Neurological Uses for Medical Marijuana

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Disclosure

- Team Neurosurgeon, Pittsburgh Steelers
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- ImPACT co-founder
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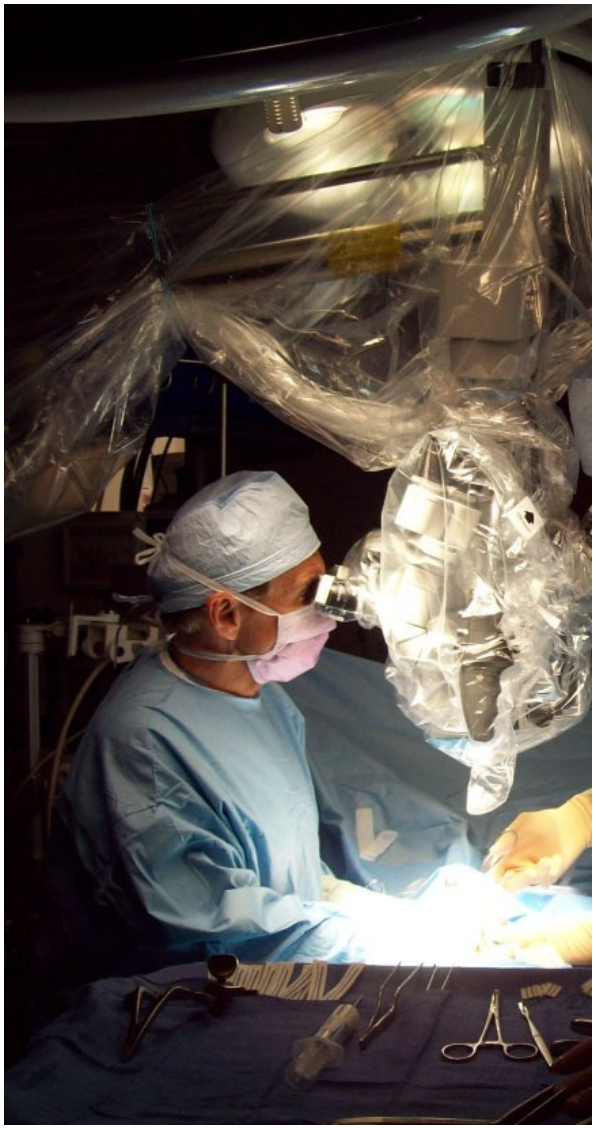


Historical Perspective (Discovery)

- R.S. Cahn: Cannabinol (CBN) isolated and elucidated early 1900s
- 1940s R.S. Adams, Wollner et al. isolated and synthesized CBN, CBD, CBDA and THC isomers
- Loewe performs first pharmacological animal studies (1946)
- Mechoulam et al: (-) Cannabidiol (CBD) enantiomer (1963)
- Gaoni and Mechoulam: Δ^9-THC elucidated & characterized (1964)
- Dewey WL: CBD and >60 other phytocannabinoids (1988)
- Bonner T: CB1 GPCR cloning/ characterizarion (1990)
- Devane WA et al: Anandamide (AEA: sine qua non endocannabinoid)→ ECS characterized (1992)
- Munro S: CB2 cloning/characterization (1993)
- Mechoulam et al: 2-AG endocannabinoid characterized (1995)
- Retrograde signaling eCBs (2001)

Discovery Of The Endocannabinoid System Has Lagged Behind The Endorphin System

Endogenous opioid system	Endocannabinoid system
4000 BC Sumerians described opiates	2000 BC Chinese described cannabis
1801 morphine isolated from opium	1940 CBD isolated from cannabis 1964 THC isolated
1973 opioid receptor	1988 cannabinoid receptor
1976 endogenous opioids - enkephalins, endorphins	1992 endogenous cannabinoids - anandamide, 2-AG

THE ENDOCANNABINOID SYSTEM

Used for patient assessment

EAT

Appetite
Nausea
Cachexia
Metabolism

SLEEP

Insomnia
Parasomnias
Narcolepsy
Apnea

RELAX

Physical: spasticity, tension

FORGET

memory extinction
PTSD
OCD
pain

PROTECT

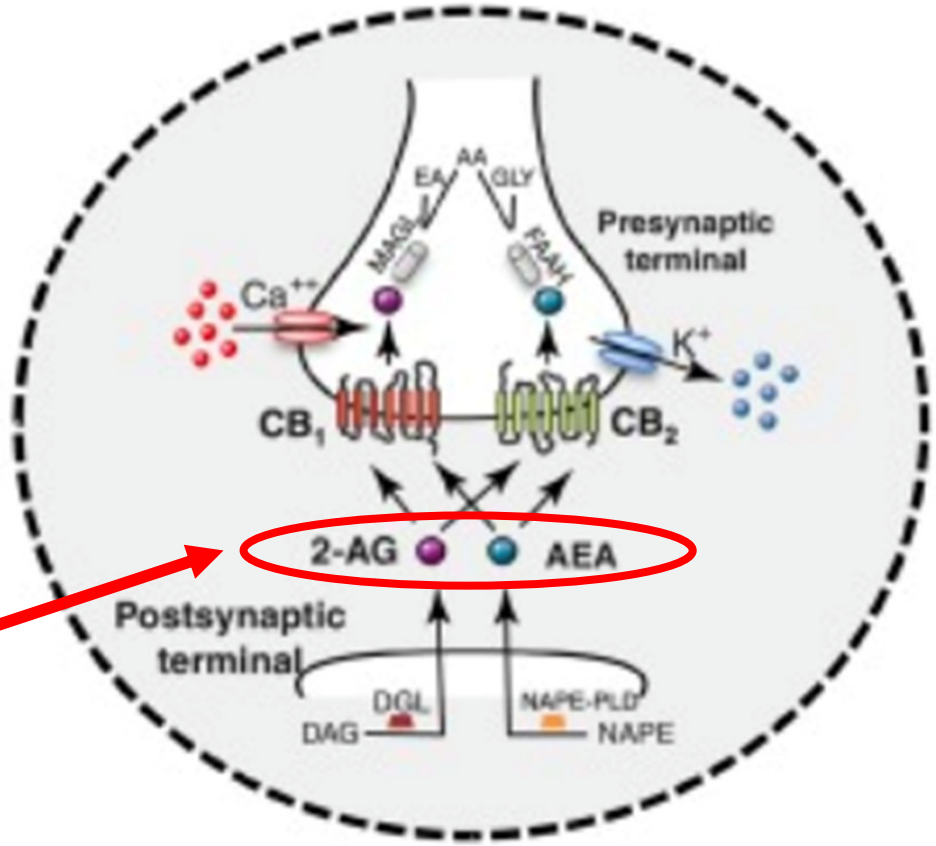
immunomodulation
Cyto-protection
neuroprotection
Cancer cell death

ECS: CB **Activation, Synthesis, Catabolism**

Endocannabinoid System (ECS):
An **internal homeostatic** regulatory system with three components (Triad):

- **Endocannabinoids (Anandamide [AEA], 2-AG)**
- **CB_1, CB_2 & TRPV1 receptors**
- **Their regulatory enzymes**

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



Aizpurua-Olaizola, et al. Targeting the endocannabinoid system: future therapeutic strategies.
Drug Discovery Today, 22(1); 2017

CANNABINOIDS:
3 VARIETIES

- **PHYTOCANNABINOIDS**

  (Pate 1994): terpenophenolic 21-C compounds found in the genus *Cannabis* ***(marijuana and Hemp)*** - e.g., THC, CBD, CBC, CBG, CBDV, THCV, CBDA, THCA, etc.

- **ENDOCANNABINOIDS**

  Devane WA et al: Anandamide (AEA: "*sine qua non*" endocannabinoid) characterized (1992): natural endogenous compounds **bind to cannabinoid receptors** (e.g., Anandamide, 2-AG, N-ADopa, EPEA, DHEA, etc.) whose functions are:

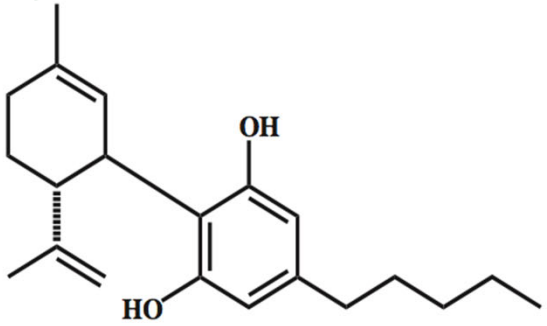
  "relax, eat, sleep, forget and protect"

- **SYNTHETIC CANNABINOIDS (Man-made)**

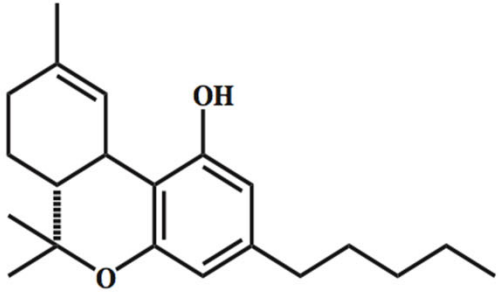
  (e.g., Ajulemic acid, JWH-018, AM2201, etc.) also affect cannabinoid receptors

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

Phytocannabinoids = Cannabis (THC, CBD, etc.)



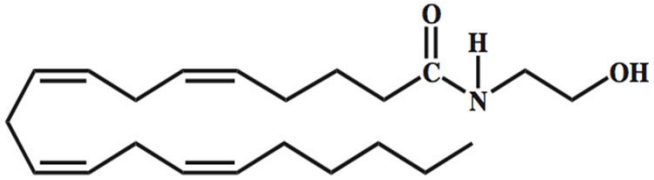
Cannabidiol (CBD)



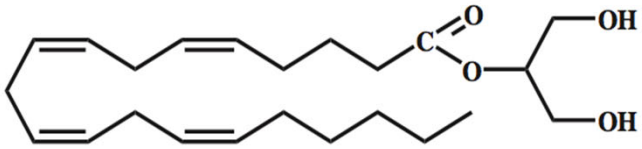
Δ^9-tetrahydrocannabinol (Δ^9-THC)

Endocannabinoids = Intrinsic Compounds

Neuromodulatory and Immunomodulatory



Arachidonoyl ethanolamide (anandamide)



2-arachidonoyl glycerol (2-AG)

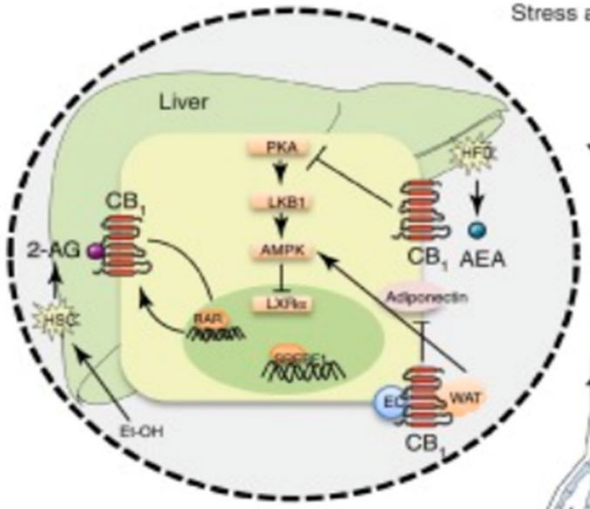
AEA – <u>CNS</u> **"stress-responsive & pain modulator"**

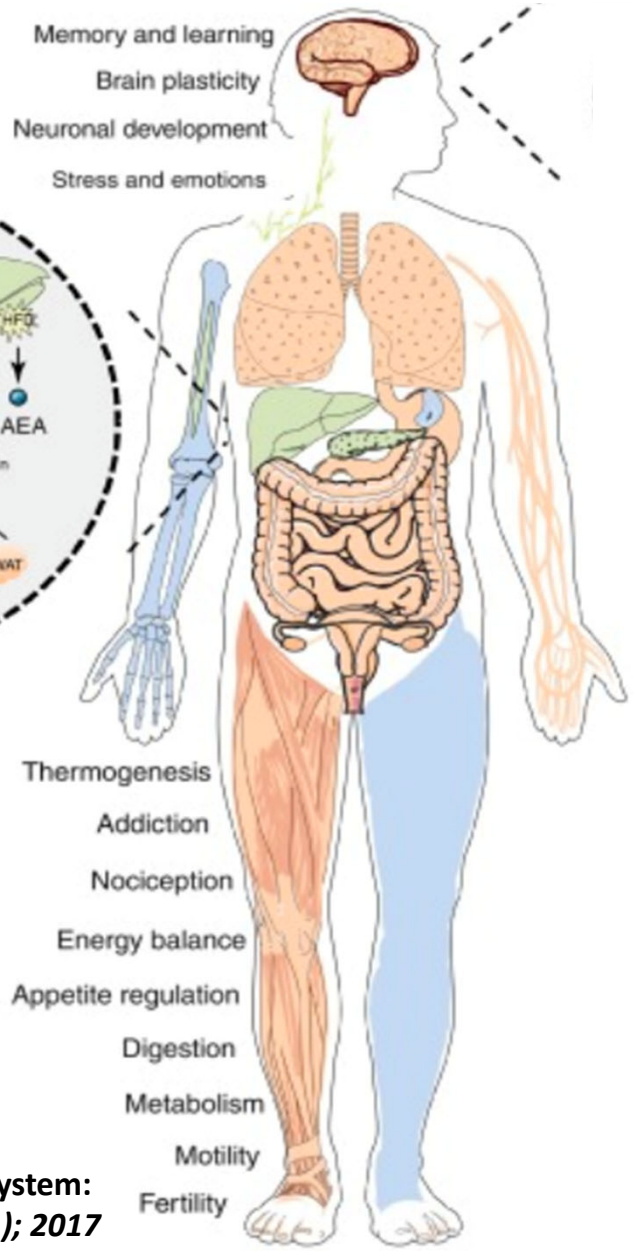
2-AG – <u>CNS</u> **"neuroendocrine-immune"**
<u>Periphery</u> **"metabolic-immune"**

Mol Pharmacol (2003) **63**:429–38. doi:10.1124/ mol.63.2.429

PSYCHO-NEURO-ENDO-IMMUNOLOGY: MIND-BODY Axes

CB_1	Brain; Lungs; Gastrointestinal tract; Reproductive system; Muscle; cardiovascular system
CB_2	Bones; spleen; skin
$CB_1 + CB_2$	Immune system; Liver Pancreas; Bone marrow





CB1 and CB2 receptor distribution throughout the Brain & Body

Aizpurua-Olaizola, et al. Targeting the endocannabinoid system: future therapeutic strategies. ***Drug Discovery Today, 22(1); 2017***

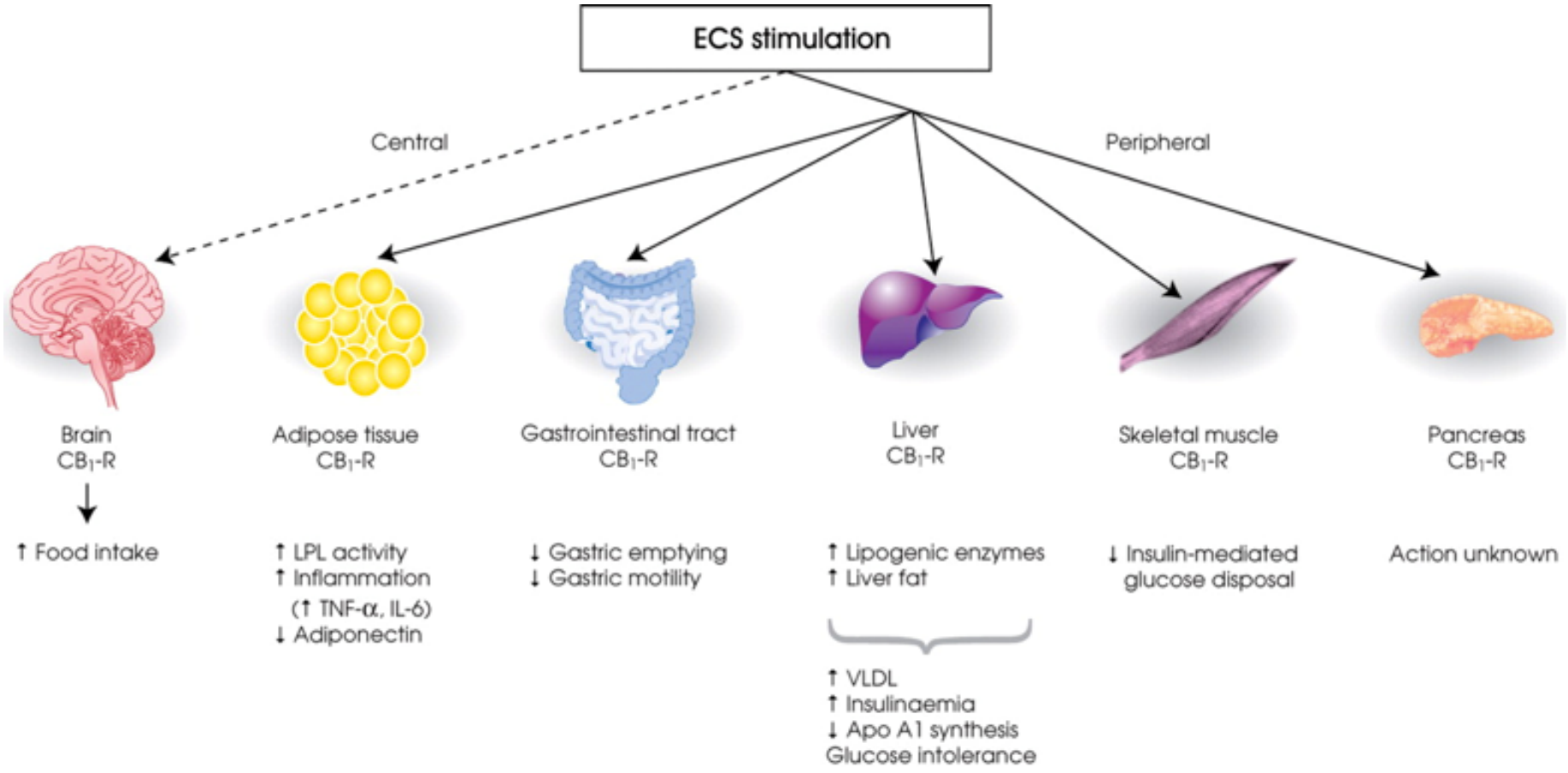
Endocannabinoid Tone

- Critical physiologic system involved in establishing and maintaining **human health and homeostasis**

- Affects lifestyle factors including diet, sleep, psychosocial stress, relationships, body weight/ composition and physical activity/ exercise affect the overall ECS function or **'endocannabinoid tone'**

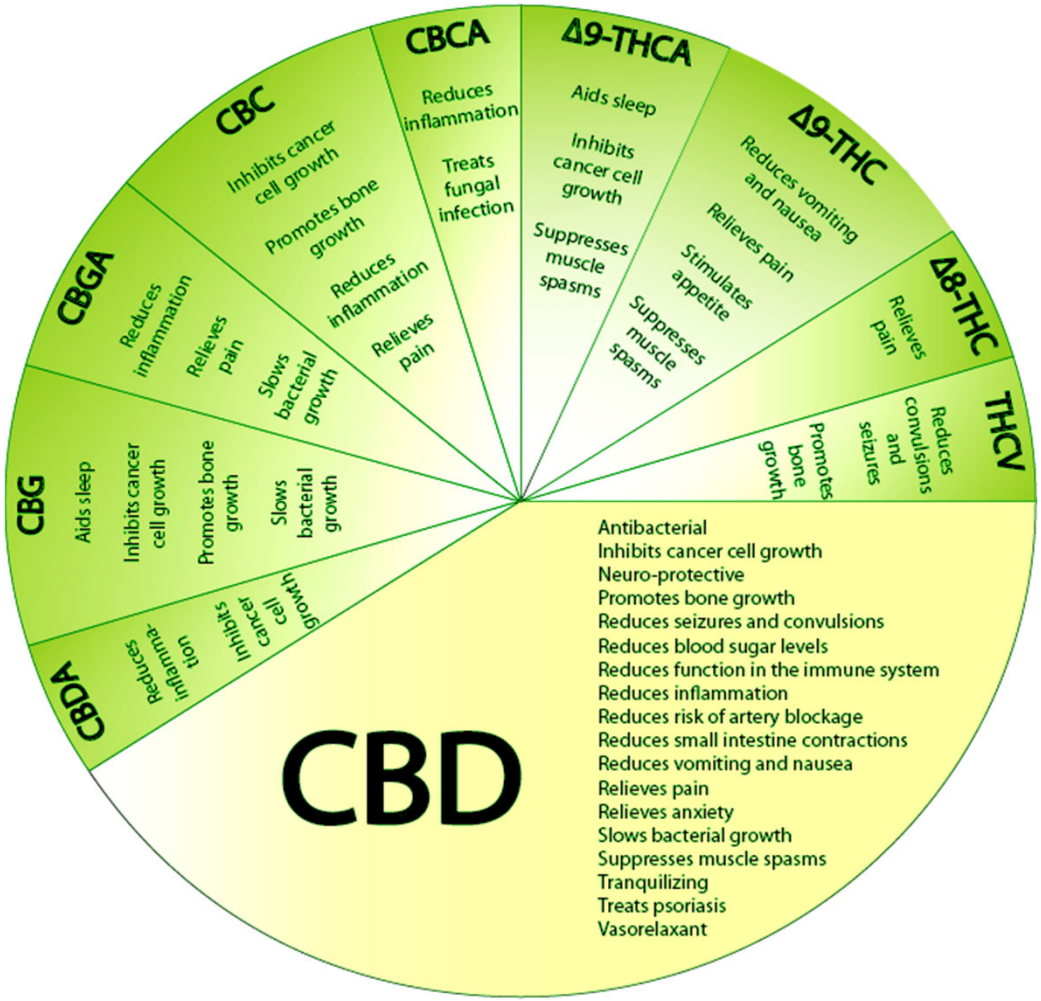
- Endocannabinoid tone is a function of:
  - **Location density of cannabinoid receptors**
  - **Relative abundance or uptake of endocannabinoids**

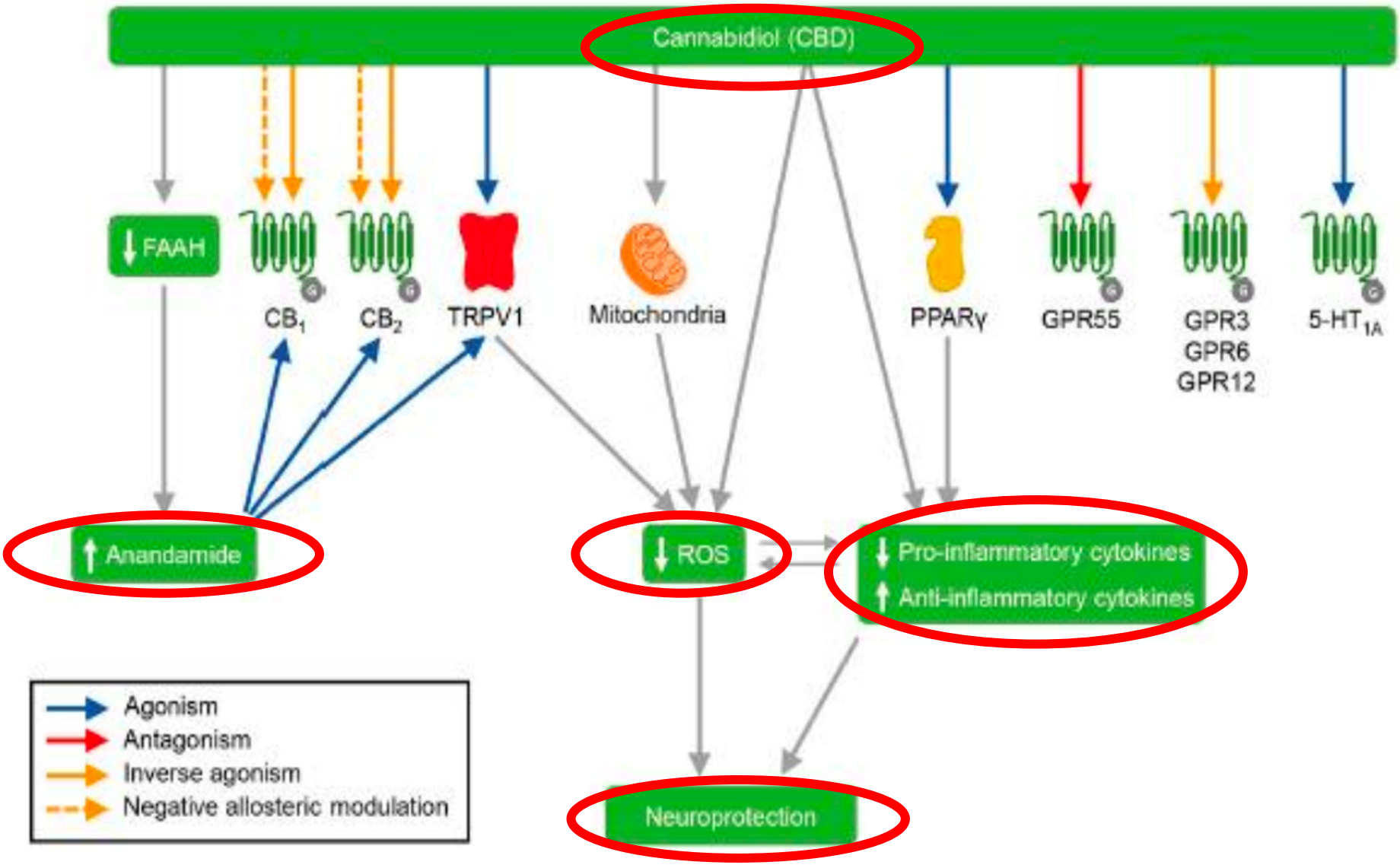
WHY SHOULD WE CARE ABOUT ECS TONE?



Source: http://eurheartjsupp.oxfordjournals.org/content/10/suppl_B/B34/F1.expansion

There are over 100 Phytocannabinoids *in Marijuana and Hemp with a Wide Variety of Actions*



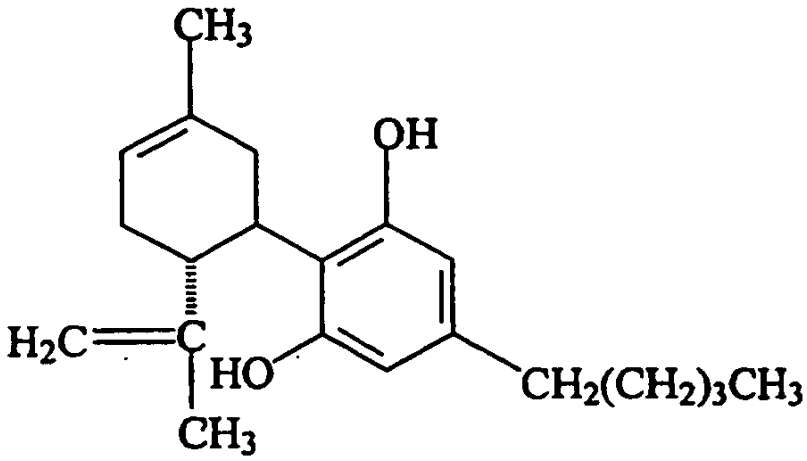


Huestis MA. Human cannabinoid pharmacokinetics. *Chem Biodivers*. 2007;4(8):1770-804.

Cannabidiol (CBD)

Physiologic Mechanisms & Benefits (*immune, neuro/brain, stress response, pain, energy intake/storage/ feeding, cell cycle-growth regulation*):

- **Anti-inflammation – Decreased Cytokine and Chemokine actions**
- **Analgesic Effects**
- **Anti-nausea, Anti-emetic & GI Benefits**
- **Reduces neural excitability and pain**
- **Anxiolytic**
- **Anti-epileptic**
- **Neuroprotective**
- **Anti-cancer**
- **Anti-oxidant**
- **Apoptotic**



Cannabidiol (CBD)

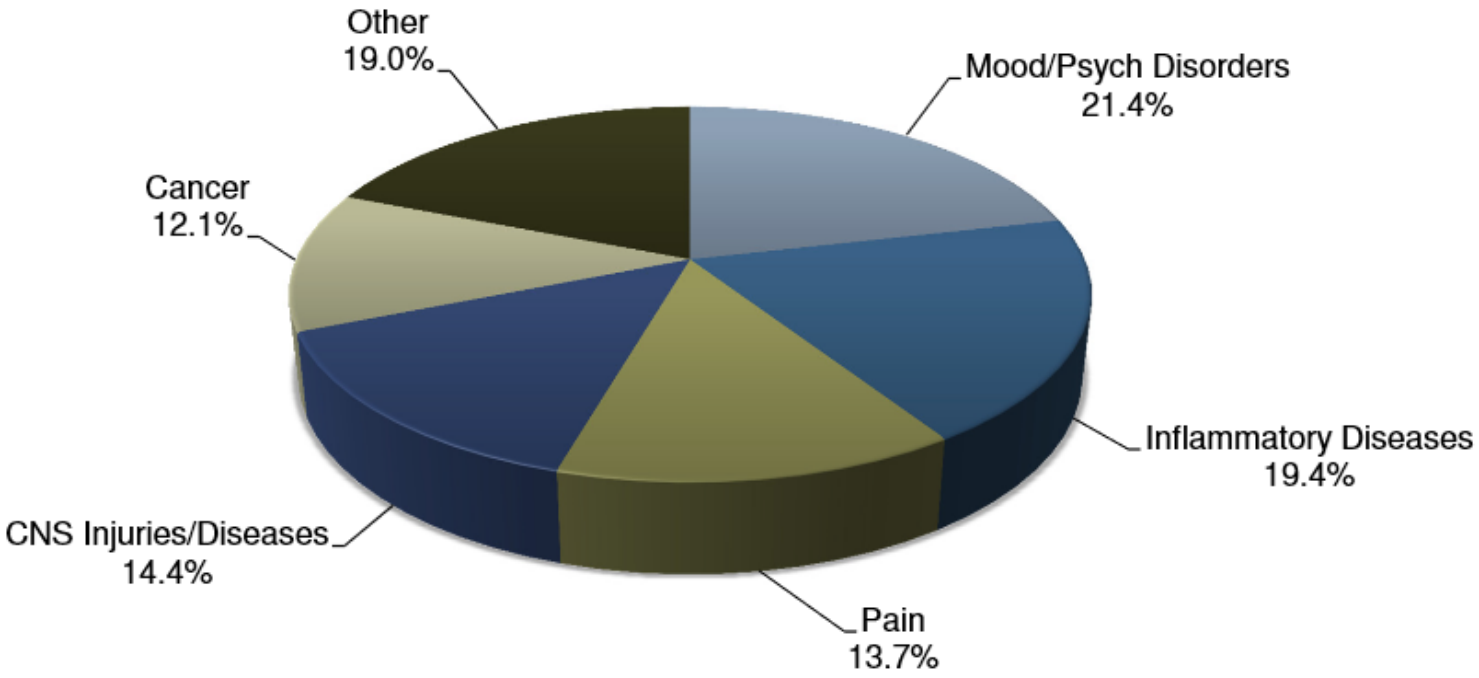
Pertwee RG. Cannabidiol as a potential medicine. Cannabinoids as Therapeutics. Milestones in Drug Therapy MDT. 2005;47-65. Evans FJ: Cannabinoids: the separation of central from peripheral effects on a structural basis. Planta Med 1991; 57(7 suppl):60–67

CBD Impact on Healthcare Treatments

CBD use has successfully resulted in the decline of prescription drugs once needed.

Key Takeaway: There have been declines in the use of oral prescription drug use in patients taking CBD for various conditions.

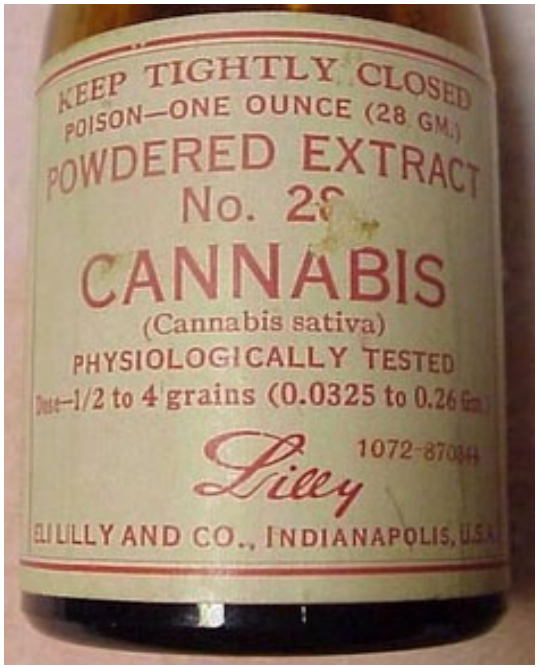
CBD Segment: Treatment Type Assessment, US, 2018

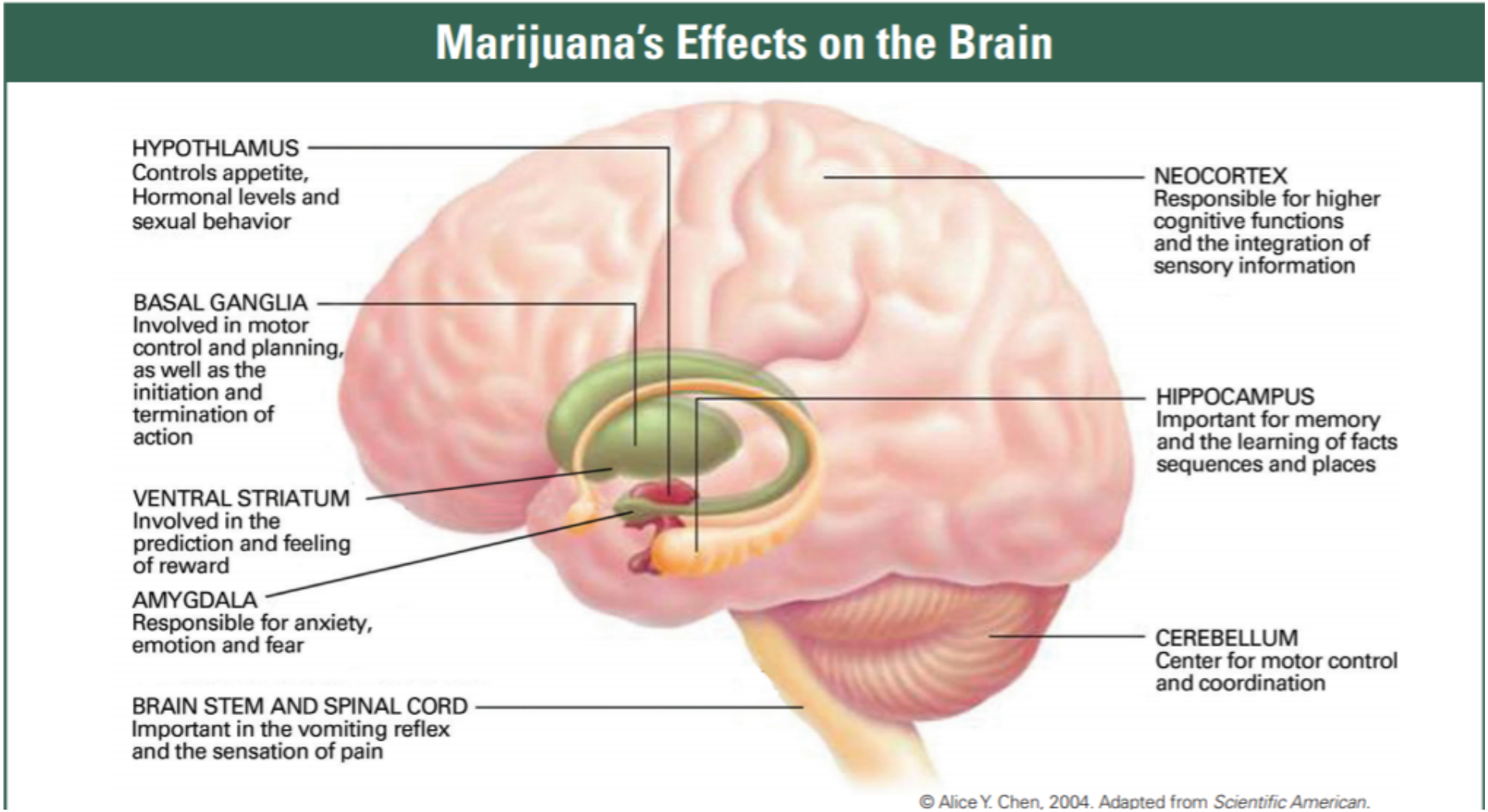


Source: New Frontier Data –CannaBit (April 2018); Frost & Sullivan

Cannabis Medical Therapeutics

- First reported as medicine > 5000 years ago
- Introduced into Western medicine in 1840's by Dr. W.B. O'Shaughnessy
- Promoted as analgesic, sedative, anti-inflammatory, antispasmotic and anticonvulstant properties
- Available in 1906 Mfg by Eli Lilly, Wyeth, Parke-Davis, Sharp & Dohme





https://teens.drugabuse.gov/sites/default/files/mjrrs_6_25.pdf

Rising Potency Marijuana Potency and its Consequences

- In **1990s,** average THC content **3.7 %** for marijuana and **7.5 %** for sinsemilla
- In **2013**, average **9.6 %** for marijuana and **16 %** for sinsemilla
- **THC-rich hash oil** extracted from the marijuana *average > 50 % THC*

"….the consequences of marijuana use could be worse than in the past, particularly among ***new users or in young people, whose brains are still developing"***

Nora D. Volkow, M.D.
Director National Institute on Drug Abuse

https://teens.drugabuse.gov/sites/default/files/mjrrs_6_25.pdf

Adverse Consequences of Marijuana Use

Acute (present during intoxication)

- Impaired short-term memory
- Impaired attention, judgment, and other cognitive functions
- Impaired coordination and balance
- Increased heart rate
- Anxiety, paranoia
- Psychosis (uncommon)

Persistent (lasting longer than intoxication, but may not be permanent)

- Impaired learning and coordination
- Sleep problems

Long-term (cumulative effects of repeated use)

- Potential for addiction
- Potential loss of IQ
- Increased risk of chronic cough, bronchitis
- Increased risk of schizophrenia in vulnerable people*
- Potentially increased risk of anxiety, depression, and amotivational syndrome*

**These are often reported co-occurring symptoms/disorders with chronic marijuana use. However, research has not yet determined whether marijuana is causal or just associated with these mental problems.*

https://teens.drugabuse.gov/sites/default/files/mjrrs_6_25.pdf

This Issue Views 29,321 | Citations 15 | Altmetric 606

JAMA
The Journal of the American Medical Association

Viewpoint

January 10, 2017

The Risks of Marijuana Use During Pregnancy

Nora D. Volkow, MD[1]; Wilson M. Compton, MD, MPE[1]; Eric M. Wargo, PhD[1]

» Author Affiliations

JAMA. 2017;317(2):129-130. doi:10.1001/jama.2016.18612

The American College of Obstetricians and Gynecologists recommends that obstetrician-gynecologists counsel women ***against using marijuana while trying to get pregnant, during pregnancy, and while they are breastfeeding***

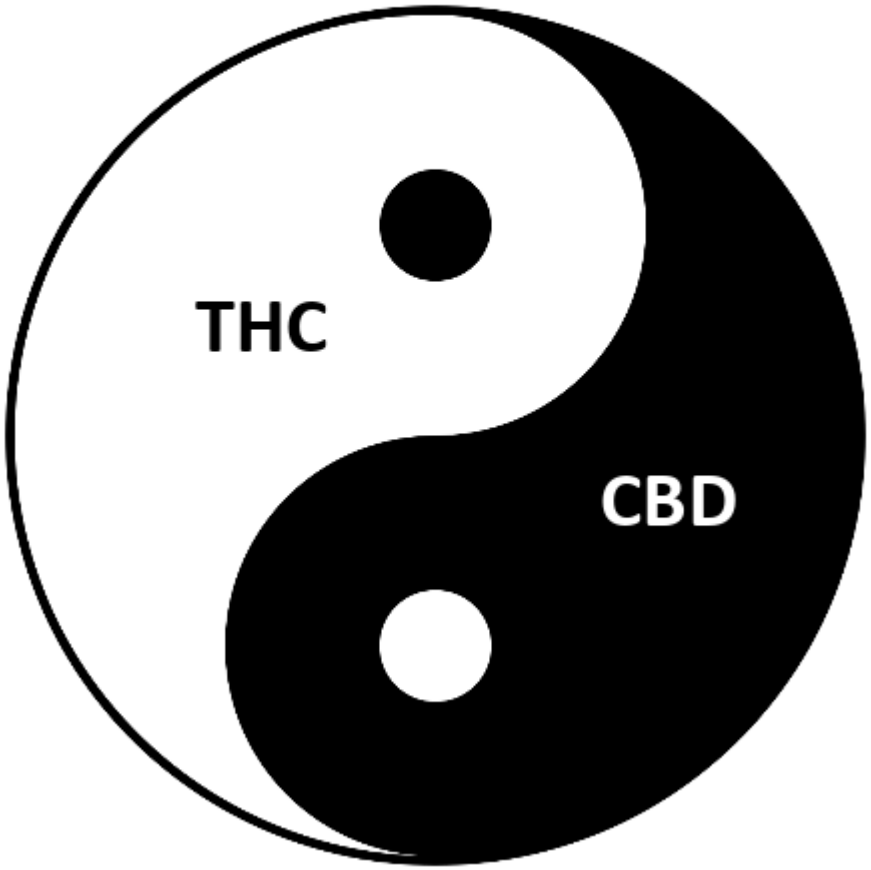
Primarily the warning is due to concerns of the developing brain and marijuana use by mothers

THE AMERICAN COLLEGE OF OBSTETRICIANS AND GYNECOLOGISTS · WOMEN'S HEALTH CARE PHYSICIANS · 1951

NIDA
NATIONAL INSTITUTE ON DRUG ABUSE

CBD with THC May Improve Both

Yin and Yang?



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Review Article

Review of the neurological benefits of phytocannabinoids

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*Corresponding author

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May 2018

What about Medical Marijuana?

Abstract

Background: Numerous physical, psychological, and emotional benefits have been attributed to marijuana since its first reported use in 2,600 BC in a Chinese pharmacopoeia. The phytocannabinoids, cannabidiol (CBD), and delta-9-tetrahydrocannabinol (Δ9-THC) are the most studied extracts from *cannabis sativa* subspecies hemp and marijuana. CBD and Δ9-THC interact uniquely with the endocannabinoid system (ECS). Through direct and indirect actions, intrinsic endocannabinoids and plant-based phytocannabinoids modulate and influence a variety of physiological sy

Methods: In 1980, Cunh with medically uncontroll trial. Since then neurolog research using medical n

Results: Recent neurol brain tumors, Parkinso neuropathic pain, and the syndromes. In addition, anxiety, depression, addi disorders are being studi

Conclusions: In this revi current clinical neurologica We will emphasize the n benefits of phytocannabir

Current research indicates the phytocannabinoids have a powerful therapeutic potential in a variety of ailments primarily through their interaction with the ECS.

CBD is of particular interest due to its wide-ranging capabilities and lack of side effects in a variety of neurological conditions and diseases

Key Words: Cannabidiol, delta-9-tetrahydrocannabinol, endocannabinoid system, neurological disease, phytocannabinoids

In PA - "Serious Medical Conditions" Approved for Medical Marijuana

Vast Majority of indications for Medical Marijuana are for Neurological Conditions

https://www.pa.gov/guides/pennsylvania-medical-marijuana-program/#Physicians

- Amyotrophic Lateral Sclerosis.
- Autism
- Cancer
- Crohn's Disease
- Damage to the nervous tissue of the spinal cord with objective neurological indication of intractable spasticity.
- Epilepsy
- Glaucoma
- HIV (Human Immunodeficiency Virus) / AIDS (Acquired Immune Deficiency Syndrome).
- Huntington's Disease.
- Inflammatory Bowel Disease.
- Intractable Seizures
- Multiple Sclerosis
- Neuropathies
- Parkinson's Disease
- Post-traumatic Stress Disorder.
- Severe chronic or intractable pain of neuropathic origin or severe chronic or intractable pain in which conventional therapeutic intervention and opiate therapy is contraindicated or ineffective.
- Sickle Cell Anemia

Neurological Research for Use of Medical Marijuana:

- Epilepsy
- Pain (various types)
- Neuropathy
- Spasticity (MS and spinal cord injury)
- Tremor, Dystonia
- Muscle cramps of ALS
- Traumatic Brain Injury (Reduce cerebral ischemia and neuro/excitotoxicity
- Tourette's syndrome
- Huntington’s & Parkinson's disease (dyskinesia)
- Intractable hiccups
- Post-traumatic stress disorder (PTSD)
- Alzheimer’s disease (behavioral/agitation, cognitive symptoms)
- Insomnia

Table 2. Total Number and Percentages of Medical Cannabis Users Reporting Use for Each Medical Condition	
Pain	874 (61.2)
Anxiety	**830 (58.1)**
Depression	**719 (50.3)**
Headache/migraine	**507 (35.5)**
Other	488 (34.1)
Nausea	392 (27.4)
Muscle spasticity	**263 (18.4)**
Arthritis	245 (17.1)
Irritable bowel	211 (14.8)
Intractable pain	164 (11.5)
Anorexia	142 (9.9)
Cancer	47 (3.3)
Ulcerative colitis/Crohn's disease	45 (3.1)
Other seizure disorder	**37 (2.6)**
Tics	**36 (2.5)**
Tremor	**33 (2.3)**
Epilepsy	**18 (1.3)**
Multiple sclerosis	**16 (1.1)**

Reasons for using Medical Marijuana

1429 participants
identified as medical Cannabis users Surveyed

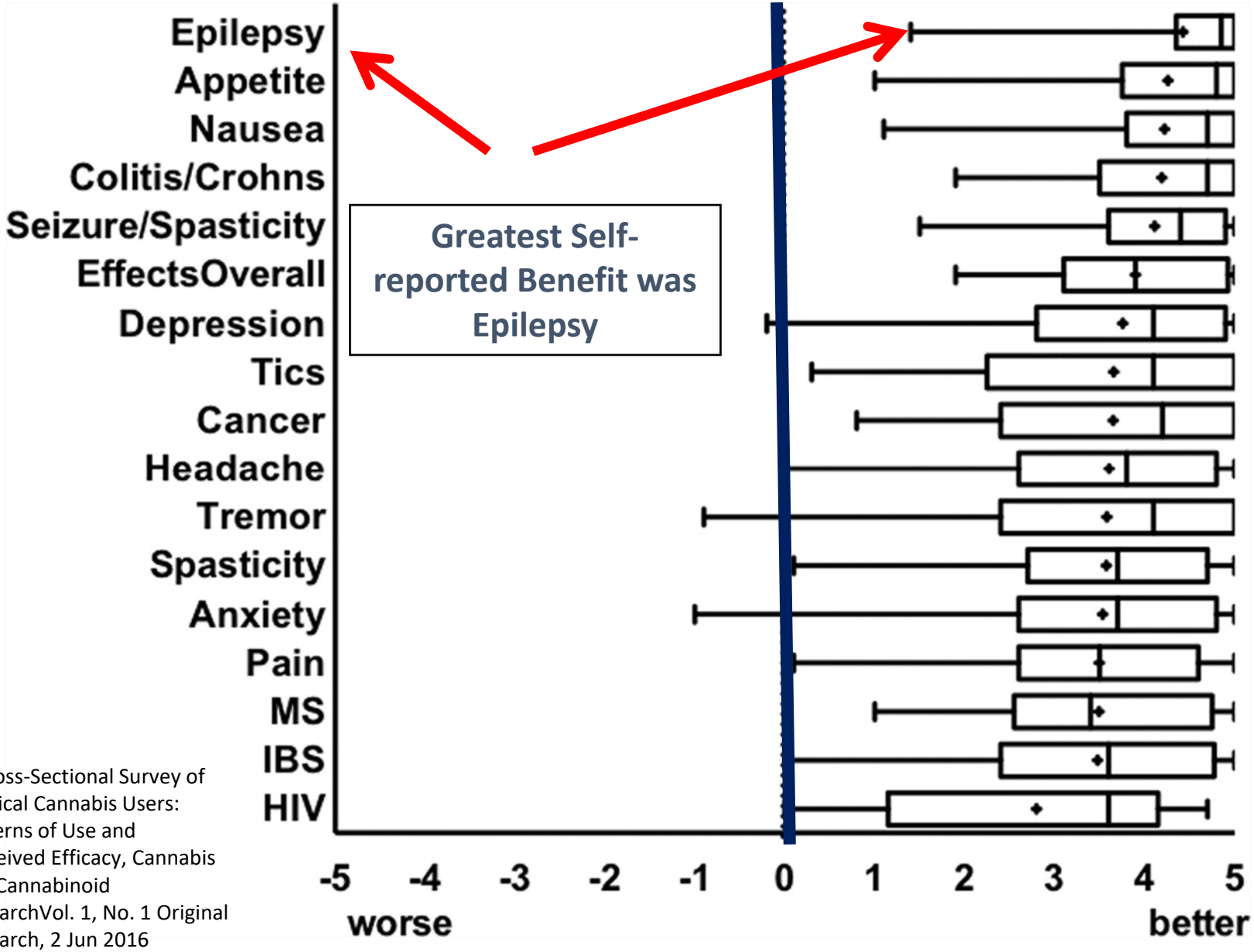
86% reported improvement in symptoms

Most are using for Neurological or Mood Disorders

A Cross-Sectional Survey of Medical Cannabis Users: Patterns of Use and Perceived Efficacy, Cannabis and Cannabinoid ResearchVol. 1, No. 1 Original Research, 2 Jun 2016

2016

Patient-reported outcomes



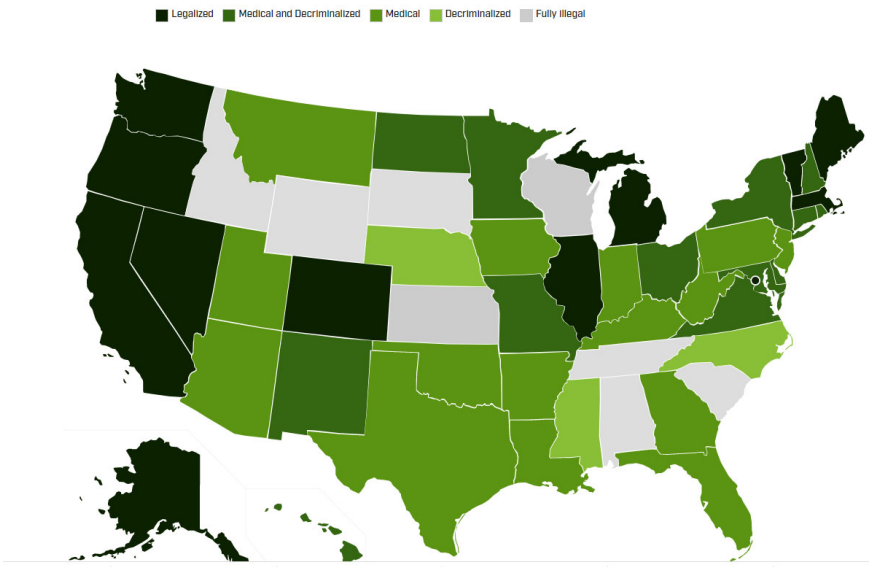
A Cross-Sectional Survey of Medical Cannabis Users: Patterns of Use and Perceived Efficacy, Cannabis and Cannabinoid ResearchVol. 1, No. 1 Original Research, 2 Jun 2016

All States who have approved Medical Marijuana included Indication of for *Epilepsy*

First Positive Studies for the use of Marijuana and CBD for Intractable Seizures

In 1975, Consroe, et al Case Report on anticonvulsant Nature of Marihuana Smoking.

In 1980, Cunha et al. reported benefits in 7 subjects for uncontrolled epilepsy using CBD in a phase I clinical trial



As of 2020 – 7 states continue to list Marijuana as illegal (seen as white)

Summary of Epilepsy Studies using Med Marijuana, THC, CBD and THC/CBD – as of 2018 (15 RCT Studies)

Table 4 An overview of the research evidence on cannabis and cannabinoids in the treatment of epilepsy

	50% reduction in seizures n=19 studies (2 RCTs)	Complete seizure freedom n=17 studies (3 RCTs)	Quality of life n=14 studies (2 RCTs)	Withdrawals n=12 studies (4 RCTs)	Adverse events n=16 studies (4 RCTs)
Cannabis sativa/extract	Two studies (no RCT)	No studies	Two studies (no RCT)	No studies	Two studies (no RCT)
Findings	Positive effect		Positive effect		AEs reported by 13%
Evidence GRADE	⊕◯◯◯ VERY LOW		⊕◯◯◯ VERY LOW		⊕◯◯◯ VERY LOW
Risk of bias	Serious to critical risk		Critical risk		Critical risk
Conclusion	Insufficient evidence		Insufficient evidence		Insufficient evidence
CBD	11 studies (2 RCT)	13 studies (3 RCT)	9 studies (2 RCT)	8 studies (3 RCT)	11 studies (4 RCT)
Findings	Small effect	Positive effect	Positive effect	Patients more likely to withdraw from CBD	AEs reported by 11%–100%
Evidence GRADE	⊕⊕◯◯ LOW	⊕⊕◯◯ LOW	⊕⊕◯◯ LOW	⊕⊕◯◯ LOW	⊕⊕◯◯ LOW
Risk of bias	Low to serious risk	Low to critical risk	Low to critical risk	Low to critical risk	Low to critical risk
Conclusion	Some evidence of effect	Some evidence of effect	Some evidence of effect	Greater likelihood of withdrawal	Mild-to-moderate AEs likely
Oral THC	No studies	No studies	No studies	No studies	One study (no RCT)
Findings					AEs reported by 12.5%
Evidence GRADE					⊕◯◯◯ VERY LOW
Risk of bias					No information
Conclusion					Insufficient evidence
CBD:THC	Five studies (no RCTs)	Three studies (no RCTs)	Two studies (no RCT)	Two studies (no RCT)	Two studies (no RCT)
Findings	Positive effect	Small effect	Positive effect	Withdrawal rate 14%	AEs reported by 42%
Evidence GRADE	⊕⊕◯◯ LOW	⊕◯◯◯ VERY LOW	⊕◯◯◯ VERY LOW	⊕◯◯◯ VERY LOW	⊕◯◯◯ VERY LOW
Risk of bias	Serious to critical risk	Serious to critical risk	Serious risk	Serious risk	Serious to critical risk
Conclusion	Insufficient evidence	Insufficient evidence	Insufficient evidence	Insufficient evidence	Insufficient evidence
Oral cannabis extracts	One study (no RCT)	One study (no RCT)	One study (no RCT)	One study (no RCT)	No studies
Findings	Positive effect	Small effect	Positive effect	Withdrawal rate 15%	
Evidence GRADE	⊕◯◯◯ VERY LOW	⊕◯◯◯ VERY LOW	⊕◯◯◯ VERY LOW	⊕◯◯◯ VERY LOW	
Risk of bias	Critical risk	Serious risk	Serious risk	Serious risk	
Conclusion	Insufficient evidence	Insufficient evidence	Insufficient evidence	Insufficient evidence	

Stockings E, et al. J Neurol Neurosurg Psychiatry 2018;89:741–753.

Research Review 2018

Goal: Safety and efficacy of cannabinoids as an adjunctive treatment to conventional antiepileptic drugs in treating drug-resistant epilepsy

Results:

- Showed qualitative evidence that cannabinoids reduced seizure frequency in some patient (mostly children)
- Reduced Szs improved other aspects of the patients' quality of life
- Cannabinoids were generally well tolerated with mild-to-moderate AEs
- CBD reduced the frequency of seizures to the greatest degree and was more likely to achieve complete seizure freedom

Stockings E, et al. J Neurol Neurosurg Psychiatry 2018;89:741–753. doi:10.1136/jnnp-2017-317168

Research Review 2018

Goal: Safety and efficacy of cannabinoids as an adjunctive treatment to conventional antiepileptic drugs in treating drug-resistant epilepsy

However

- Because anti-sz medications and CBD are both metabolized in the cytochrome P450 pathway, the pharmacokinetic interactions of these drugs still need to be fully determined
- Further randomized, double-blind studies with a placebo or active control are needed to strengthen this conclusion

Stockings E, et al. J Neurol Neurosurg Psychiatry 2018;89:741–753. doi:10.1136/jnnp-2017-317168

Pharmaceutical
GW- EPIDIOLEX STUDY 2018

METHODS:

In this randomized, double-blind, placebo-controlled trial done at 24 clinical investigated the *efficacy of cannabidiol (CBD) as add-on therapy for patients with treatment-resistant Lennox-Gastaut syndrome*

Eligible patients (**aged 2-55 years**) had Lennox-Gastaut syndrome

14-week treatment period, N=171 patients to receive cannabidiol (n=86) or placebo (n=85).

Thiele EA, Marsh ED, French JA, et al. Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomized, double-blind placebo-controlled phase 3 trial. *Lancet* 2018;391;10125:1085-1096.

Pharmaceutical
GW- EPIDIOLEX STUDY 2018

RESULTS:

- Reduction in monthly **drop seizure frequency from baseline was 43.9% in the Cannabidiol group vs. 21.8% in the placebo**

- **Adverse events occurred in 74 (86%) of 86 patients** in the cannabidiol group and 59 (69%) of 85 patients placebo - most were mild or moderate.
  - **The most common - diarrhea, somnolence, pyrexia, decreased appetite, and vomiting**

- **12 (14%) patients in the cannabidiol group** and one (1%) patient in the placebo group **withdrew**

Thiele EA, Marsh ED, French JA, et al. Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomized, double-blind placebo-controlled phase 3 trial. *Lancet* 2018;391;10125:1085-1096.

CONCLUSION

Add-on ***cannabidiol (CBD) is efficacious for the treatment of patients with drop seizures associated with Lennox-Gastaut syndrome and is generally well tolerated***

The long-term efficacy and safety of cannabidiol is currently being assessed in the open-label extension of this trial

EPIDIOLEX

GW pharmaceuticals

Thiele EA, Marsh ED, French JA, et al. Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomized, double-blind placebo-controlled phase 3 trial. *Lancet* 2018;391;10125:1085-1096.

FDA Approves First CBD Drug

Reuters

U.S. approves first marijuana plant-derived drug

June 25, 2018

The U.S. Food and Drug Administration approved GW Pharmaceuticals for Lennox-Gastaut syndrome (LGS) or Dravet syndrome in patients two years of age or older, making it the first cannabis-based drug to win approval in the country.

The landmark approval could potentially open floodgates for more research into the medicinal properties of cannabis.

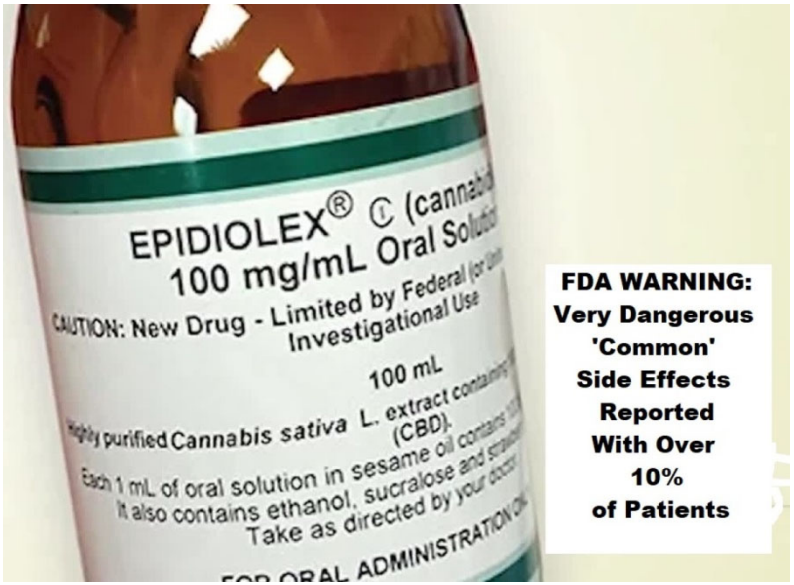
EPIDIOLEX

GW pharmaceuticals

Pharmaceutical formulation of highly purified, **plant-derived cannabidiol (CBD)**

EPIDIOLEX – Label Warnings

- loss of appetite, nausea, vomiting
- fever, feeling unwell, unusual tiredness
- yellowing of the skin or the whites of the eyes (jaundice)
- itching
- unusual darkening of the urine
- right upper stomach area pain or discomfort



$32,500 per patient, per year

Refractory Epilepsy – Recent Israel Experience with Tolerance to CBD

Development of tolerance in the treatment of refractory epilepsy: (Mostly Children)

- **92 patients**, (1 to 37 years (mean age, **11.8** years)
- **All had treatment-resistant epilepsy**; **2** - Dravet syndrome; **3** - Lennox-Gastaut syndrome (LGS), **87** - other types of epilepsy syndromes
- **CBD to THC was 20:1, 12.6 mg/kg/day for 19.8 months**
- **Tolerance** was defined as a **30%** or greater reduction in response rate that continued for more than 3 months

American Epilepsy Society (AES) 72nd Annual Meeting 2018: Abstract 2.233.
Presented December 2, 2018

Refractory Epilepsy – Recent Israel Experience with Tolerance to CBD

Results

- **29% experienced a initial reduction in seizures by 50% to 75%**
- **25% - developed tolerance (receptor desensitization)**
- **The mean time for tolerance - 7.3 months**
- None of the patients with Dravet syndrome or LGS developed tolerance
- **To counteract tolerance, the CBD dose was increased. After this 20% of the patients were able to achieve the same response rate as before the development of tolerance**

American Epilepsy Society (AES) 72nd Annual Meeting 2018: Abstract 2.233.
Presented December 2, 2018

Conclusion

- Findings suggest that ***cannabidiol tolerance exists*** and it limits the efficacy of this antiseizure treatment in the long-term clinical management of epilepsy in the pediatric and adults population
- ***Drug Holidays may help*** to restore receptor function

https://www.aesnet.org/meetings_events/annual_meeting_abstracts/view/501344

Headache Benefits shown using Medical Marijuana:

- **Headache and facial pain: chronic headaches**

Forsch Komplementarmed. 1999;**6**(Suppl. 3):28-36, *Compr Psychiatry*. 1974;**15**:531-535.

- **Migraine**

Headache. 1987;**27**:442-443, *Int J Clin Pharmacol Res*. 1985;**5**:243-246. *South Med J*. 1989;**82**:805

- **Cluster headache**

Headache. 2009;49:914-916. J Neurol Neurosurg Psychiatry. 2007;78:1354-1358

- **Pseudotumor cerebri**

Headache. 2004;44:726-727

- **Multiple sclerosis-associated trigeminal neuralgia**

- Eur Neurol. 1997;38:44-48.

Eric P. Baron DO **Comprehensive Review of Medicinal Marijuana, Cannabinoids, and Therapeutic Implications in Medicine and Headache: What a Long Strange Trip It's Been …**First published: 25 May 2015

Case Report: Migraine Headaches/PCS

28 y/o Physician Assistant – Concussion and PCS with migraine Headaches. Takes NSAIDs, Botox

"Botox helps for 4 weeks but I can only get the injections every 3 months. I think its work trying supplements or oils to see if I get any relief. I take ibuprofen as needed and my stomach will get irritated. I would love to be able to take something more natural than an NSAID."

Recommended CBD – 2 (15 mg Tabs) and oral spray 1-2 mg Three X/day

Case Report: Migraine Headaches

After 4 months

Dr. Maroon,

I have only had 2 migraines in the past 2 weeks, which is good! I did have a headache resolve after just taking a CBD in the am. I am going to give this a few months though to get a better idea how I respond.

Thank you!! Have a great weekend!

Case Report: Migraine Headaches

Hi Dr. Maroon, **After 1 year**

I am still using the CBD oil. ***It has made a huge difference for me!!*** I also have continued with botox.

I did stop taking the CBD oil regularly for a few months last spring and I did have an increase in headaches. **I now continue with a maintenance of the CBD oil BID.**

Very nice to hear from you

Case Report: Post-Concussion Syndrome

30 – something, TV Reporter – Concussion with **Chronic Headaches** and Anxiety

Recommended CBD – 2 (15 mg Tabs) & oral spray 1 -2 mg *prn*

Dear Dr Maroon, ***After 3 months***

I believe it truly makes a ***huge difference****. I carry around one of the* ***spray bottles with me everywhere I go to use if I start to feel a headache*** *coming on* ***or feel anxious and it helps****.*

And I'm still taking the ***CBD pill every day all of the other vitamins. And I use 2 to 3 pills when I have really bad headaches*** *or migraines and it helps a lot.*

I hope all is well with you! Thank you so much!

Case Report: Post-Concussion Syndrome

30 – something, TV Reporter – Concussion with **Chronic Headaches** and Anxiety

Recommended CBD – 2 (15 mg Tabs) & oral spray 1 -2 mg *prn*

Hi Dr. Maroon, ***After 1 year***

I haven't been using CBD regularly for about a year now. I would say I feel pretty lucky to ***not have regular headaches*** during my recent pregnancy.

I do believe CBD made a big difference in my journey with PCS especially when I was using it daily and I do plan on using it again as needed after pregnancy.

Thank you!

Headache Benefits of Medical Marijuana:

- Both Δ9-THC and CBD **have analgesic properties**
- **Δ9-THC doses of 15-20 mg have been shown to be comparable to the analgesic effects of codeine 60-120 mg**
- But the psychotropic side effects of Δ9-THC **can limit its use for pain** (or used in a reduced amt. compared to CBD)
- Medicinal cannabis and its cannabinoid extracts **increase pain thresholds**
- A review of 38 published RCTs evaluating cannabinoids in pain management –**showed 71% (27) concluded that cannabinoids had empirically demonstrable and statistically significant pain-relieving effects**

Eric P. Baron DO **Comprehensive Review of Medicinal Marijuana, Cannabinoids, and Therapeutic Implications in Medicine and Headache: What a Long Strange Trip It's Been …**First published: 25 May 2015

Epilepsy and Neuropathic Pain CBD Relief by a Common Pathway

- Both phytocannabinoids and endogenous cannabinoids function as retrograde messengers that **provide feedback inhibition of both excitatory and inhibitory transmission** in brain
- Marijuana (**MORE THC and LESS CBD**) can increased seizure frequency in animals and humans (**excitatory**)
- **Isolated CBD**, increases the release and duration of **Anandamide (AEA) with in the synapse**
- Activation of **Anandamide inhibits electroshock-induced seizures in animals and humans and reduces neuropathic pain humans**

Fine PG, Rosenfeld MJ. Cannabinoids for neuropathic pain.Curr Pain Headache Rep. 2014 Oct;18(10):451. doi: 10.1007/s11916-014-0451-2.

Meta-Analysis of Med Marijuana and Neuropathic Pain

Summary Results of 3 Meta-analyses

- **Andreae et al, 2015: 5 trials, 178 patients with HIV, trauma, diabetes, complex regional pain syndrome, or spinal cord injury-related neuropathy**
  - All used whole cannabis plant for 2 weeks
  - **Results – 20 % of patients treated had at least a 30% pain reduction**
- **Nugent et al, 2017: 13 trials, 246 patients with peripheral neuropathic pain from various conditions.**
  - Used cannabis-based preparations (Studies mostly short duration)
  - **Treatment group reported a 30% improvement in neuropathic pain**
- **Cochrane review, 2018: 16 trials, 1,750 patients lasting 2 to 26 weeks**
  - Used combination of THC and CBD, nabilone, inhaled herbal cannabis, and plant-derived THC
  - With **cannabis-based treatments, significantly more people achieved 50% or greater pain relief than with placebo**
  - **30% pain reduction was achieved in 39% of treated patients**

Cleve Clin J Med. 2018 Dec;85(12):943-949. doi: 10.3949/ccjm.85a.17115. **Cannabis for peripheral neuropathy: The good, the bad, and the unknown.** Modesto-Lowe V[1,2,3], Bojka R[2], Alvarado.

Meta-Analysis of Med Marijuana and Neuropathic Pain

Conclusion:

Most studies **show moderately improved pain from inhaled cannabis use**, but adverse effects such as impaired cognition and respiratory problems are common, especially at high doses.

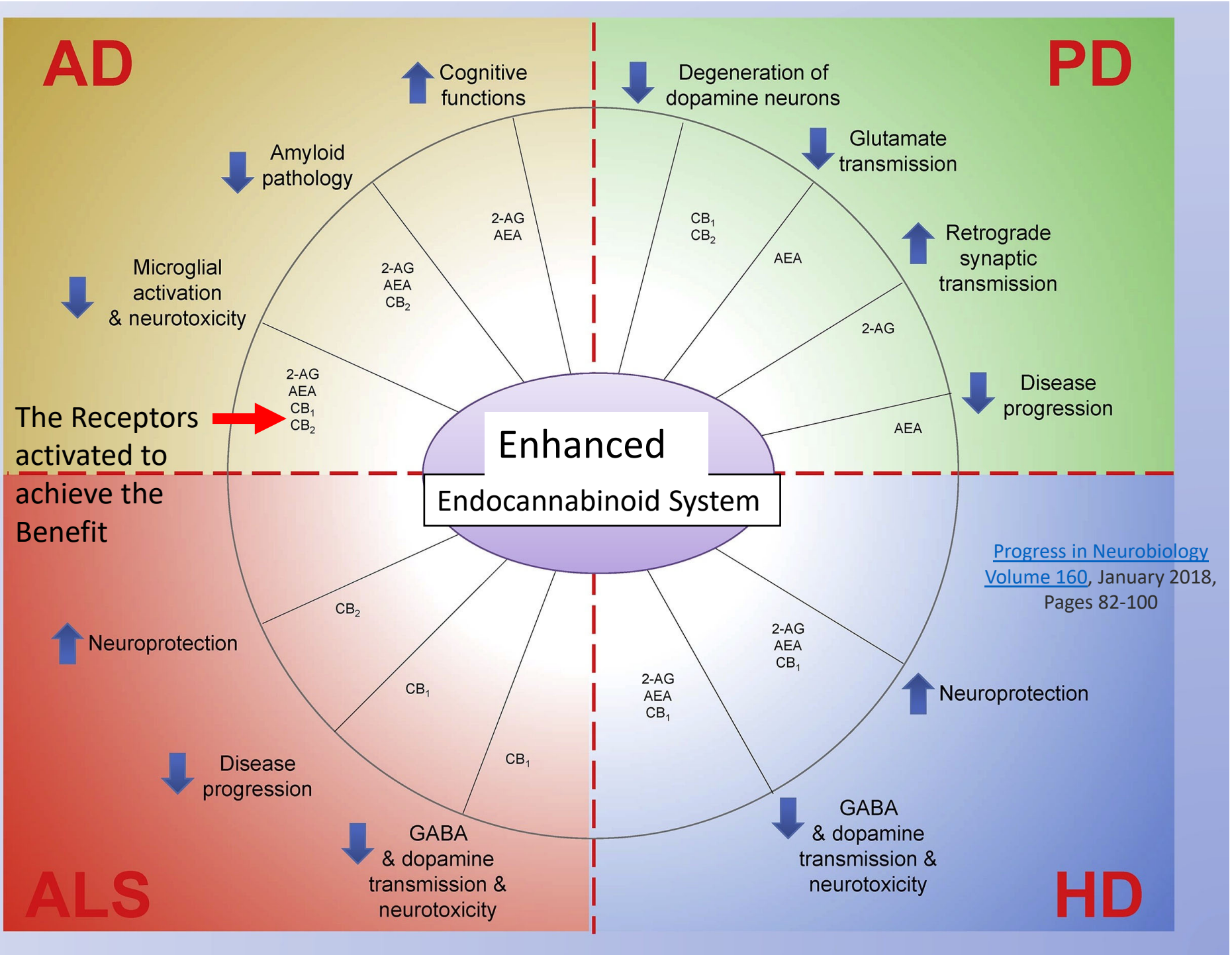
Data on the long-term safety of cannabis treatments are limited

Cleve Clin J Med. 2018 Dec;85(12):943-949. doi: 10.3949/ccjm.85a.17115. **Cannabis for peripheral neuropathy: The good, the bad, and the unknown.** Modesto-Lowe V[1,2,3], Bojka R[2], Alvarado.

Neuroprotective Benefits and CBD and Δ9-THC

- Neuronal protection from excitotoxicity, hypoxia, and glucose deprivation; in vivo
- Cannabinoids **decrease hippocampal neuronal loss and infarct volume after cerebral ischemia, acute brain trauma, and induced excitotoxicity**.
- These effects have been ascribed to:
  - **Inhibition of glutamate transmission**
  - **Reduction of calcium influx**
  - **Reduced microglial activation**
  - **Inhibition of noxious cascades, such as tumor necrosis factor-alpha generation and oxidative stress**

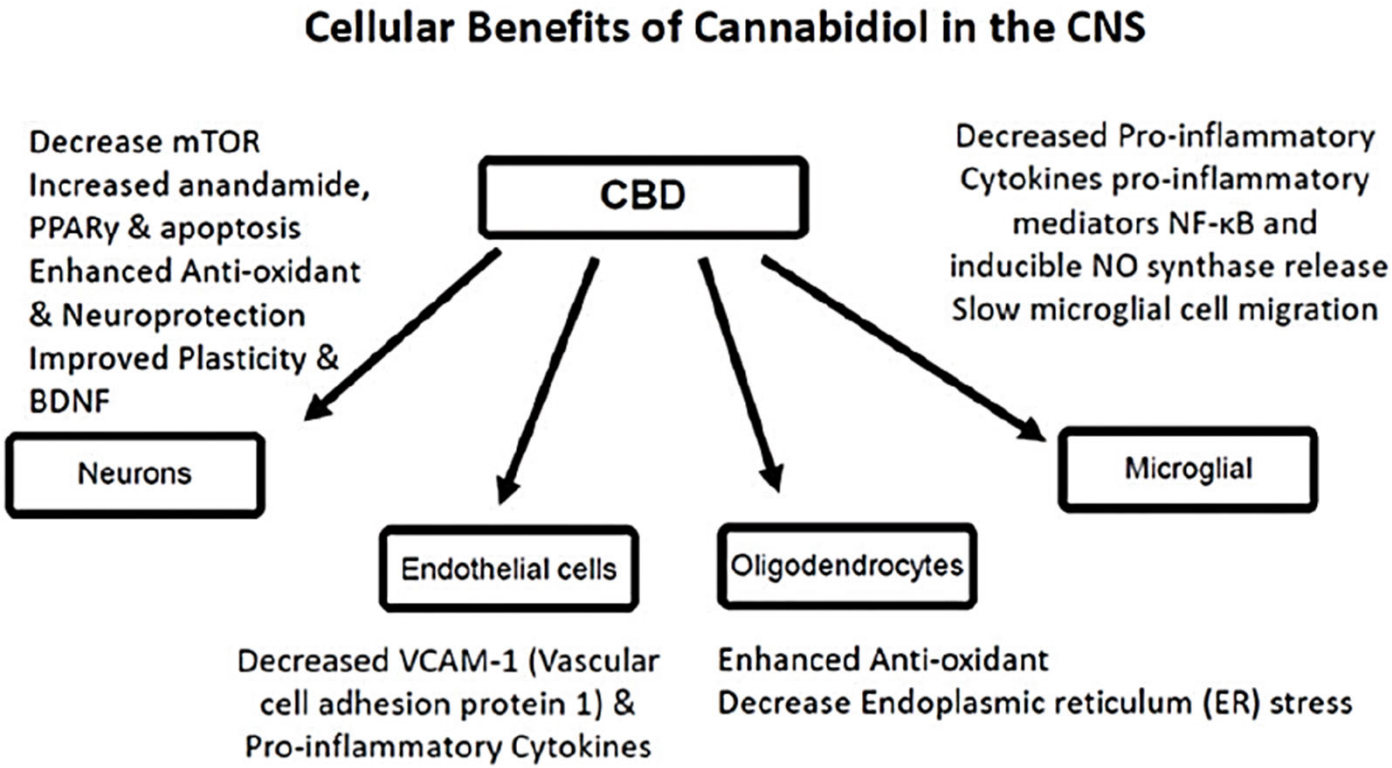
Maroon J, Bost J, Surg Neurol Int. 2018 Apr 26;9:91. doi: 10.4103/sni.sni_45_18. eCollection 2018. Review of the neurological benefits of phytocannabinoids.



Progress in Neurobiology Volume 160, January 2018, Pages 82-100

CBD Neuroprotective Actions

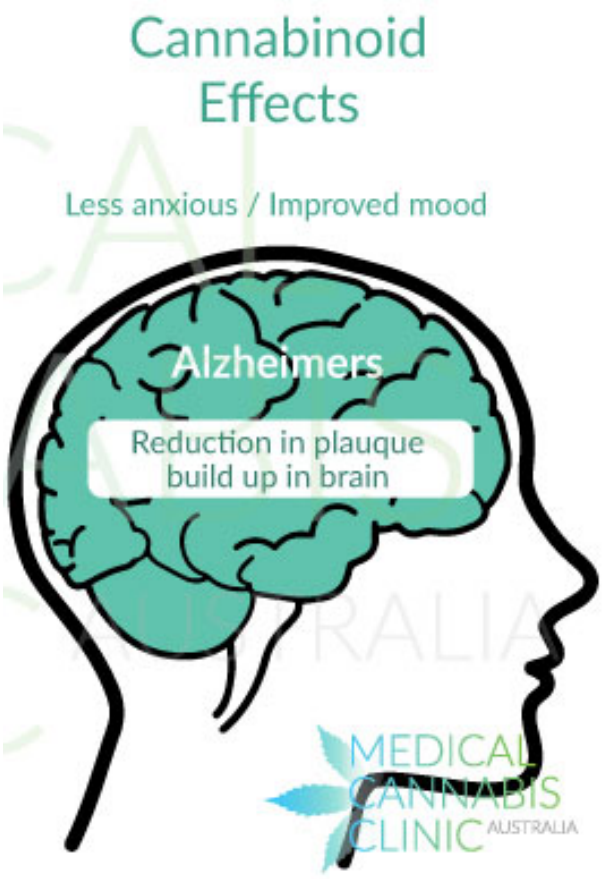
- **CBD/AEA reduces Microglia inflammatory response**
- **Enhance Anti-oxidant and Neuroprotection**
- **Improve Plasticity and BDNF**
- **Preserves cerebral circulation**
- **Reduce Pro-inflammatory Cytokines**



Joseph Maroon* and Jeff Bost . Review of the neurological benefits of phytocannabinoids Surg Neurol Int. 2018; 9: 91

Phytocannabinoids Neuroprotection for AD

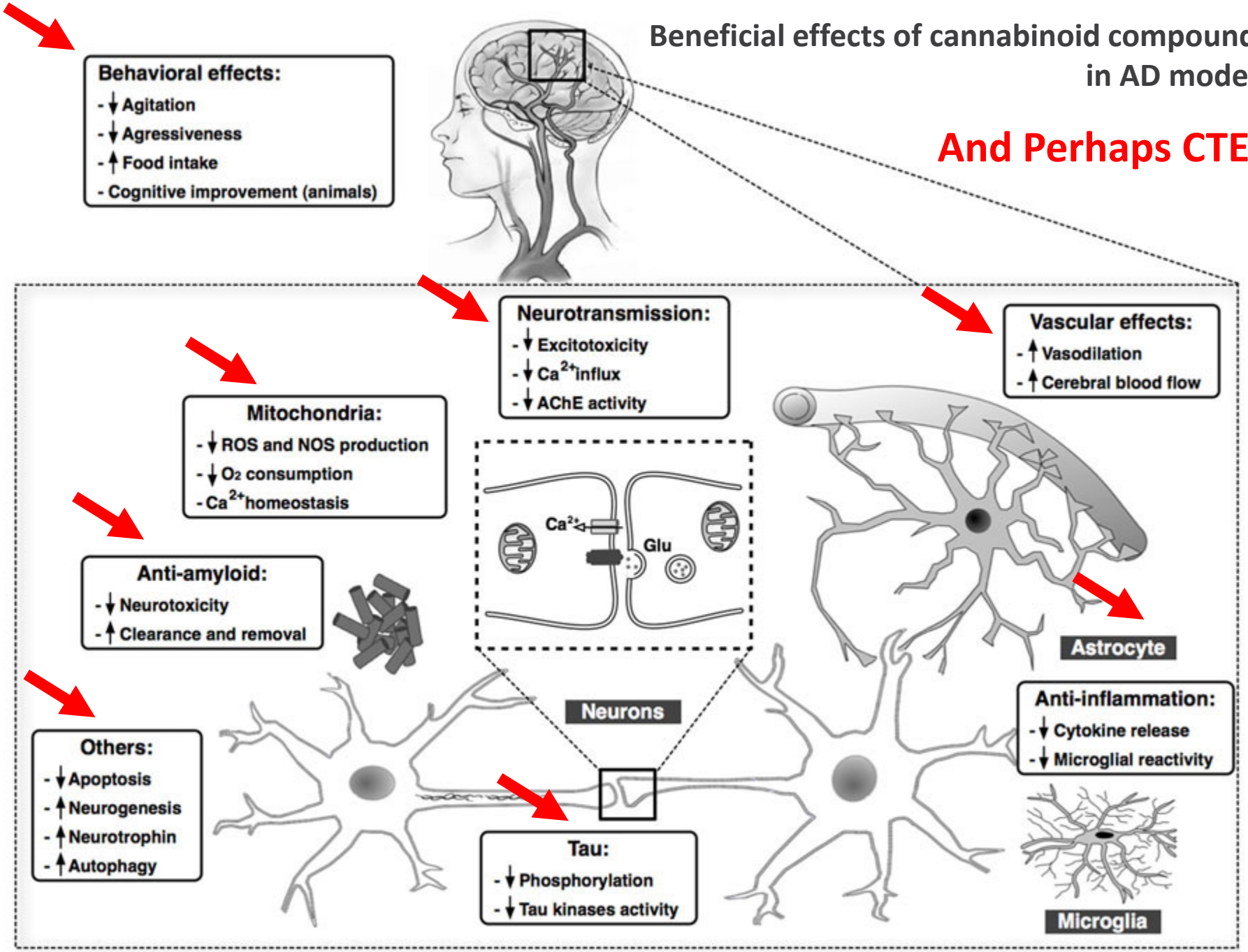
- Phytocannabinoids prevent tau hyperphosphorylation in cultured neurons
- In AD animals phytocannabinoids reduces, microglial activation, inhibited neuronal changes and reduced behavioral changes



Maroon J, Bost J, Surg Neurol Int. 2018 Apr 26;9:91. doi: 10.4103/sni.sni_45_18. eCollection 2018. Review of the neurological benefits of phytocannabinoids.

Beneficial effects of cannabinoid compounds in AD models

And Perhaps CTE?



Ester Aso, Isidre Ferrer, Cannabinoids for treatment of Alzheimer's disease: moving toward the clinic, Front. Pharmacol., 05 March 2014

Multiple sclerosis (Benefits from Enhanced Endocannabinoid Tone)

- In models of experimental MS, stimulation of CB1 and CB2 receptors has been shown to **reduce the inflammatory process**
- Individuals with MS experience a **reduction in the frequency of relapses** when smoking marijuana

Table 1. Targets for Controlling Multiple Sclerosis

Target for Control	Influence of Disease
* IMMUNITY-INFLAMMATION	SLOW RELAPSE RATE
*** NEURODEGENERATION Adaptive Immunity-Dependent	SLOW PROGRESSION
AdaptiveImmunity-Independent/ Innate Immunity Dependent	
** SYMPTOMATIC CONTROL	IMPROVED QUALITY OF LIFE
* REPAIR	REVERSAL OF DEFICITS

CNS & Neurological Disorders - Drug Targets, 2012, 11, 000-000 1 1871-5273/12 $58.00+.00 © 2012 Bentham Science Publishers
Potential Control of Multiple Sclerosis by Cannabis and the Endocannabinoid System Gareth Pryce* and David Baker

Human Trials and MS Spasticity

Mechanisms

- **THC** acts on cannabinoid receptors CB1 and CB2 as a partial agonist and can modulate the excitatory effects of glutamate and the inhibitory effects of gamma-aminobutyric acid (GABA), **achieving muscle relaxation and improvement of spasticity**
- **CBD** acts as an antagonist at CB2 receptors, can **reduce some unwanted reactions to THC** such psychoactive effects and modify pain

Oreja-Guevara, Clinical efficacy and effectiveness of Sativex, a combined cannabinoid medicine, in multiple sclerosis-related spasticity, Expert Rev Neurother. 2012 Apr;12(4 Suppl):3-8. doi: 10.1586/ern.12.11.

Sativex ® GW Pharma MS Spasticity Trials

- Sativex® (**delta-9-tetrahydrocannibinol and cannabidiol in the EU only) in a 1:1 ratio**
- Approved as adjunctive treatment for MS neuropathic (spasticity)pain as a spray
- Five randomized controlled trials (RCTs)
  - 368 patients with various neurological conditions (including MS) were recruited.
  - **Results - THC:CBD spray significantly reduced neuropathic pain, spasticity, muscle spasms and sleep disturbances**
  - (AEs) dizziness, sleepiness, fatigue, feeling of intoxication and a bad taste.

J Cent Nerv Syst Dis. 2019; 11: 1179573519831997.Daily Practice Managing Resistant Multiple Sclerosis Spasticity With Delta-9-Tetrahydrocannabinol: Cannabidiol Oromucosal Spray: A Systematic Review of Observational Studies Katja Akgün,[1] Ute Essner,[2] Cordula Seydel,[3] and Tjalf Ziemssen[1]

American Academy of Neurology statement on medical marijuana

- In **2014**, a review article of 34 studies investigating the use of medical marijuana **found strong support for symptoms of spasticity and spasticity-related pain, using oral cannabis extracts.**
- They reported inconclusive support for symptoms of urinary dysfunction, tremor, and dyskinesia

https://www.aan.com/Guidelines/Home/GetGuidelineContent/650

CANNABINOID SCIENCE SHEDS NEW LIGHT ON THE DARKNESS OF PTSD

Recent scientific research highlights the crucial role of the endocannabinoid system in protecting against post-traumatic stress disorder.

BY **MARTIN A. LEE** ON FEBRUARY 25, 2014

Updated September 24, 2015

A recent article in the journal *Neuroendocrinology* highlights the crucial role of the endocannabinoid system in protecting against posttraumatic stress disorder (PTSD), a debilitating chronic condition involving horrific memories that cannot be erased.

In an effort to understand the neurobiological mechanisms that underlie the onset and development of PTSD, a team of U.S. and Canadian scientists analyzed 46 subjects who were near the World Trade Center in New York City during the September 11 terrorist attacks. Twenty-four of these subjects suffered from PTSD following the attacks; 22 did not.

The researchers found that people with **PTSD had lower serum levels of anandamide**, compared to those who did not show signs of PTSD after 9/11.

PTSD – Clinical Improvements with CBD

- CBD decrease intensity and impact of symptoms associated with PTSD (chronic anxiety in stressful environments)
- In rodent models, CBD blocked formation of fearful memories and enhanced fear extinction
- CBD attenuated contextual memories and disrupt harmful memories

References in chronological order	Subjects/test(s) used	Effective dose/route of administration	Effect	Possible mechanisms of action
Passie et al., 2012.	19 year-old male with PTSD (case report)	CBD + THC (cannabis resin from Turkey – 1/1 proportion)/smoked	Patient experienced reduced stress, less involvement with flashbacks and a significant decrease of anxiety.	Not shown
Das et al., 2013.	Healthy humans/Pavlovian fear-conditioning paradigm	CBD 32 mg inhaled	Enhanced consolidation of explicit fear extinction	Not shown
Greer et al., 2014.	80 patients with PTSD	CBD + THC (cannabis – unknown proportion)/smoked	Cannabis (CBD + THC) is associated with PTSD symptom reduction.	Not shown
Shannon and Opila-Lehman, 2016.	10 year-old girl with PTSD (case report)	CBD oil at least 25 mg daily for 5 months/oral capsules	Maintained decrease in anxiety and a steady improvement in the quality and quantity of the patient's sleep.	Not shown

Front Neurosci. 2018; 12: 502. Cannabidiol as a Therapeutic Alternative for Post-traumatic Stress Disorder: From Bench Research to Confirmation in Human Trials, Rafael M. Bitencourt1,* and Reinaldo N. Takahashi2

Summary

Traditional neurological therapeutics focus mostly on symptomatic treatment of neurodegenerative disorders

Cannabis-based medicines have demonstrated safety, efficacy and consistency sufficient for regulatory approval in spasticity in multiple sclerosis (MS) (Outside US), and in Dravet and Lennox-Gastaut Syndromes (LGS) (US FDA –Approved)

Neurological therapeutics using various amounts and ratios of phytocannabinoids has shown benefits as adjunctive treatment for intractable epilepsy, Parkinson disease (PD), Alzheimer disease (AD) and traumatic brain injury (TBI)/chronic traumatic encephalopathy (CTE) outside of the traditional regulatory process. (Legal State-by-State)

These interventions that harness endocannabinoid system, mediated through a variety of targets and may have advantages over the current single-target pharmaceutical model.

Thank you