, decreased appetite 19%, diarrhea 19%. Only 3% discontinued due to AEs.
- Sedation prominent with Clobazam
- Median change in total seizures was -34.6%, greatest with focal sz. (-55%)
- 39% had >50% reduction in motor spells, 21% had >70% reduction, 9% >90% reduction. Effective for Dravet and Lennox-Gastaut syndromes.

DEVINSKY, O. et al. 2017. Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome. *N Engl J Med,* 376, 2011-2020.

Table 2. Primary Efficacy End Point of Percentage Change in Convulsive-Seizure Frequency in Each Trial Group.*

Variable	Cannabidiol	Placebo	Adjusted Median Difference (95% CI)	P Value†
			percentage points	
No. of convulsive seizures per mo — median (range)				
Baseline	12.4 (3.9 to 1717)	14.9 (3.7 to 718)		
Treatment period	5.9 (0.0 to 2159)	14.1 (0.9 to 709)		
Percentage change in seizure frequency — median (range)	−38.9 (−100 to 337)	−13.3 (−91.5 to 230)	−22.8 (−41.1 to −5.4)	0.01

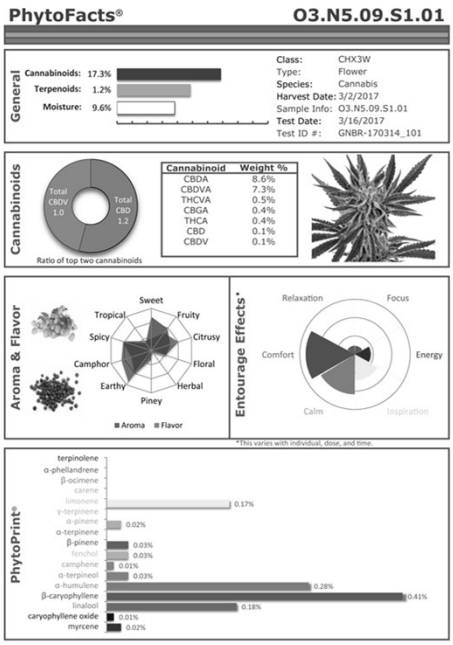
* CI denotes confidence interval.
† The P value was calculated with the use of a Wilcoxon rank-sum test with the Hodges–Lehmann approach.

- RCT in 120 Dravet patients, Epidiolex 20 mg/kg/d vs placebo.
- Median monthly sz. frequency fell from 12.4->5.9 vs. 14.9->14.1 (p=0.01)
- 43% of CBD pts. had 50% or more sz. reduction vs. 27% for placebo
- 5% CBD pts. became sz.-free vs. 0% for placebo
- Caregiver GIC improved 1 category or better on CBD vs. placebo (p=0.02)

Type III, CBD/CBDV-Predominant

Contains 4 potential anticonvulsants:
CBD
CBDV
THC
Linalool
plus the anti-inflammatory CB_2 agonist, caryophyllene

LEWIS, M. A., RUSSO, E. B. & SMITH, K. M. 2018. Pharmacological Foundations of Cannabis Chemovars. *Planta Med* 84(4):225-233.



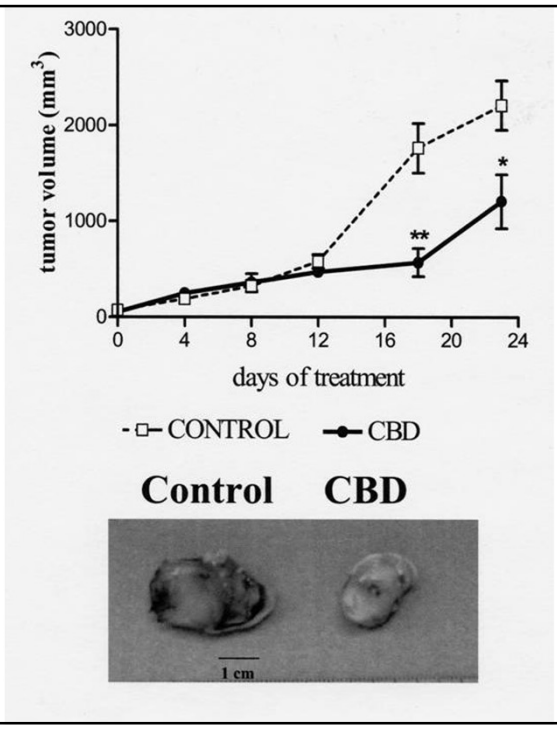
"Because of the therapeutic failures and because of the toxicity associated with the currently used antiepileptics, the search for relatively non-toxic drugs with different mechanisms of action is an obvious goal in epilepsy research. Both the lack of toxicity and the anticonvulsant properties of CBD combine to enhance its therapeutic potential as an antiepileptic."

What year would you guess this observation was made?

Karler, R., and S. A. Turkanis. 1979. "Cannabis and epilepsy." In *Marihuana biological effects: Analysis, metabolism, cellular responses, reproduction and brain.*, edited by G. G. Nahas and W. D. M. Paton, 619-641. Oxford, UK: Pergamon Press.

"Because of the therapeutic failures and because of the toxicity associated with the currently used antiepileptics, the search for relatively non-toxic drugs with different mechanisms of action is an obvious goal in epilepsy research. Both the lack of toxicity and the anticonvulsant properties of CBD combine to enhance its therapeutic potential as an antiepileptic."

p. 639



Cannabis Effects on Tumors

Massi, P., A. Vaccani, S. Ceruti, A. Colombo, M. P. Abbracchio, and D. Parolaro. 2004. Antitumor effects of cannabidiol, a non-psychotropic cannabinoid, on human glioma cell lines. *J Pharmacol Exp Ther* 308 (3):838-845.

Foroughi, M., *et al.* (2011) Spontaneous regression of septum pellucidum/forniceal pilocytic astrocytomas--possible role of Cannabis inhalation. *Childs Nerv Syst* 27, 671-679

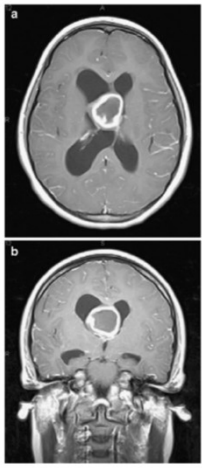


Fig. 1 a & b Case 1: Contrast-enhanced T1-weighted MRI scans in axial (a) and coronal (b) planes showing a large mass with peripheral enhancement in the septum pellucidum/forniceal region causing intraventricular obstructive hydrocephalus

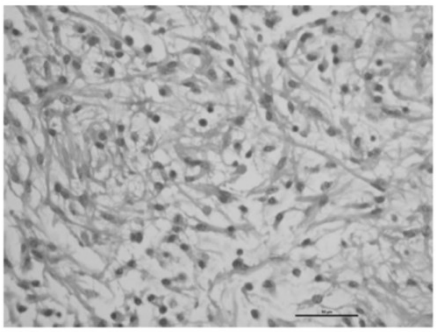


Fig. 2 Histologically, the tumor demonstrated the features of pilocytic astrocytoma with bipolar cells with "hair-like" cell processes, and eosinophilic granular bodies (H&E, ×400 magnification)

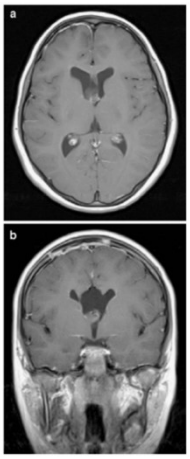


Fig. 3 a & b Contrast-enhanced T1-weighted MRI scans in axial (a) and coronal (b) planes 33 months post-resection show residual tumor at the foramen of Monro

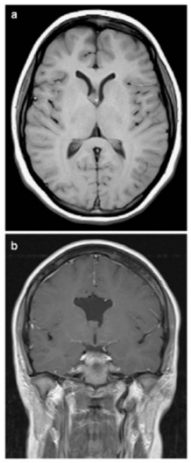
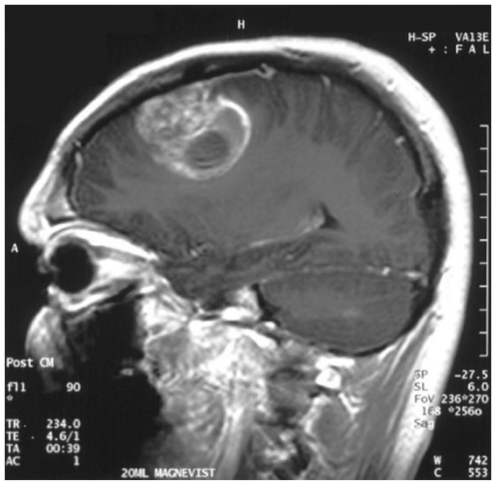


Fig. 4 a & b Contrast-enhanced MRI scans in axial (a) and coronal (b) planes 6 years post-surgical resection show regression of the tumor remnant, which was measured to be about 25% of early post-operative size

Sativex® and Glioblastoma Multiforme



GBM in 15 YO boy, Wikipedia

- Phase II RCT of 21 patients with recurrent GBM on temozolomide plus Sativex vs. placebo.
- 83% 1-year survival vs. 53% in controls (p=0.042)
- Survival was >550 days vs. 369 on controls
- 2 withdrawals in each group due to AEs (www.gwpharm.com)

ELROD, H. A. & SUN, S. Y. 2008. PPARgamma and Apoptosis in Cancer. *PPAR Res* 2008**,** 704165.

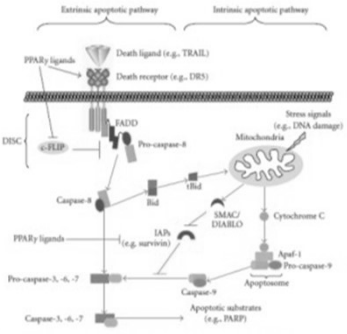


FIGURE 1: *Schema for basic apoptotic signaling pathways and possible mechanisms underlying PPARγ ligand-induced apoptosis.* Ligation of death ligands (e.g., TRAIL) with their receptors (e.g., DR5) results in formation of the death-inducing signaling complex (DISC), in which pro-caspase-8 will be recruited through the death adaptor protein FADD and cleaved to generate activated caspase-8. This process is inhibited by c-FLIP. Certain stress signals (e.g., DNA damage) can target mitochondria and induce cytochrome C release from the mitochondria into the cytosol leading to caspase-9 activation by forming an apoptosome via binding to Apaf-1. Both caspase-8 and caspase-9 activate downstream procaspase-3, -6, and -7, leading to cleavages of their target death proteins such as PARP. In addition, truncated Bid (tBid), activated by caspase-8 via cleavage, facilitates insertion of Bax into the mitochondrial membrane leading to cytochrome C release. Therefore, tBid may serve as a link between the extrinsic and intrinsic apoptotic pathways. Inhibitors of apoptosis proteins (IAPs) such as survivin can bind to activated caspase-9 and prevent its action on effector caspases, whereas SMAC/DIABLO binds to IAPs, leaving caspase-9 free to activate the effector caspases. PPARγ ligands may induce apoptosis through induction of DR5 and/or downregulation of c-FLIP and/or survivin.

- PPARs are ligand-binding transcription factors, on nuclear membranes
- Affect adipogenesis, apoptosis and many other functions
- PPARγ stimulation may kill cancer cells without toxicity to normal cells, such as astrocytes.
- Effects are additive with other cytotoxic agents
- Butyrate and capsaicin may be natural ligands

SHEN, Y. et al. 2016. Peroxisome Proliferator-Activated Receptor-gamma and Its Ligands in the Treatment of Tumors in the Nervous System. *Curr Stem Cell Res Ther* 11:208-15.

- The peroxisome proliferator-activated receptor-γ (PPARγ) has been identified in cancers, especially breast stomach colon, lung and brain.
- PPARγ regulates target gene transcription.
- Activation of the receptor inhibits tumor cell growth.
- PPARγ agonists may prove useful in treating brain tumors.

NADAL, X. et al. 2017 Tetrahydrocannabinolic acid is a potent PPARgamma agonist with neuroprotective activity. *Br J Pharmacol*

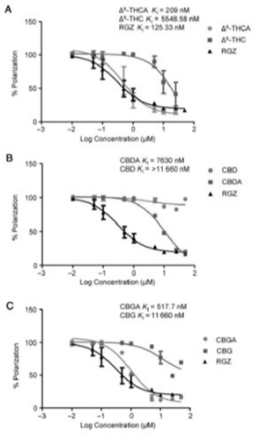
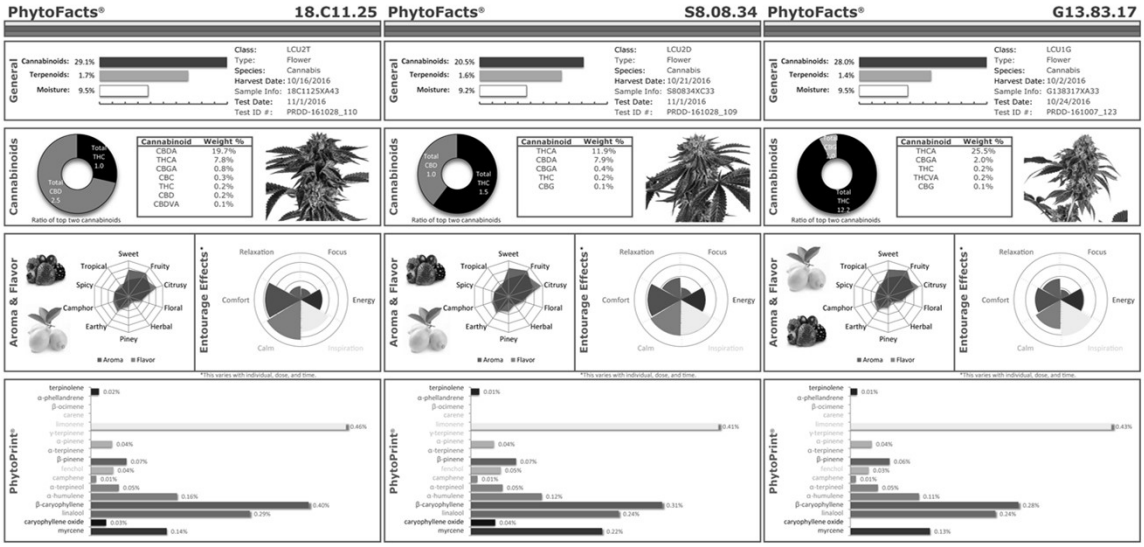


Figure 1
The carboxylic acid group of phytocannabinoids is critical for enhanced PPARγ binding. Cannabinoid binding affinities were tested at the indicated concentrations and compared with the binding affinity of rosiglitazone (RGZ). Data were transformed to a logarithmic function, and the K_i values were calculated and are shown in the Figure ($n = 3$).

- **THCA is a PPARγ agonist (IC_{50} = 470 nM, K_i = 209 nM) > CBGA (517.7 nM) and >> than CBDA, CBD or THC**
- THCA improved neuronal viability in an animal model of Huntington disease, and decreased striatal neurodegeneration (blocked by PPARγ antagonist)
- Suggested as a therapeutic agent in HD

Type I, II & III Chemovars with Preservation of Limonene-predominant Terpenoid Profile

LEWIS, M. A., RUSSO, E. B. & SMITH, K. M. 2018. Pharmacological Foundations of Cannabis Chemovars: No "Strain," No Gain. *Planta Med* 84(4):225-233.



Traumatic Brain Injury (TBI) (Russo)

- Both THC and CBD are neuroprotective antioxidants with extensive documentation (Hampson 1998)
- Additionally, the anti-glutamatergic effect of CBD may help prevent glutamate excitotoxicity that leads to neuronal demise after TBI and CTE.
- Anecdotally, cannabis, particularly chemovars combining THC and CBD, have been extremely helpful in treatment of chronic traumatic encephalopathy symptoms: headache, nausea, insomnia, dizziness, agitation, substance abuse, and psychotic symptoms.

Russo, E. B. 2018. Cannabis Therapeutics and the Future of Neurology. *Frontiers in Integrative Neuroscience, 12*, 1-11.

ASO, E. & FERRER, I. 2014. Cannabinoids for treatment of Alzheimer's disease: moving toward the clinic. *Front Pharmacol,* 5, 37.

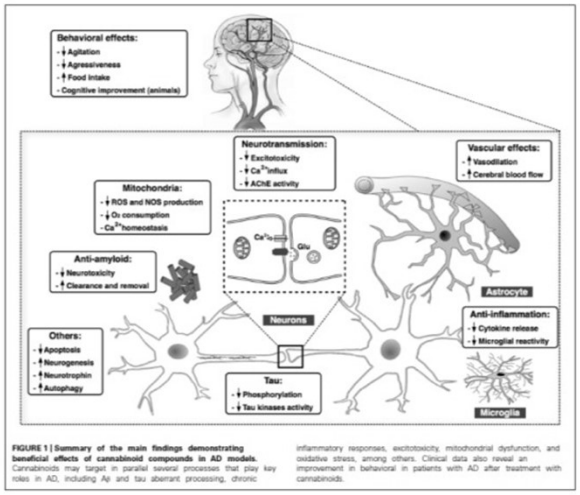
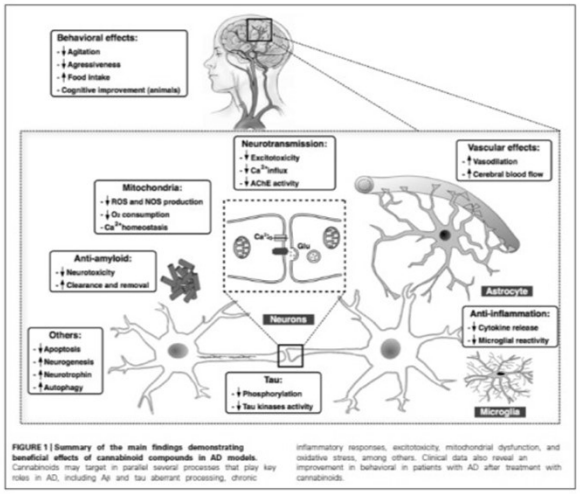


FIGURE 1 | Summary of the main findings demonstrating beneficial effects of cannabinoid compounds in AD models. Cannabinoids may target in parallel several processes that play key roles in AD, including Aβ and tau aberrant processing, chronic inflammatory responses, excitotoxicity, mitochondrial dysfunction, and oxidative stress, among others. Clinical data also reveal an improvement in behavioral in patients with AD after treatment with cannabinoids.

- AD a neurodegenerative disease with senile plaques formed of fibrillar β-amyloid (Aβ) from cleavage of the Aβ precursor protein (APP) by β- and γ-secretases and by presence of neurofibrillary tangles composed of hyper-phosphorylated and nitrated tau protein. The latter precedes Aβ deposition in sporadic cases.
- Once the process begins, it stimulates momentum of progressive deterioration.

83

ASO, E. & FERRER, I. 2014. Cannabinoids for treatment of Alzheimer's disease: moving toward the clinic. *Front Pharmacol,* 5, 37.



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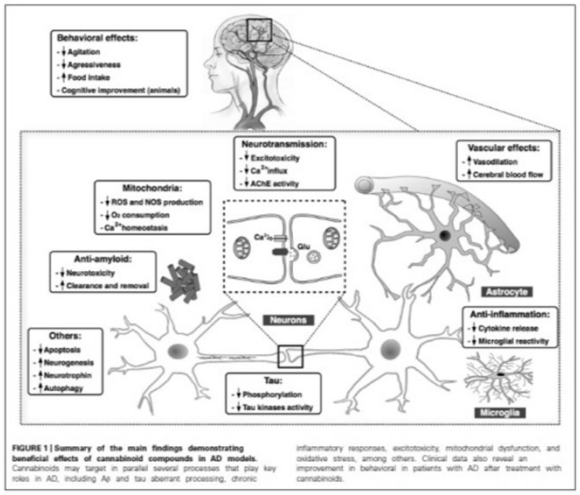
- Additional pathology includes functional mitochondrial defects, increased ROS and RNS and failure of enzymes involved in energy production that produce nerve cell exhaustion.
- Eventually, synapses and dendritic branching fail with progressive neuronal wastage.
- Dementia and cognitive decline develop and no treatment arrests the process.

84

ASO, E. & FERRER, I. 2014. Cannabinoids for treatment of Alzheimer's disease: moving toward the clinic. *Front Pharmacol,* 5, 37.



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- Intervention must begin at an earlier preclinical stage.
- Endocannabinoid function modulates the primary pathological processes of AD during the silent phase of neurodegeneration: protein misfolding, neuroinflammation, excitotoxicity, mitochondrial dysfunction and oxidative stress.
- CB_2 levels increase in AD esp. in microglia around senile plaques, and its stimulation stimulates Aβ removal by macrophages.

85

Current Pharmacotherapy for Alzheimer Disease/Dementia

- No drugs are approved for agitation.
- Commonly used anti-psychotics, antidepressants, anxiolytics and hypnotics are often associated with increased mortality in demented patients (Kales 2007) (FDA “Black Box Warning”).
- Four acetylcholinesterase inhibitors are approved in the USA to improve memory: galantamine, donepezil, tacrine and rivastigmine.
- None show strong evidence of efficacy, and are of limited benefit on a temporary basis.
- Various NMDA receptor antagonists have proven largely ineffective on progression, or toxic.

86

HAMPSON, A. J. et al. 1998. Cannabidiol and (-)Delta9-tetrahydrocannabinol are neuroprotective antioxidants. *Proc Natl Acad Sci U S A* 95:8268-73.

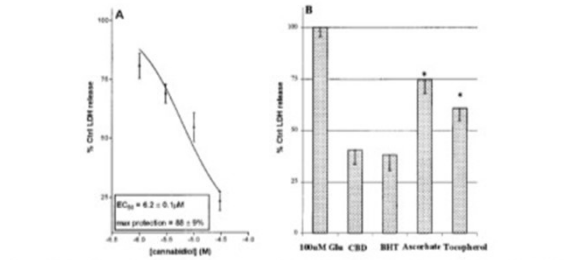
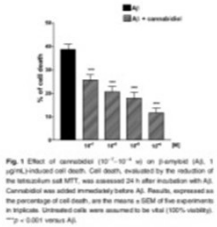


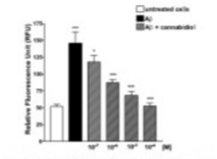
FIG. 5. (*A*) The effect of cannabidiol on oxidative toxicity in neuronal cultures. *Tert*-butyl hydroperoxide-induced toxicity was examined in the presence or absence of cannabidiol. (*B*) Comparison of antioxidants and cannabidiol for their ability to prevent glutamate toxicity in neurons. The effects of cannabidiol, BHT, ascorbate, and α-tocopherol (10 μM) were examined in a model of AMPA/kainate receptor-dependent toxicity. All drugs were present throughout the glutamate exposure period. Each experiment represents the mean of four replicates repeated on three occasions. See *Materials and Methods* for further experimental details. Significant differences between cannabidiol and other antioxidants are indicated with an asterisk.

- CBD is a neuroprotective antioxidant, more potent than ascorbate or tocopherol.
- A US patent is in place

87

IUVONE, T. et al. 2004. Neuroprotective effect of cannabidiol, a non-psychoactive component from Cannabis sativa, on beta-amyloid-induced toxicity in PC12 cells. *J Neurochem* 89:134-41.





- **CBD inhibited Aβ plaque formation**
- **CBD prevented ROS production** and peroxidation of lipids in PC12 cells exposed to Aβ
- CBD limited neuronal apoptosis from caspase 3 reduction
- **CBD counteracted increases in intracellular Ca^{++} from Aβ**

88

ESPOSITO, G. et al. 2006. The marijuana component cannabidiol inhibits beta-amyloid-induced tau protein hyperphosphorylation through Wnt/beta-catenin pathway rescue in PC12 cells. *J Mol Med* 84:253-8.

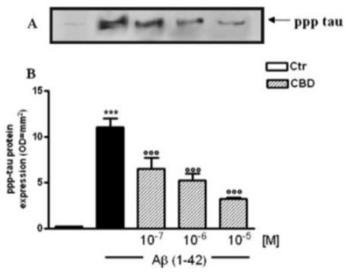
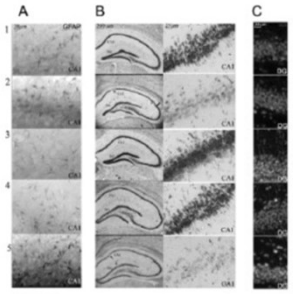


Fig. 3 Effect of Aβ (1–42) (1 μg/ml) on hyperphosphorylated tau (*ppp-tau*) protein expression at 24 h in PC12 rat pheochromocytoma cells in the absence or in the presence of cannabidiol (*CBD*) (10^{-7}–10^{-5} M); **a** ppp-tau protein expression (68 kDa) in cell homogenates; **b** densitometric analysis of corresponding bands (optical density). **a** Representative of n=3 separated experiments. Each *bar* in **b** shows the mean±SEM of three experiments. ***P<0.001 vs control; °°°P<0.001 vs Aβ

- In an *in vivo* model, CBD was AI via reduction in inducible nitric oxide synthase (iNOS) and IL-1β expression and release
- **CBD inhibited tau protein hyper-phosphorylation in Aβ-stimulated PC12 neurons.**

89

ESPOSITO, G., et al. 2011. Cannabidiol reduces Abeta-induced neuroinflammation and promotes hippocampal neurogenesis through PPARgamma involvement. *PLoS One,* 6, e28668.



1. Vehicle
2. Aβ 30ng
3. Aβ 30ng + CBD 10mg/kg
4. Aβ 30ng + CBD 10mg/kg + MK886 10mg/kg
5. Aβ 30ng + CBD 10mg/kg + GW9662 1mg/kg

Figure 4. Effects of CBD on reactive gliosis, neuronal survival, and neurogenesis in rat hippocampi. A: representative photomicrographs of the CA1 area of rat hippocampus showing the results of immunohistochemical evaluation of GFAP. B: representative photomicrographs showing the results of Nissl staining of the whole rat hippocampus (2X magnification) and the corresponding CA1 region (10X magnification). C: immunofluorescence photomicrographs showing a particular (10X magnification) of DCX-labeled cells in the dentate gyrus (DG) of rat hippocampi.
doi:10.1371/journal.pone.0028668.g004

- **CBD's MOA seemed to be selectively mediated via PPARγ**: dose dependently antagonizing pro-inflammatory NO, TNF-α, and IL-1β, an effect blocked by GW9662 (PPARγ antagonist)
- CBD reduced reactive gliosis via selective PPARγ-related NFκB inhibition.
- Both AEA and **CBD promoted neurogenesis after Aβ exposure**

90

EUBANKS, L. M. et al. 2006. A molecular link between the active component of marijuana and Alzheimer's disease pathology. *Mol Pharm* 3:773-7.

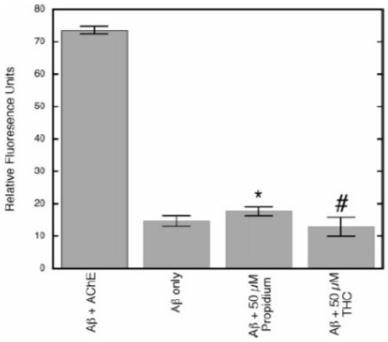


Figure 4. Inhibition of AChE-induced Aβ aggregation by THC and propidium ((*) $p < 0.05$ versus Aβ only; (#) $p < 0.05$ versus Aβ + propidium).

- **THC competitively inhibits acetylcholinesterase, increasing levels, and preventing Aβ aggregation** via binding to the enzyme in a critical region affecting amyloid production.

91

VOLICER, L. et al. 1997. Effects of dronabinol on anorexia and disturbed behavior in patients with Alzheimer's disease. *Int J Geriatr Psychiatry,* 12, 913-9.

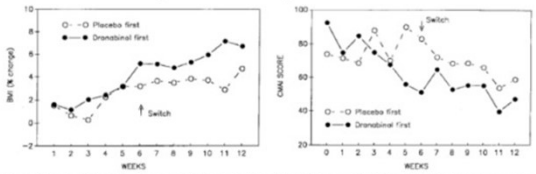


Fig. 1. Changes of the body mass index (BMI) during the placebo and dronabinol phases of the study. The treatment was switched after 6 weeks. For statistical analysis see text

Fig. 2. Changes of the Cohen-Mansfield Agitation Inventory (CMAI) (14) score during the placebo and dronabinol phases of the study. For statistical analysis see text

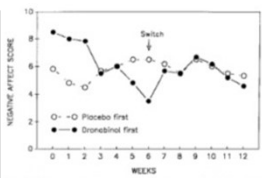


Fig. 3. Changes of the negative affect score (15) during the placebo and dronabinol phases of the study. For statistical analysis see text

- 15 institutionalized dementia patients refusing nutrition
- RCT 6-week crossover trial of THC (Marinol®) 2.5 mg BID
- Increased BMI on THC
- Decreased Cohen-Mansfield Agitation Inventory (CMAI) scores on THC
- Improved negative affect scores
- Carry-over noted when THC administered first.

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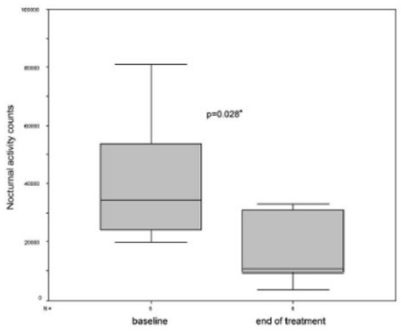
WALTHER, S. 2006. Delta-9-tetrahydrocannabinol for nighttime agitation in severe dementia. *Psychopharmacology* 185:524-8.

Fig. 1 Effects of 14 days of dronabinol treatment (2.5 mg at 7 PM) on nocturnal motor activity in patients with agitation in severe dementia. *Wilcoxon signed rank test



- Open label two-week study of 5 AD and 1 VD patient
- THC 2.5 mg at 19:00 h
- Benefit noted on nocturnal motor activity, agitation, appetite, irritability.
- No adverse events.

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What About Herbal Cannabis for Alzheimer Disease?

- Initial trials have begun sporadically, with a more focused effort in a California nursing home (data from Hergenrather, 2017).
- Patients were treated with a variety of preparations: THC-predominant (2.5-30 mg/dose), CBD –predominant, and THCA, mainly in tinctures and confections

- Marked benefit noted on: neuroleptic drug sparing, decreased agitation, increased appetite, aggression, sleep quality, objective mood, nursing care demands, self-mutilation, and pain control.

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Cannabis and Symptom Management in Alzheimer Disease

- Target symptom:
- Agitation: THC, CBD, linalool
- Anxiety: CBD, THC (low dose), linalool
- Psychosis: CBD
- Insomnia/Restlessness: THC, linalool
- Anorexia: THC
- Aggression: THC, CBD, linalool
- Depression: THC, limonene, CBD
- Pain: THC, CBD
- Memory: alpha-pinene + THC
- Neuroprotection: CBD, THC, THCA

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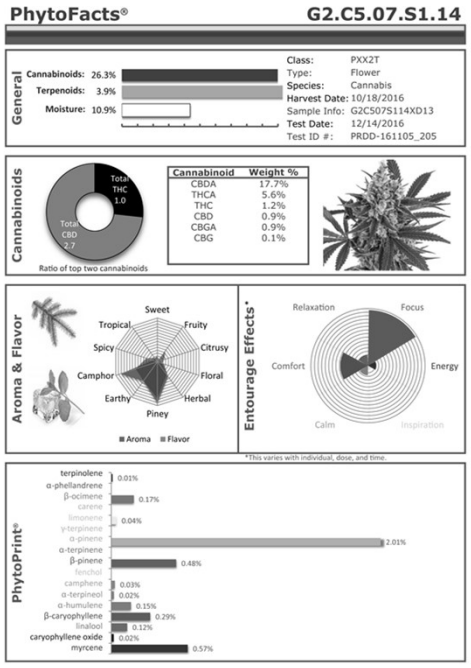
Type II, Pinene-Dominant

A non-sedating alternative

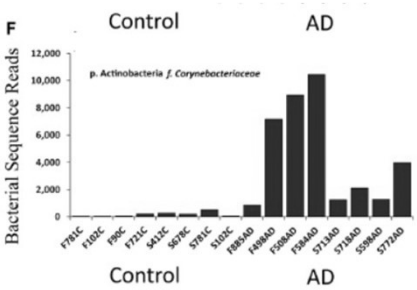
Pinene will reduce STM-impairment from THC, allowing focus and concentration

LEWIS, M. A., RUSSO, E. B. & SMITH, K. M. 2018. Pharmacological Foundations of Cannabis Chemovars: No "Strain," No Gain. *Planta Med* 84(4):225-233.

Pinene 2.01% out of a 3.9% terpenoid total.



EMERY, D. C., et al. 2017. 16S rRNA Next Generation Sequencing Analysis Shows Bacteria in Alzheimer's Post-Mortem Brain. *Front Aging Neurosci* 9:, 195.



- Neuroinflammation is a stimulus to AD development and is triggered by infectious insults.
- **AD brains demonstrated 5-10X greater bacterial loads, esp. with Actinobacteria, particularly *Propionibacterium acnes*,** a gram-positive anerobic resident of skin, mouth and gut.
- **It has been cultured from AD brains, and can grow there.**
- May stimulate biofilm formation [opposed by limonene, alpha-pinene and cannabinoids], alpha synuclein fibrillar formation in PD and amyloid fibrillization in AD

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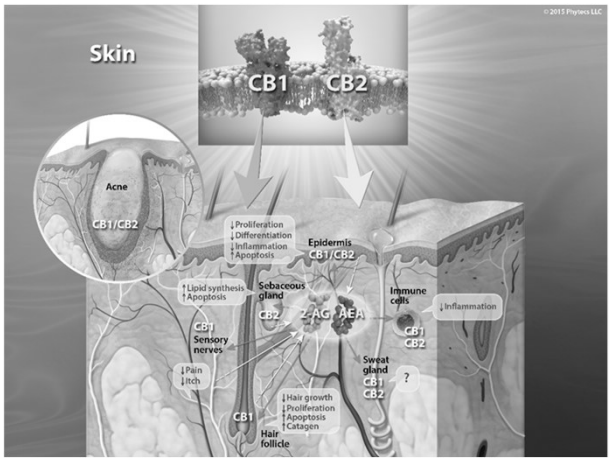
Acne and Neurodegeneration: Summary



Russo, E. B. (2018). Cannabis Therapeutics and the Future of Neurology. *Frontiers in Integrative Neuroscience, 12*, 1-11.

- Acne epidemiology prominently favors industrial societies (Cordain 2002) with altered microbiomes, and parallels that of AD (Russo 2018)
- TRPV4 implicated in pathogenesis of AD (Zhang 2013)
- CBD is a TRPV4 agonist and sebostatic agent in acne (Olah 2014)
- Limonene, linalool (Kim 2008) and pinene (Raman 1995) suppress *Propionibacterium acnes*
- **Intestinal microbiota, skin inflammation and psychiatric sx. are intertwined in a "gut-brain-skin axis." (Bowe 2011)**

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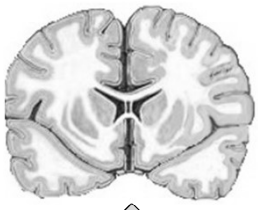
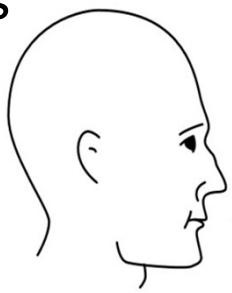
ECS & the Gut-Brain-Skin Axis

Beta-Amyloid, Neurofibrillary Tangles

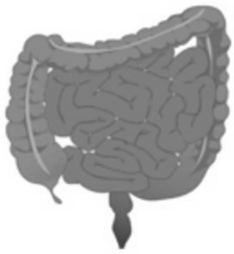




Propionibacterium acnes

Probiotics
Prebiotics
THC
CBD
THCA?

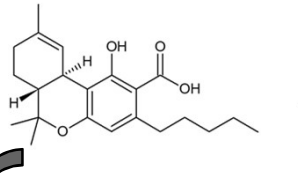
Enteric microbiota
Propionibacterium acnes



Russo, E. B. 2018. Cannabis Therapeutics and the Future of Neurology. *Frontiers in Integrative Neuroscience, 12*, 1-11.

"Grand Unified Theory"= GUT

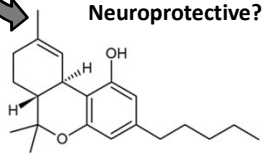
Diagrams of brain, gut by Mikael Hagstrom, face by Mouagip, all public domain.



delta-9-tetrahydrocannabinolic acid

decarboxylation

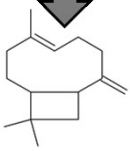
Anti-TNF-α
Anticonvulsant
Antineoplastic
PPARγ agonist
Neuroprotective?



delta-9-tetrahydrocannabinol

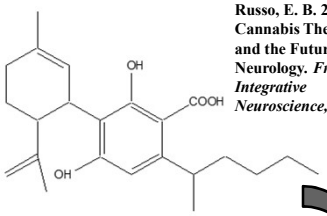
Neuroprotective
Anticonvulsant
Muscle relaxant
Pro-microbiome

Cannabis flower



beta-caryophyllene

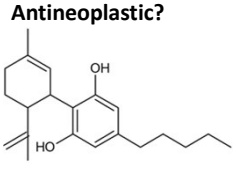
CB_2 agonist
Anti-inflammatory



cannabidiolic acid

5-HT1A agonist
Anti-emetic
Anticonvulsant
Antineoplastic?

decarboxylation



cannabidiol

Neuroprotective antioxidant
Anticonvulsant
Antineoplastic
Anti-anxiety/anti-psychotic
Antibiotic/anti-acne

Russo, E. B. 2018. Cannabis Therapeutics and the Future of Neurology. *Frontiers in Integrative Neuroscience, 12*, 1-11.

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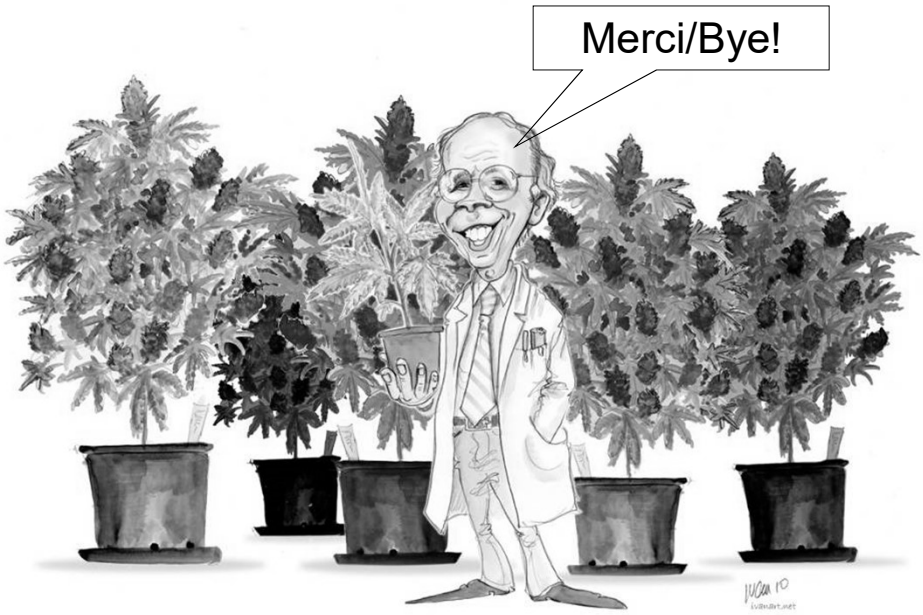

IvanArt, Bern, Switzerland, 2010 http://www.ivanart.net/index.html