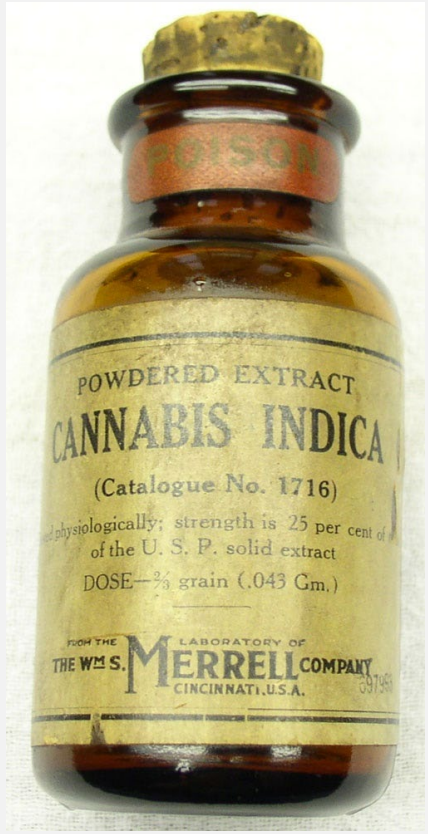
THE HISTORY

- Marijuana has been used for over 5000 years
- Cannabinoids isolated in 1960's
- Cannabinoid receptor discovered in 1980's
- Endocannabinoids discovered in 1990's



CHALLENGES WITH STUDYING CANNABIS

- Political climate
- Lack of pharma interest
- Formal RCTs of smoked cannabis are “limited”
- Public perception
- Most research has been done in animals
- Since 1960s THC increased from 1 - 5 % to 10-15%

WAYS OF CONSUMPTION

BIOAVAILABILITY (OF THC)

- Smoked - 10-25%, peaks in minutes
- Oral/Sublingual – 5-20%, peaks 1-3h later

ACTIVE INGREDIENTS

- ***tetrahydrocannabinol* (THC)**
- ***cannabidiol* (CBD)**
- Cannabavarin
- Cannabigerol
- Cannabichromene
- Delta-8-THC
- Cannabicyclol
- Cannabitiol
- + 70 other cannabinoids
- + terpenes
- + other bioactive compounds

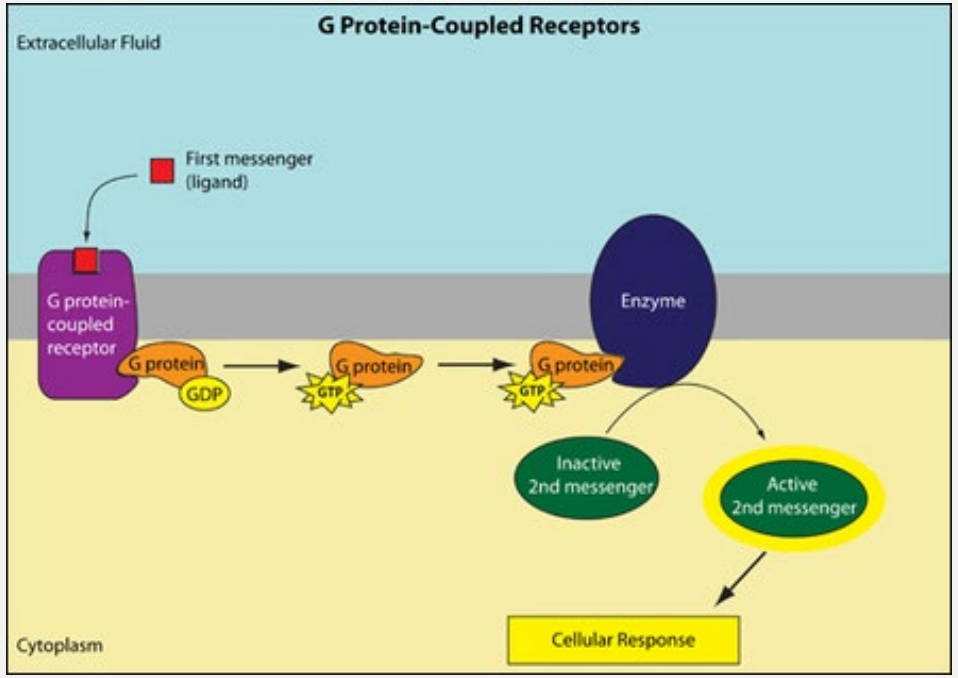
Cannabis sativa contains a higher ratio of Δ9-THC to CBD, producing more stimulating, psychotropic effects. *Cannabis indica* strains contains a higher ratio of CBD:Δ9-THC and are typically more sedating

THE BASICS

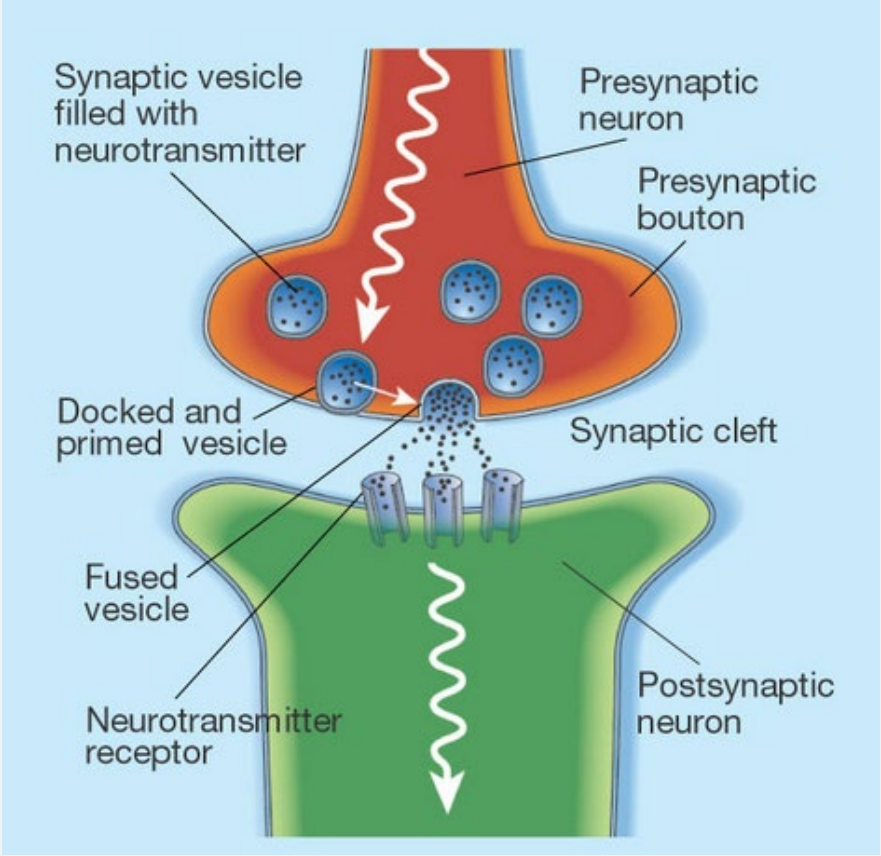
- The compounds:
  - Endocannabinoids
    - anandamide (AEA)
    - 2-arachidonoylglycerol (2-AG)
  - Phytonannabinoids
    - delta-9-tetrahydrocannabinol (THC)
    - cannabidiol (CBD)
  - Synthetic cannabinoids
    - Nabiximol
    - Dronabinol
    - Nobilone

TYPES OF RECEPTORS

- CB1:
  - regulation of neurotransmitter release
  - the heart
  - vascular smooth muscles and endothelial cells
- CB2:
  - in the immune cells
  - hematopoietic cells
- GPR55, PPARy
  - Regulation of neuronal excitability
  - Cell proliferation



EXAMPLE


Synaptic vesicle filled with neurotransmitter
Presynaptic neuron
Presynaptic bouton
Docked and primed vesicle
Synaptic cleft
Fused vesicle
Neurotransmitter receptor
Postsynaptic neuron

EFFECTS OF CANNABINOIDS ON RECEPTORS

- Δ9-THC is a partial agonist at central nervous system CB1 and CB2 in the immune system
  - The high is from its action on CB1 in the CNS
  - Regulates mood, learning, memory, food intake
  - Anti-inflammatory functions via CB1 and CB2
- CBD is an agonist at GPR55 TRPV1, TRPV2, TRPA1, GRP55, adenosine receptors
  - Limits the excitability of neurons by modulating calcium release
  - Reduces inflammation and oxidative stress
  - Reduces reperfusion injury post-stroke
  - Antiarrhythmic effects

CURRENT EVIDENCE: PAIN

Table 1 Summary of select clinical studies (RCT) on cannabis

Lead author	Year	Type of study	Study focus	Subjects	Drug	Results
RJ Noyes	1975	RCT	Cancer pain	10	Oral THC vs placebo	Improved pain relief at higher doses (with side effects)
RJ Noyes	1975	RCT	Cancer pain	36	Oral THC vs codeine vs placebo	Equianalgesic
PR Jochimsen	1978	RCT	Cancer pain	35	Benzopyranoperidine vs placebo	Not as effective as codeine
JR Johnson	2010	RCT	Cancer pain	177	Nabiximols vs THC vs placebo	Nabiximols showed pain reduction >30 %
RK Portenoy	2012	RCT	Cancer pain	263	Nabiximols vs placebo	Did not reach response rate goal but per patient report, superior analgesia overall
M Karst	2003	RCT	Neuropathic pain	21	CT-3 vs placebo	Reduction in pain scores
JS Berman	2004	RCT	Neuropathic pain	48	Nabiximols vs THC vs placebo	Did not meet study target for clinical significance, but improved pain scores and quality of sleep
DT Wade	2003	RCT	Neuropathic pain	20	THC vs CBD vs nabiximols vs placebo	THC and CBD superior to placebo
DJ Rog	2005	RCT	Neuropathic pain	66	Nabiximols vs placebo	Superior to placebo in pain reduction/sleep disturbance
TJ Nurmikko	2007	RCT	Neuropathic pain	125	THC:CBD vs placebo	Greater reduction in pain scores, allodynia, improved sleep over placebo
DI Abrams	2007	RCT	Neuropathic pain	50	Inhaled THC vs placebo	Greater pain reduction vs placebo
RJ Ellis	2009	RCT	Neuropathic pain	28	Inhaled THC vs placebo	Greater pain reduction vs placebo
B Wilsey	2008	RCT	Neuropathic pain	38	Inhaled THC vs placebo	Superior to placebo in pain reduction
MA Ware	2010	RCT	Neuropathic pain	21	Inhaled THC vs placebo	Highest dose reduced pain and improved quality of sleep over placebo
A Holdcroft	2006	RCT	Acute pain (post-op)	20	Cannador	Dose-dependent pain reduction overall
DJ Buggy	2003	RCT	Acute pain (post-op)	40	Dronabinol vs placebo	Did not show benefit for post-op pain
P Beauliu	2006	RCT	Acute pain (post-op)	41	Nabilone vs placebo	Did not show benefit for post-op pain (actually increased pain)
AK Jain	1981	RCT	Acute pain (post-op)	56	Levonantradol vs placebo	Better analgesic effects over placebo, but no significant dose-response curve
D Raft	1977	RCT	Acute pain	10	IV THC vs diazepam vs placebo	Diazepam>low-dose THC>placebo for analgesia. High dose<both placebo and diazepam
S Narang	2008	RCT	Chronic pain	30	Dronabinol vs placebo	Decreased pain intensity/increased satisfaction
DR Blake	2005	RCT	Chronic pain	58	Nabiximols vs placebo	Improved pain control/quality of sleep
W Notcutt	2004	RCT	Chronic pain	34	Sublingual THC vs cannabidiol vs Both in 1:1 combo vs placebo	THC and THC:CBD combo most effective in pain relief/sleep improvement

THE CURRENT EVIDENCE: SEIZURES

Table 2 Clinical trials of cannabidiol (CBD) and epilepsy (adapted from [11, 13])

Study	Seizure type	Population size	Treatment (subjects per group)	Continued AEDs?	Duration	Outcome	Toxicity	Limitations
Mechoulam and Carlini [261]	Treatment-resistant, temporal lobe epilespy	9	CBD, 200 mg/day (4) Placebo (5)	NS	3 months	CBD: seizure free (2), partial improvement (1), no change (1); placebo: no change (4)	None	No baseline seizure frequency; no definition of improvement; unclear if AEDs were changed; not truly randomized or blinded; unknown if groups were matched
Cunha et al. [262]	Treatment-resistant, temporal lobe epilespy	15*	CBD 200–300 mg/day (8*) Placebo (8*)	Yes	3–18 weeks	CBD: near seizure freedom (4), partial improvement (3), no change (1); placebo: no change (7), partial improvement (1)	Somnolence	Not clearly blinded (1 patient transferred groups); doses were adjusted in CBD group, not in placebo; CBD group received longer average treatment
Ames and Cridland [263]	Treatment-resistant epilepsy, intellectual/ developmental disability	12	CBD 300 mg/day for 1 week; 200 mg/day for 3 weeks (6?) Placebo (6?)	NS	4 weeks	No difference between CBD and placebo	Somnolence	Brief letter to the editor, details lacking on specifics; discontinued owing to "technical difficulties in preparing the drug"
Trembly and Sherman [264]	Treatment-resistant epilepsy	10–12†	CBD 100 mg once daily Placebo	Yes	3 months baseline, 6 months CBD or placebo, then 6 months crossover to alternative treatment	No difference between CBD and placebo (seizure frequency or cognitive/behavioral tests)	None	Differences in sample size reporting; dada reported are incomplete (conference abstract)‡

AEDs = antiepileptic drugs; NS = not stated

*1 patient switched groups after 1 month

† Abstract and subsequent book chapters have different numbers

‡ Only truly double-blind study

THE CURRENT EVIDENCE: SATIVEX (NABIXIMOL)

- Treatment of multiple sclerosis complications
  - Neuropathic pain, overactive bladder, spasticity
    - Mean difference of - 0.32 (out of 10) compared to placebo

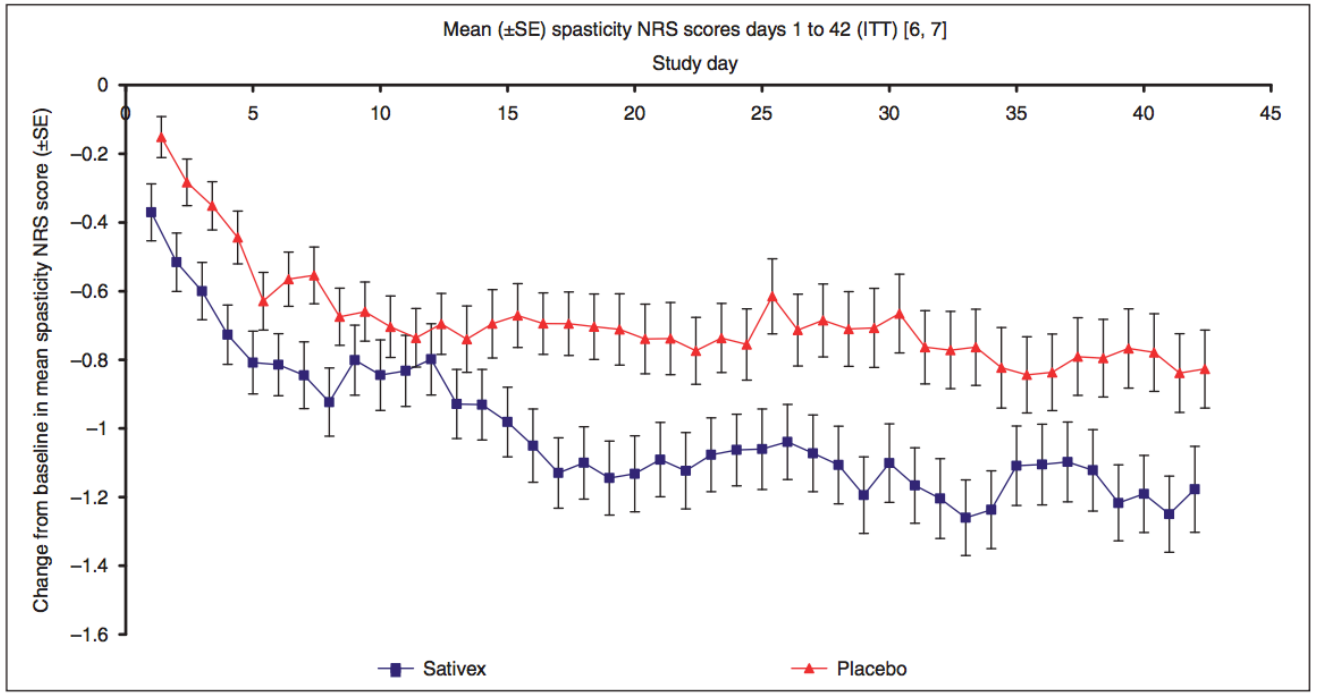


Figure 1. Change from baseline in spasticity over time.

THE CURRENT EVIDENCE: DRONABINOL (MARINOL)

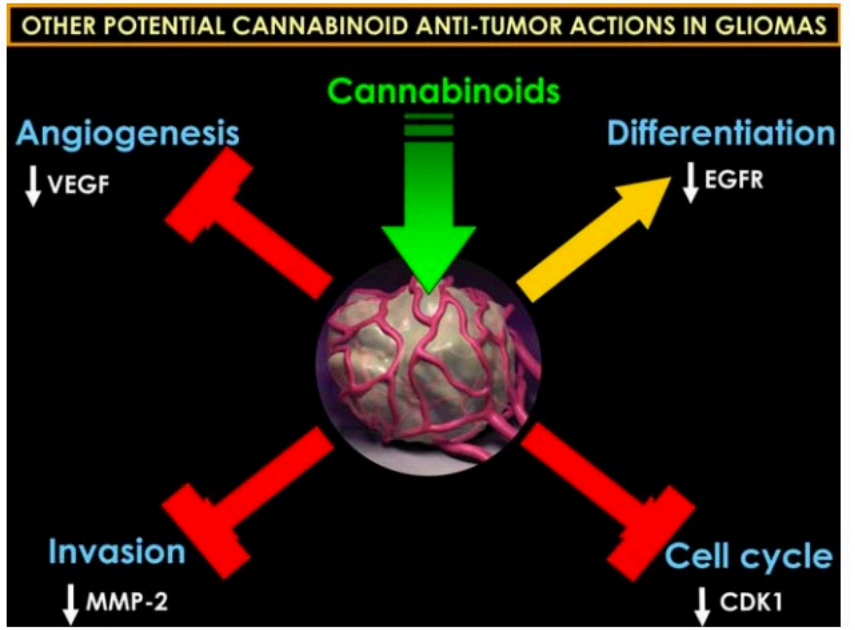
- Anorexia
  - Found to be most effective in HIV/AIDS induced anorexia
- Chemotherapy nausea and vomiting
  - Superior to placebo, inferior to metaclopramide
- Chronic pain

THE CURRENT EVIDENCE: NABILONE (CESAMET)

- Fibromyalgia
  - Modest effect
- Nausea
  - Better efficacy than metoclopramide for some forms of chemo
- Neuropathic pain

THE CURRENT EVIDENCE: NEEDS MORE WORKS

- Stoke
  - Reducing reperfusion injury
- Glaucoma
- Cancer
  - inhibits growth of some tumors *in vitro* and in animal models
  - Variety of cancers expressing CB1 or CB2 receptors
  - No good human clinical trials as of yet***



CANNABIDIOL

- Decreased brain edema following brain injury
- Increased fracture healing
- Decreased development of diabetes
- Improved arthritis

CANNABIDIOL

MR.PANUPAN SRIPAN

SAFETY

- Need to smoke 1500 lbs in 15 minutes to achieve lethal dose
- Side effects
  - euphoria and easy laughter, temporal and spatial perception alterations and disorientation, drowsiness, dizziness and motor incoordination, confusion, memory lapses and difficulty concentrating
  - tachycardia and hypotension, conjunctival injection, bronchodilation, muscle relaxation, and decreased gastrointestinal motility
- Synthetic cannabinoids are well tolerated