BRAIN INJURY ASSOCIATION OF PENNSYLVANIA

Medical Marijuana & Brain Injury: Culture and Science of Cannabinoids

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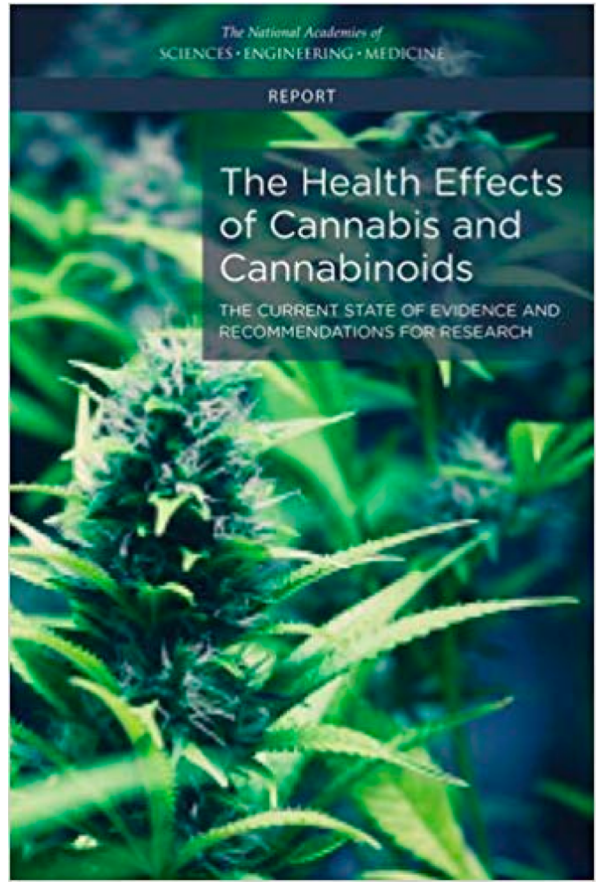
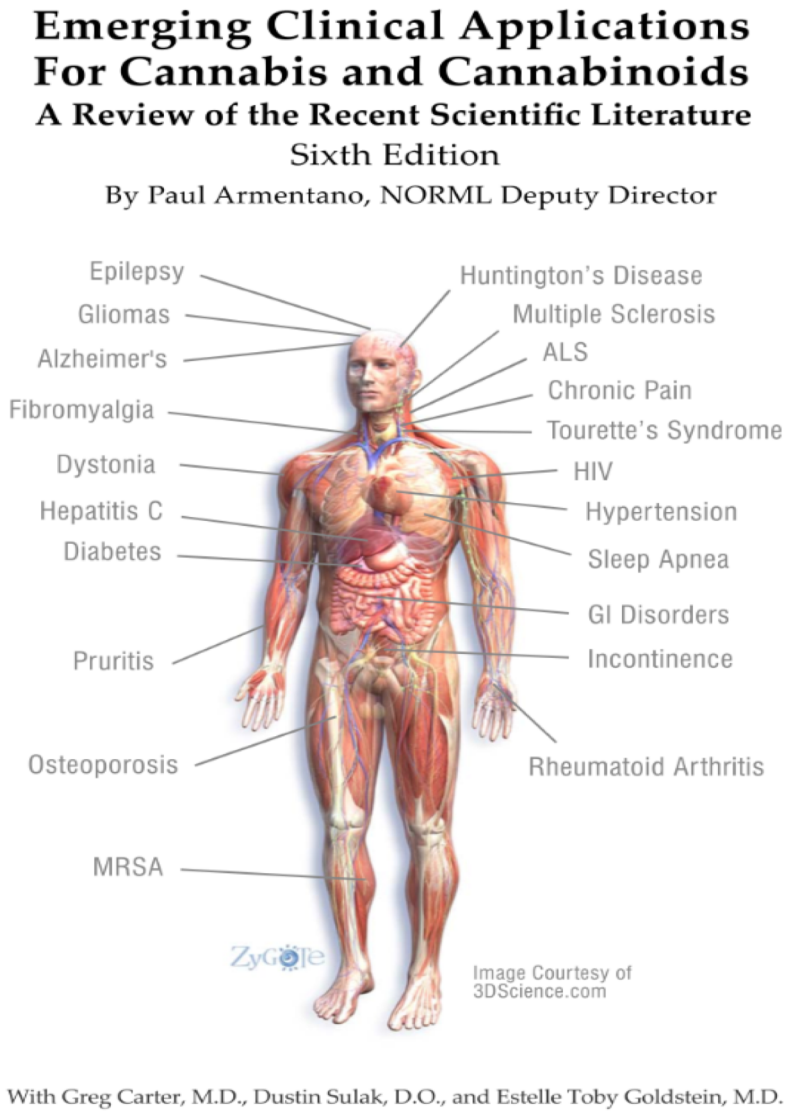


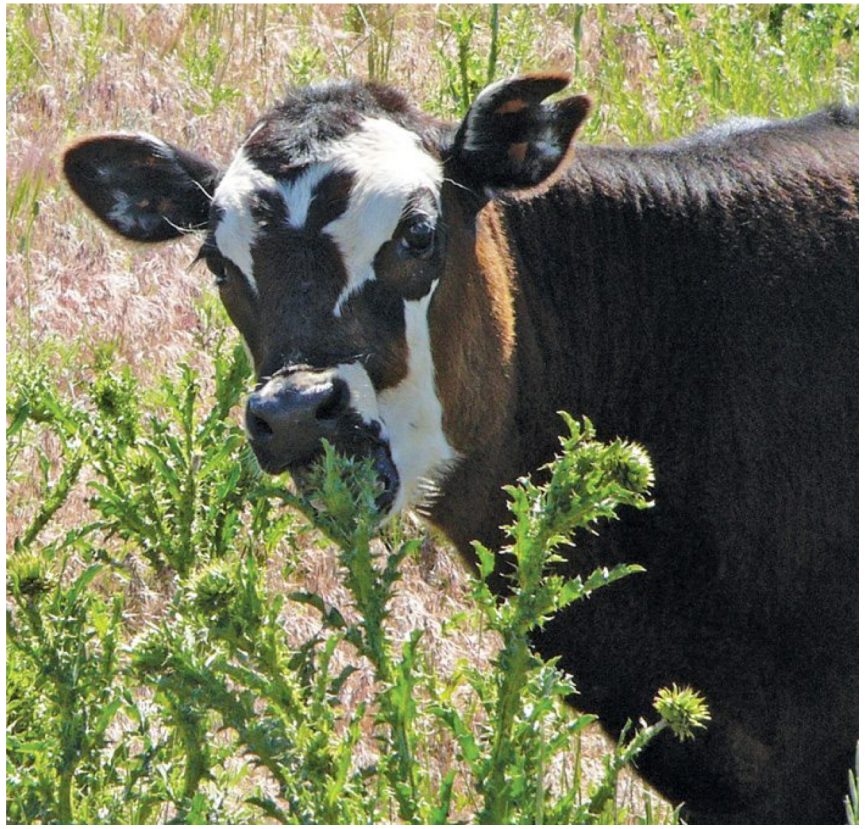
Disclosures

- Speakers bureau
  - BDSI
  - Indivior
  - Salix
- Grew up in the sixties



Why do plants produce molecules that seem perfectly designed to manipulate human biochemical circuitry ?

- Many plants, including cannabis, might make these molecules to defend themselves from other organisms
- Cannabinoids display antibacterial, antifungal and insecticidal properties as well.
- Their ability to engage our native cannabinoid receptors may be a result of millions of years of biochemical warfare directed at would-be grazers.
- Cannabinoids: Neuroprotective or Neuro-destructive?



Case Study: Scott 47 yo TBI, Multiple fxs, Heterotopic Ossification, TransTibial Amputation

- 2003 Trauma –motorcycle accident
- InPt rehab x 3 mos
- D/C Fentanyl, Oxycodone
- 1st clinic visit 2008
- Pain 8-9/10 and difficulty w RUE/hip/ residual limb
- Contractures shoulder/elbow
- Scattered thoughts, angry, tearful but eager to return to life-restoring antique cars
- 2019-Transitioned meds
  - Suboxone (buprenorphine)
- Neudexta – re PseudoBulbar Affect
- Dronabinal + Indica strains of Medical Marijuana
- Added CBD for balancing THC
- Psych + D&A counseling
- New TT prosthesis, shoulder/elb injections
- Active in shop and Independent ADLs, driving –pain 4-6/10

Cannabis: the Myth and the Science

Cannabis and pain: a clinical review.

Hill, K. et al. Cannabis and Cannabinoid Research Vol 2.1, 2017

- *"Cannabis is now being considered in the same way that opioids were decades ago"*

Science

- As a drug class with expectations as pain-relieving medication + immune defense + anti-inflam + disease/condition modulating

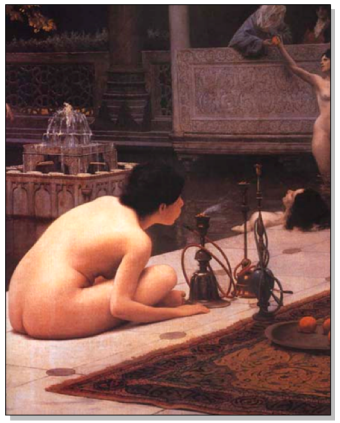
Recreation

- Additionally.. Seen in the context of a social movement supporting treatment for pleasure and relieving suffering of many social (and medical) conditions.

Dispensary Bud Tender / Seattle Hemp Fest

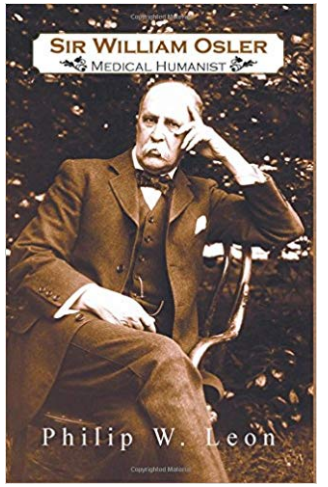
Cannabis Use Time Line

- 2737 BC – Cannabis referenced in Chinese pharmacopia
- 1000 BC – spread to India
- 500BC- familiar to Greeks
- 1000 AD- social and medical use in Muslim world, North Africa



- 1545 Spainish bring Cannabis to New World
- 1611 English in Jamestown grow hemp
- 1700s G. Washington promotes hemp culture
- 1800s Cannabis popular with French as non toxic used for pain, mm relax and anti-Sz

Medical Cannabis Time Line



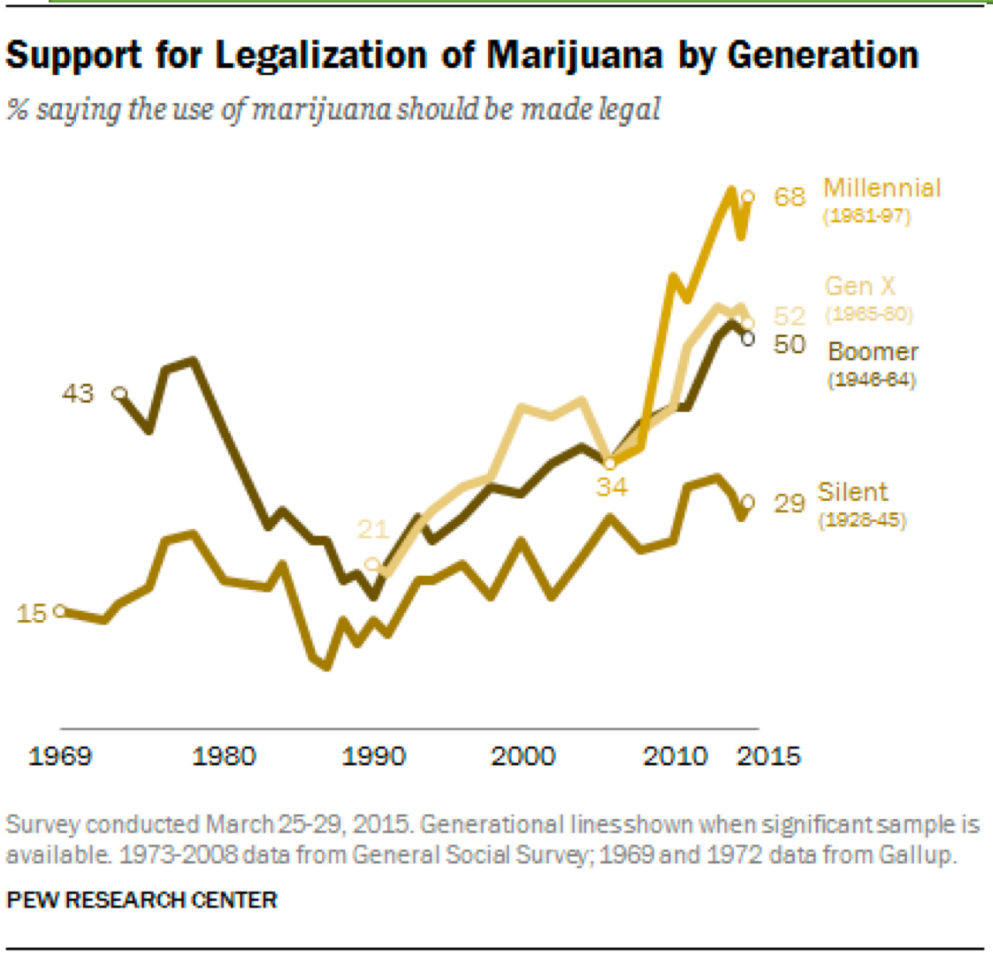
- 1800-1900s Queen Victoria and Sir Wm Osler report use of Cannabis for headaches and migraines
- 1949 reports find cannabis effective in seizure tx when dilantin failed
- 1972 report demonstrates reduction of ocular pressure in glaucoma
- 1975 THC relieves nausea due to anti-cancer drugs
- 1980-1990s – Cannabis used in HIV clinics
- 2006 Rimonabant a selective CB1 receptor antagonist introduced in Europe as anti-obesity drug –Withdrawn worldwide 2008 (dep/suicide/NV/Sz/Spasm)

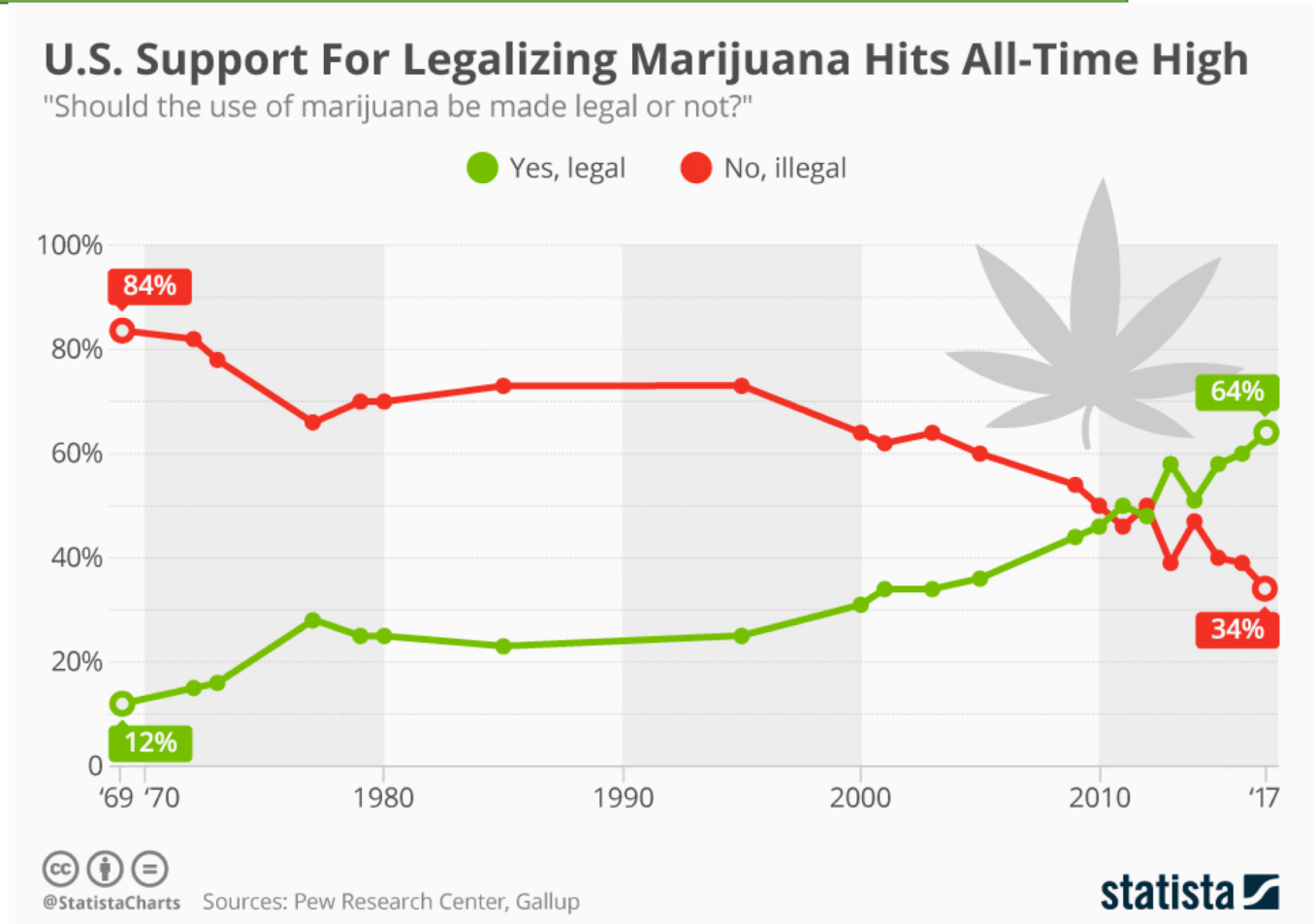
Marijuana in US Culture 1930-1940s: racial & cultural overtones

Marijuana Politics:

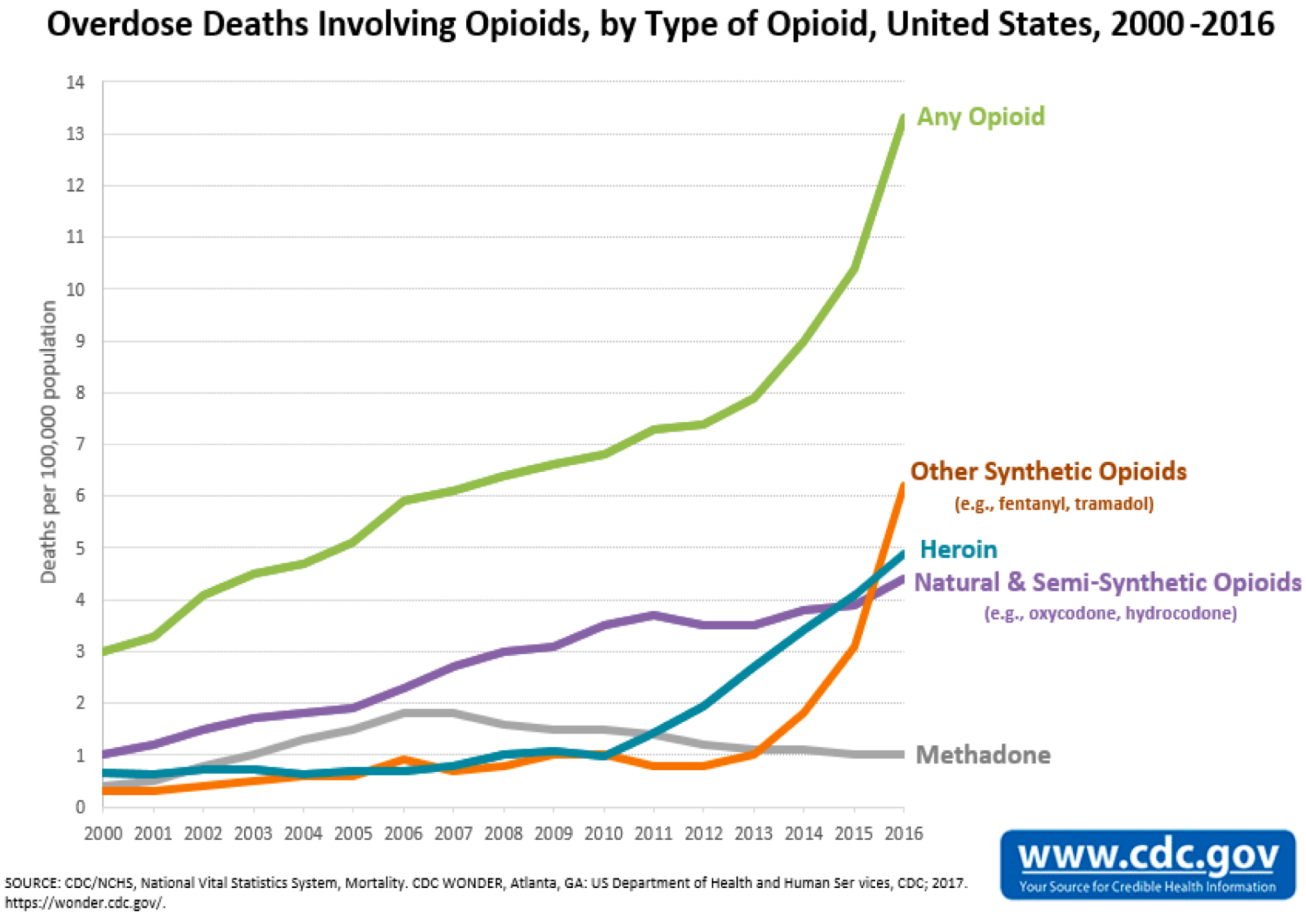
- 1930 – Harry Anslinger appointed Bureau of Narcotics (prior Bureau Prohibition)
- Loathed Mexican & African Americans
- Hated Jazz
- Promoted Marijuana Madness public campaign
- 1937 –Congress passes Marijuana Tax Act
- 1970 – Pres. Nixon signs Controlled Substance Act (against advice of science advisors)
- 2019 - Marijuana remains DEA Schedule 1 i.e. No Medicinal Value

Support for Medical Marijuana in US 2015-2017

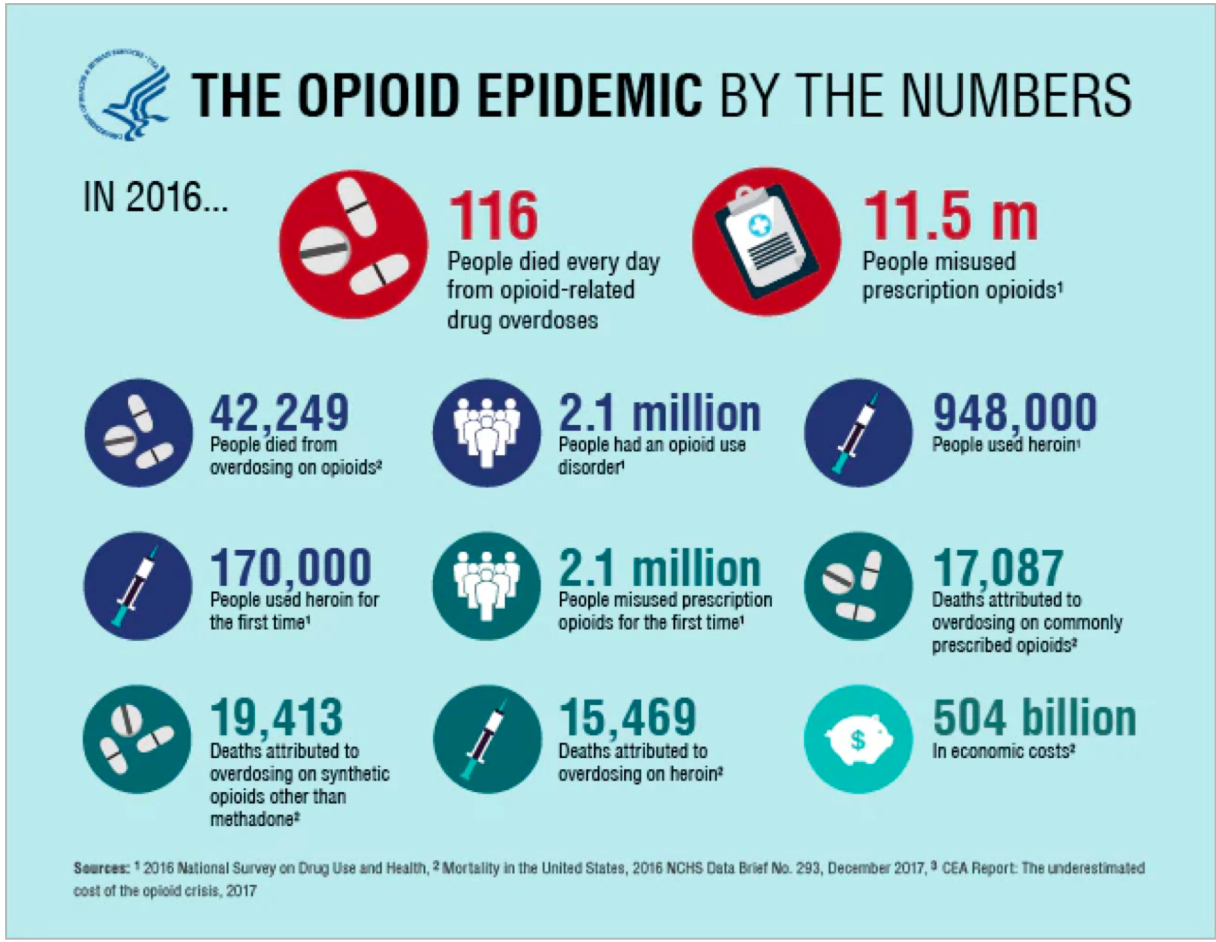




Is medical marijuana the answer to the opioid crisis?

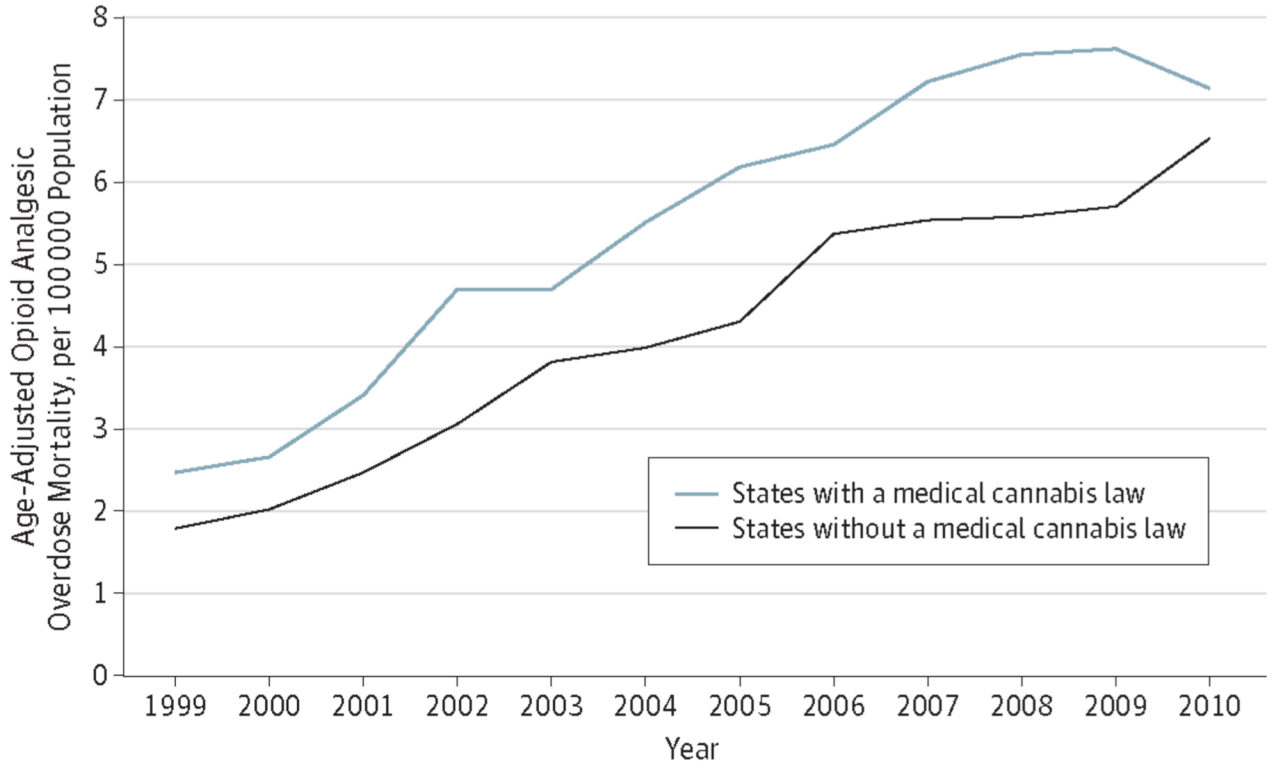


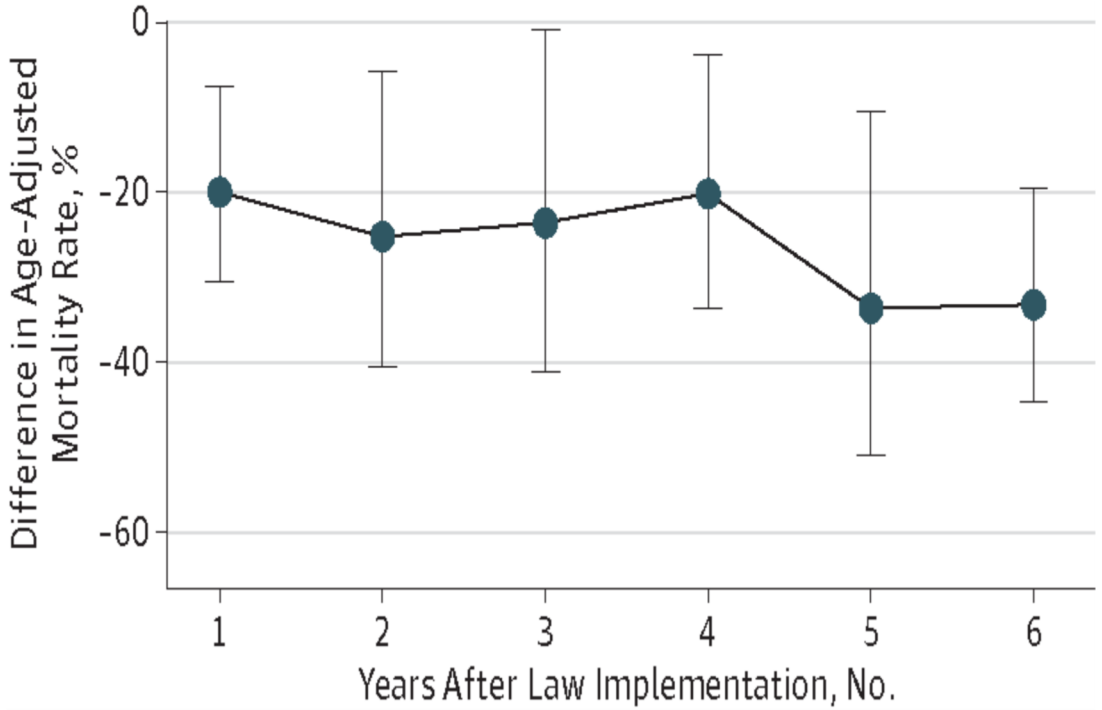
SOURCE: CDC/NCHS, National Vital Statistics System, Mortality. CDC WONDER, Atlanta, GA: US Department of Health and Human Ser vices, CDC; 2017. https://wonder.cdc.gov/.



Medical Cannabis Laws and Opioid Analgesic Overdose Mortality in the United States, 1999-2010

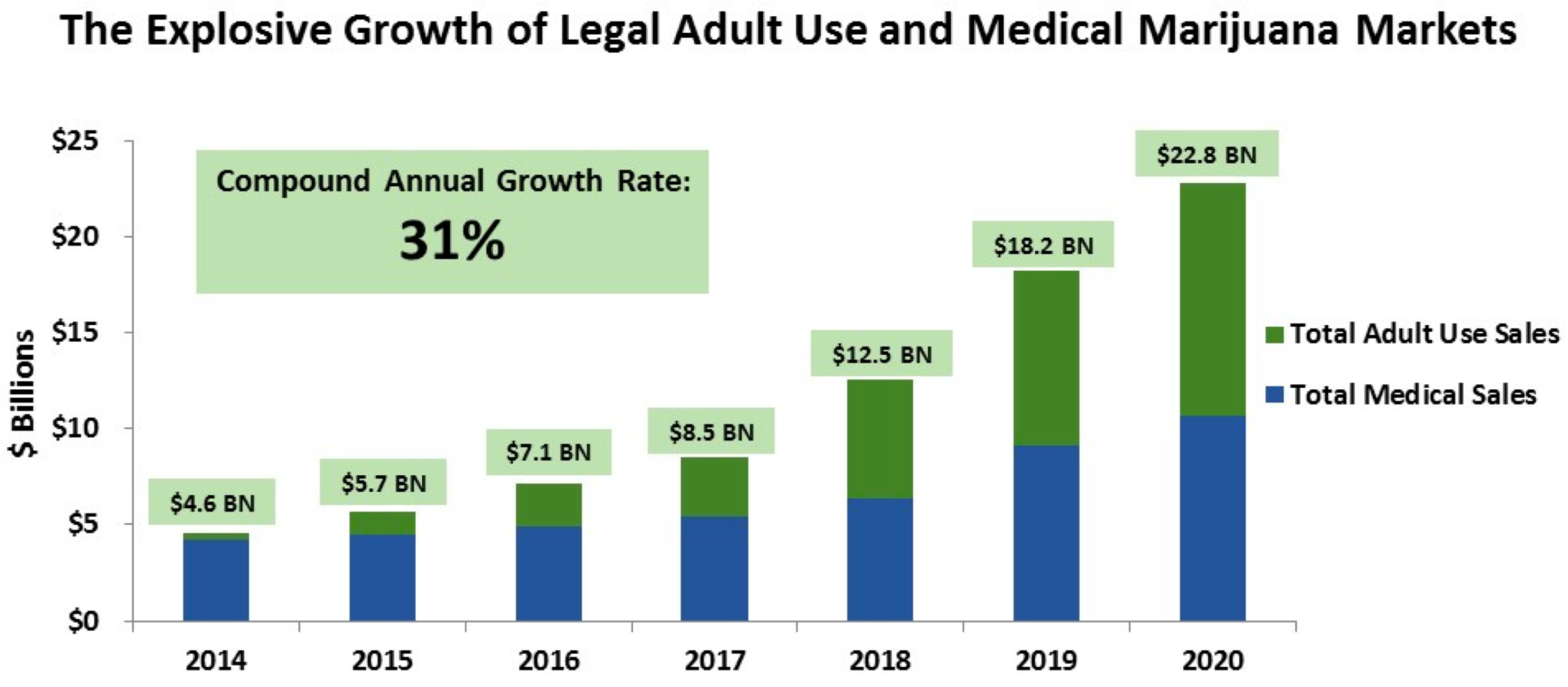
JAMA Intern Med. 2014;174(10):1668-1673. doi:10.1001/jamainternmed.2014.4005

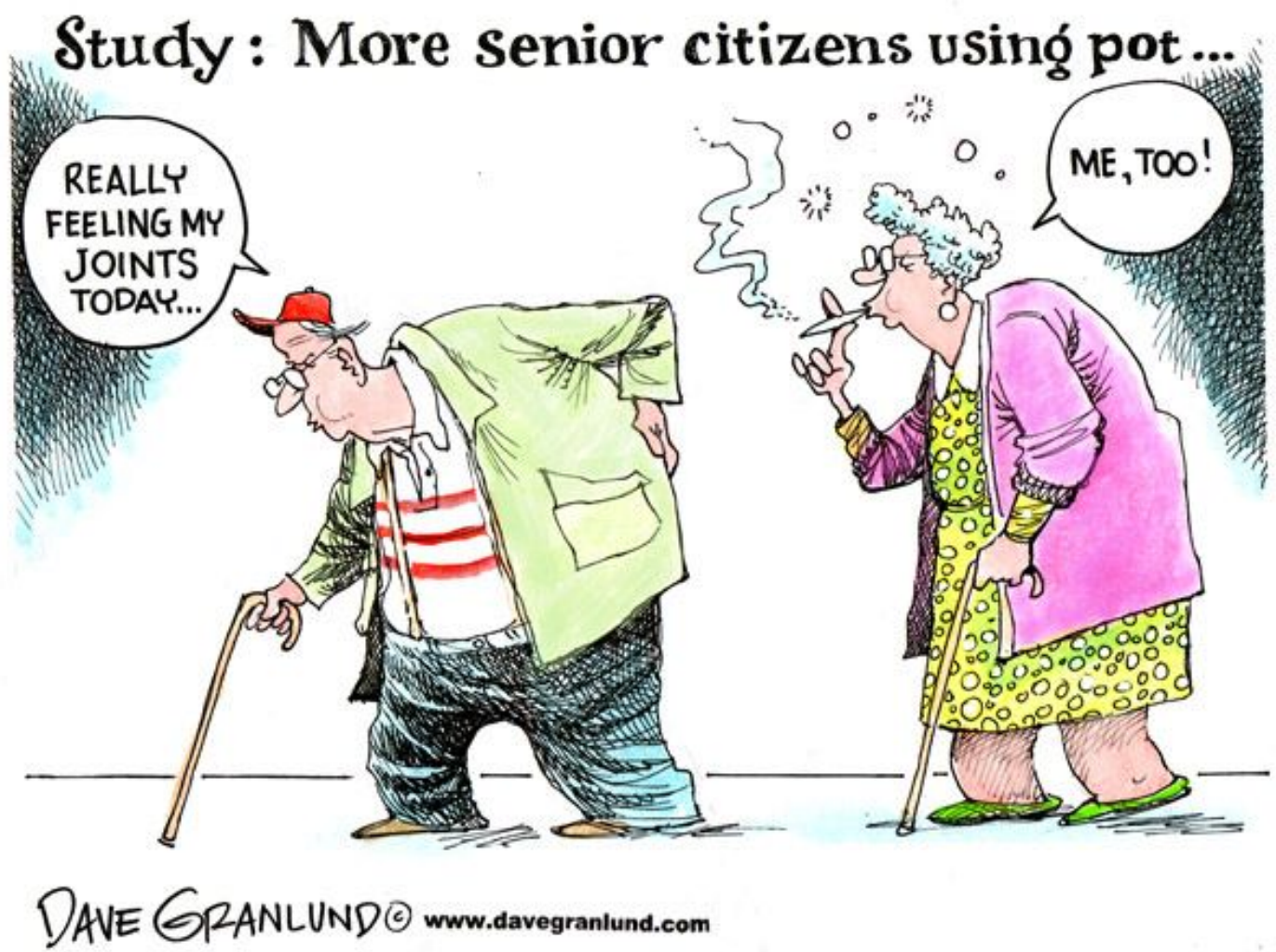




States with medical cannabis laws had a 24.8% lower mean annual opioid overdose mortality

Now approved in 29+ states...still Federally Schedule 1




Study : More senior citizens using pot ...
REALLY FEELING MY JOINTS TODAY...
ME, TOO!
DAVE GRANLUND© www.davegranlund.com

Medical Cannabis Laws (MCLs)and Opioid Prescriptions in the Medicare Population:

Bradford, JAMA Intern Med. 2018;178(5):667-673.

- 2010 to 2015 - 23.08 million daily doses of any opioid dispensed per year / per average state under Medicare Part D.
- States with active dispensaries saw 3.742 million fewer daily doses filled
- Hydrocodone use decreased by 2.320 million daily doses (or 17.4%) filled with is states w dispensary-based MCLs
- Morphine use decreased by 0.361 million daily doses (or 20.7%) filled with dispensary-based MCLs
- States with home cultivation only MCLs saw 1.792 million fewer doses
- Hydrocodone decreased by 1.256 million daily doses (or 9.4%) filled with home-cultivation–only-based MCLs

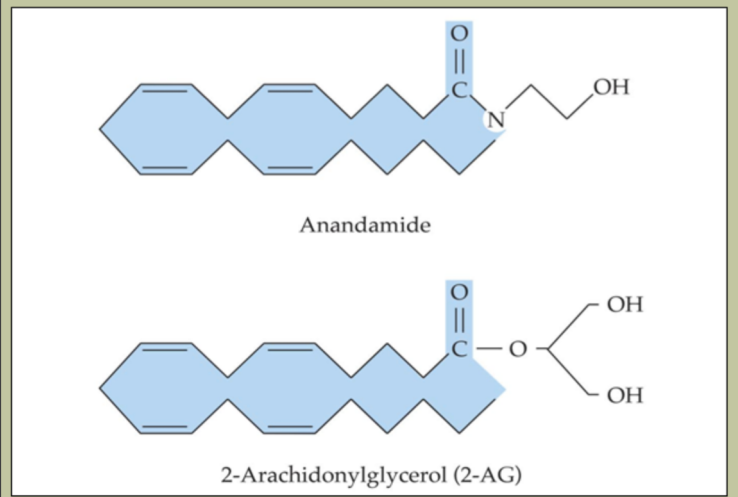
*What is a "serious medical condition" constituting legitimate use under the **Pennsylvania Medical Marijuana Act** 2019*

- Amyotrophic lateral sclerosis
- Autism
- Cancer, including remission therapy
- Crohn's disease
- **Damage to the nervous tissue of the central nervous system (brain-spinal cord) with objective neurological indication of intractable spasticity, and other associated neuropathies**
- Dyskinetic and spastic movement disorders
- Epilepsy
- Glaucoma
- HIV / AIDS
- Huntington's disease
- Inflammatory bowel disease
- Intractable seizures
- Multiple sclerosis
- Neurodegenerative diseases
- Neuropathies
- **Opioid use disorder** for which conventional therapeutic interventions are contraindicated or ineffective, or for which adjunctive therapy is indicated in combination with primary therapeutic interventions
- Parkinson's disease
- Post-traumatic stress disorder
- Severe chronic or intractable pain of neuropathic origin or severe chronic or intractable pain
- Sickle cell anemia
- Terminal illness

Cannabinoid: classification

- Based on origin or source of substance
  - Phytocannabinoids
  - Endocannabinoids
  - Synthetic cannabinoids

Chemical structures of the **endocannabinoids** anandamide and 2-arachidonylglycerol (2-AG)



Endocannabinoids *

Substance	Receptors
Anandamide (AEA)	CB-1, CB-2, TRPV-1
2-Arachidonyl glycerol (2-AG)	CB-1
2-Arachidonyl glyceryl ether	CB-1, CB-2
N-Arachidonyl dopamine (NADA)	CB-1

*All substances are agonists at the mentioned receptors unless specified otherwise.

CB-1: Cannabinoid-1 receptor

CB-2: Cannabinoid-2 receptor

Synthetic Cannabinoids *

Substance	Receptors
Dronabinol (synthetic Δ9-THC)	CB-1, CB-2
Nabilone (Δ9-THC analogue)	CB-1,CB-2
CP-55940	CB-1, CB-2
WIN-55,212-2	CB-1
HU-210	CB-1,CB-2
HU-211	None
JWH-133	CB-2

*All substances are agonists at the mentioned receptors unless specified otherwise

CB-1: Cannabinoid-1 receptor

CB-2: Cannabinoid-2 receptor

Table 1

Plant-derived cannabinoids (phytocannabinoids)

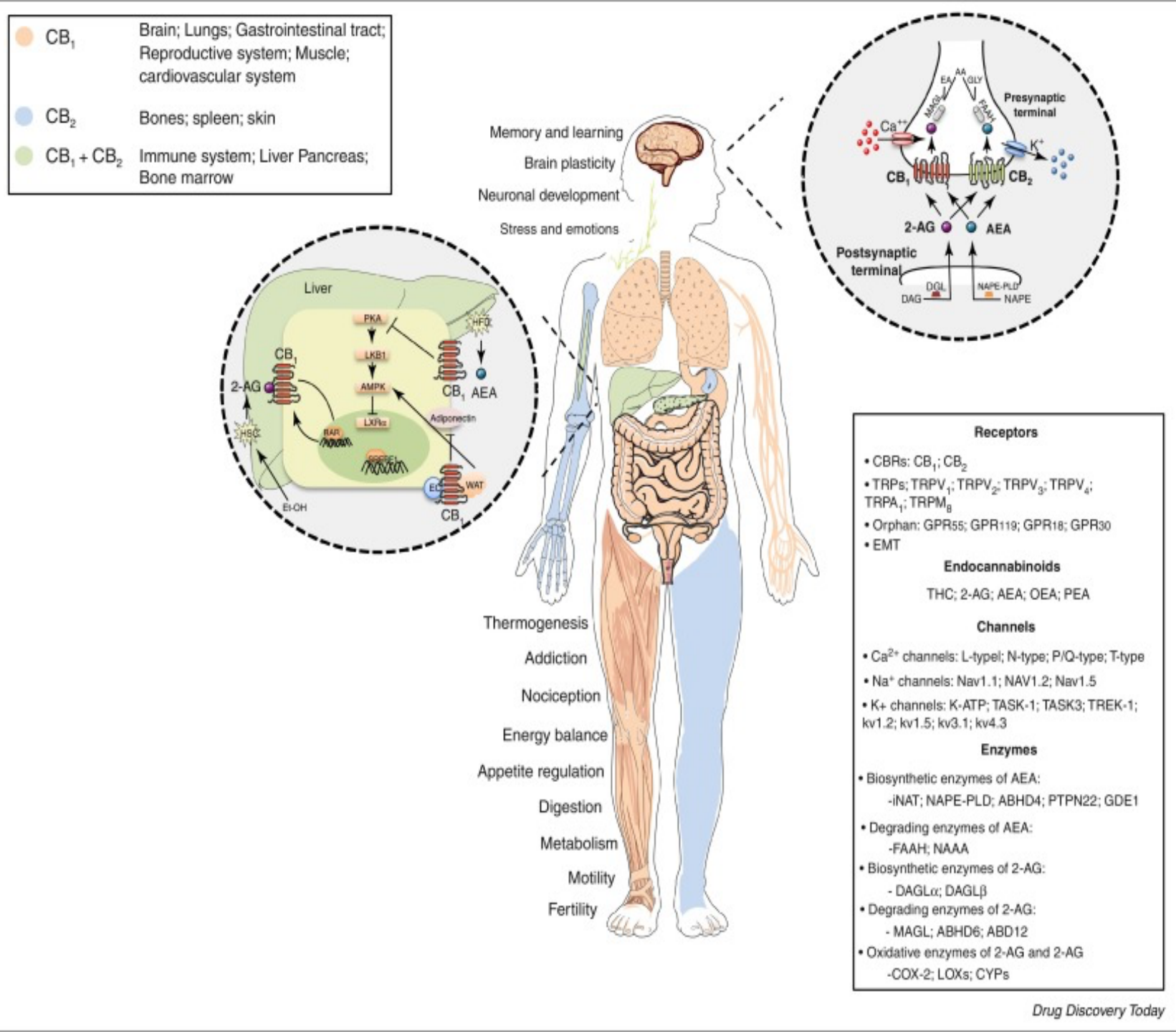
Table 1 Plant-derived cannabinoids (phytocannabinoids)

- Δ^9-tetrahydrocannabinol-type (9)
- Δ^8-tetrahydrocannabinol-type (2)
- Cannabidiol-type (7)
- Cannabigerol-type (6)
- Cannabichromene-type (5)
- Cannabicyclol-type (3)
- Cannabielsoin-type (5)
- Cannabitriol-type (9)
- Miscellaneous-type (11)
- Cannabinol and cannabinodiol-types (air-oxidation artefacts)

The number of each of the listed types of cannabinoid that has been found in cannabis is shown in parenthesis (reviewed in ElSohly, 2002). Tincture of cannabis (right hand panel) was a commercial product that was prepared from *Cannabis sativa* grown in Pakistan and imported into Britain under licence (Gill *et al.*, 1970).

Human EndoCannabinoid Receptor System

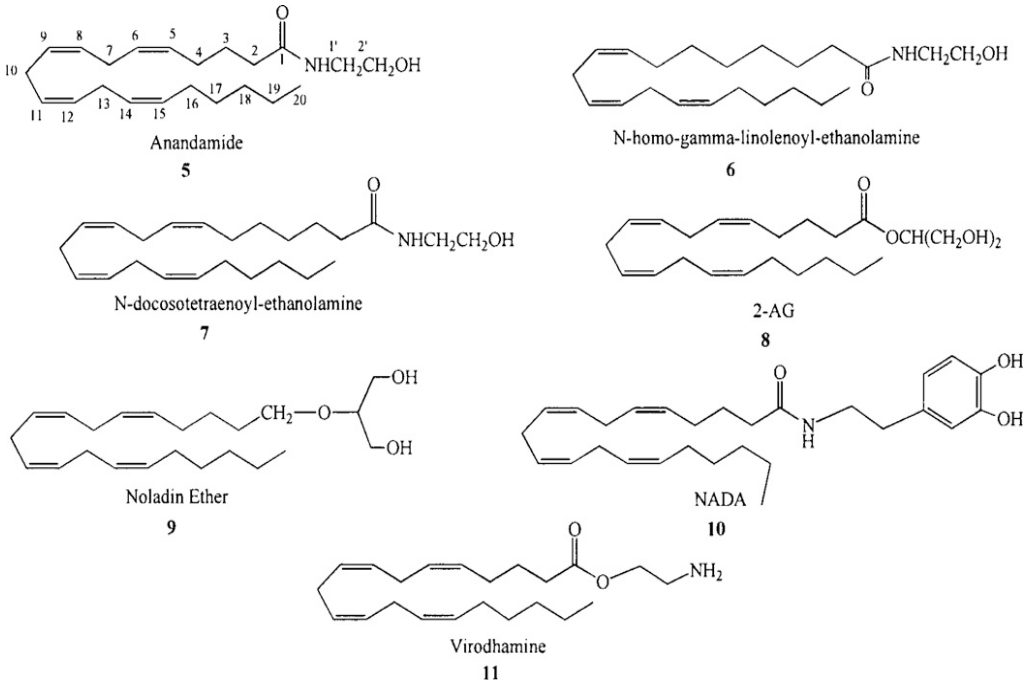
- CB1 Receptors
  - Brain
  - Lungs
  - Liver (CB1&2)
  - Vascular System
  - Reproductive Organs
  - Muscles
- CB2 receptors
  - Colon
  - Immune System
  - Spleen
  - Pancreas (CB1&2)
  - Bones



Endocannabinoid Binding to the Cannabinoid Receptors: What Is Known and What Remains Unknown. Reggio P. Curr Med Chem. 2010; 17(14): 1468–1486.

Anandamide (AEA)

- Sleep
- Pleasure
- Reproduction
- Cognition
- Appetite
- Mood
- Fear
- Pain
- Attention
- Immune Function
- Movement



2-arachidonoylglycerol (2-AG)

- Mood
- Metabolism
- Immune Function
- Reproduction
- Memory
- Movement
- Pain
- Sleep
- Bone Health
- 170x > concentration than AEA

PHARMACEUTICAL CANNABINOIDS ARE NOT MEDICAL MARIJUANA

Synthetic Cannabinoids

Made in laboratories; examples include FDA approved Marinol® (dronabinol) and Cesamet (nabilone)

Phytocannabinoids

Found in the plants, contains hundreds of cannabinoids, most notably THC and CBD

Marinol®: Synthetic Oral THC

Cesamet®: Synthetic Oral THC Analogue

Sativex® (Canada/UK): Herbal *Cannabis* Extract

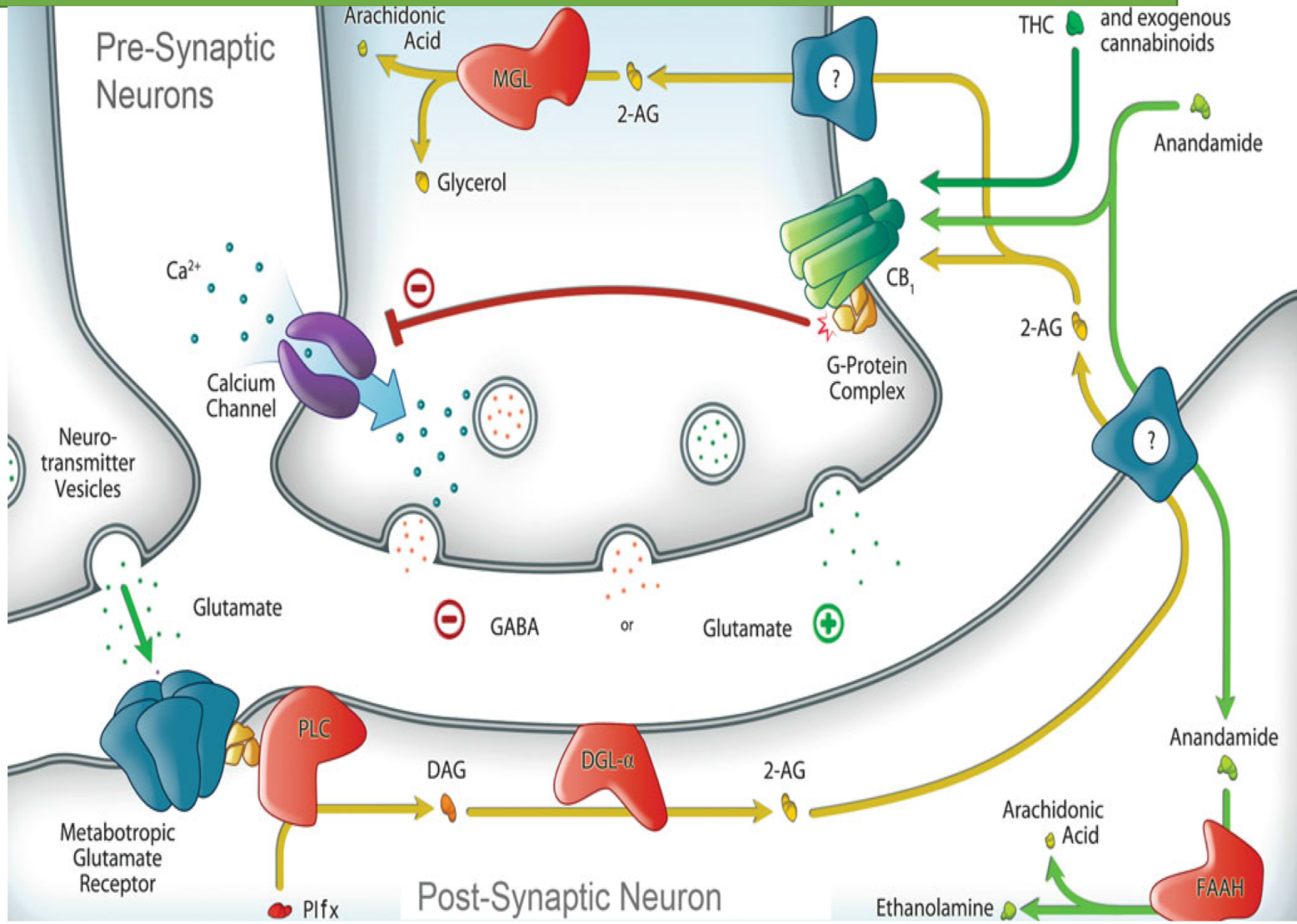
Dronabinol

Nabilone

- Nabilone & Dronabinol ..1st generation synthetic THC analogs, used as an anti-emetic
- Illicit agents based on THC the natural cannabinoid with the strongest binding affinity to the CB_1 receptor
- Potency and additives uncontrolled
- deaths from synthetic cannabinoid use tripled between 2014 and 2015

Endocannabinoids Mechanism of Action (MOA): Produced on demand…

- Produced in post-synaptically depolarized neurons
- Released immediately to regulate synaptic transmission
- Travel to pre-synaptic terminals
- Activate CB1 receptors
- Generally decrease release of glutamate or GABA
- Can be inhibitory or excitatory



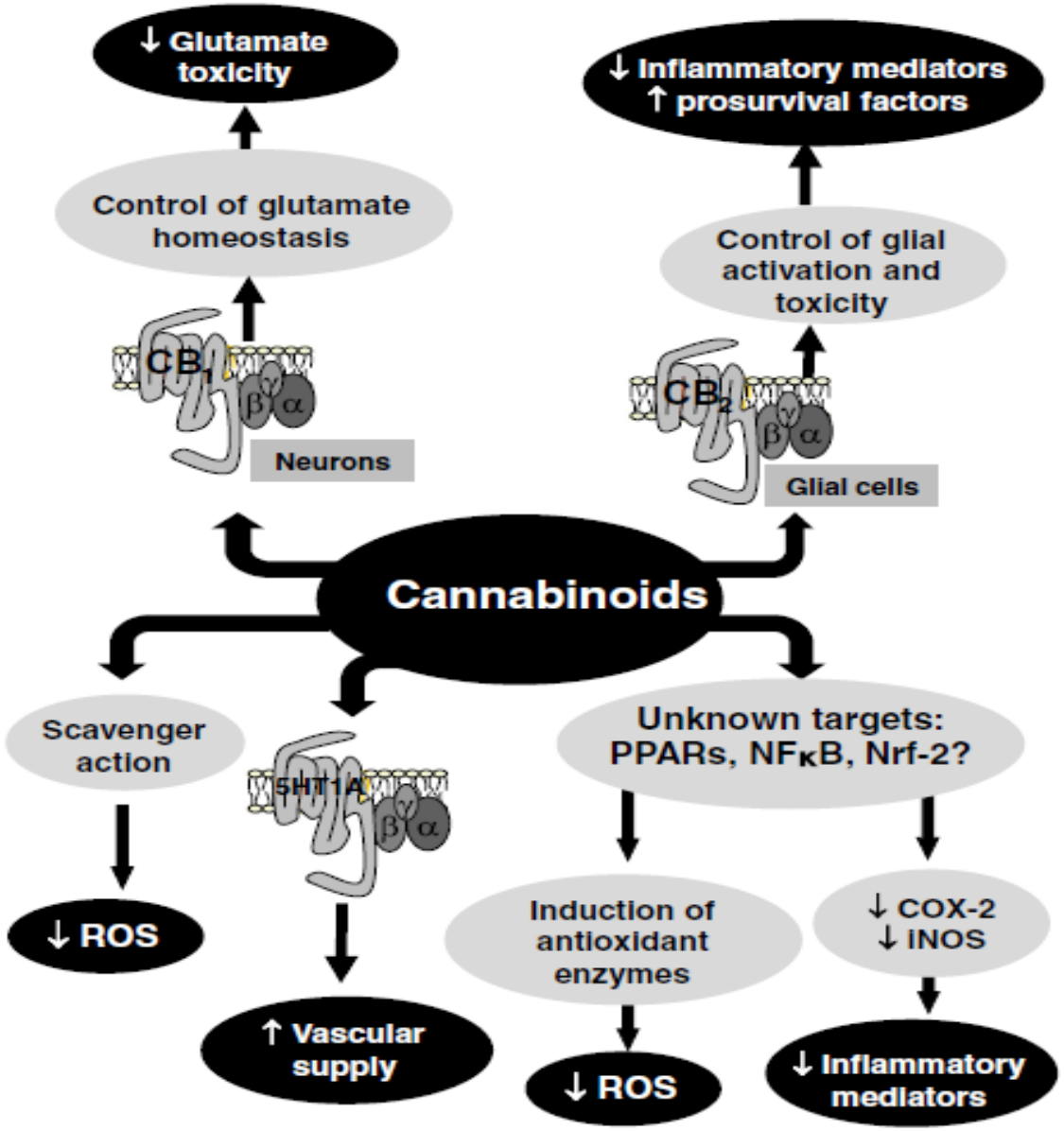


Fig. 1 Overview of the molecular and cellular mechanisms enabling the neuroprotective properties of cannabinoids. CB_1=cannabinoid type 1

Endocanabinoids (EC) regulate neuronal homeostasis.

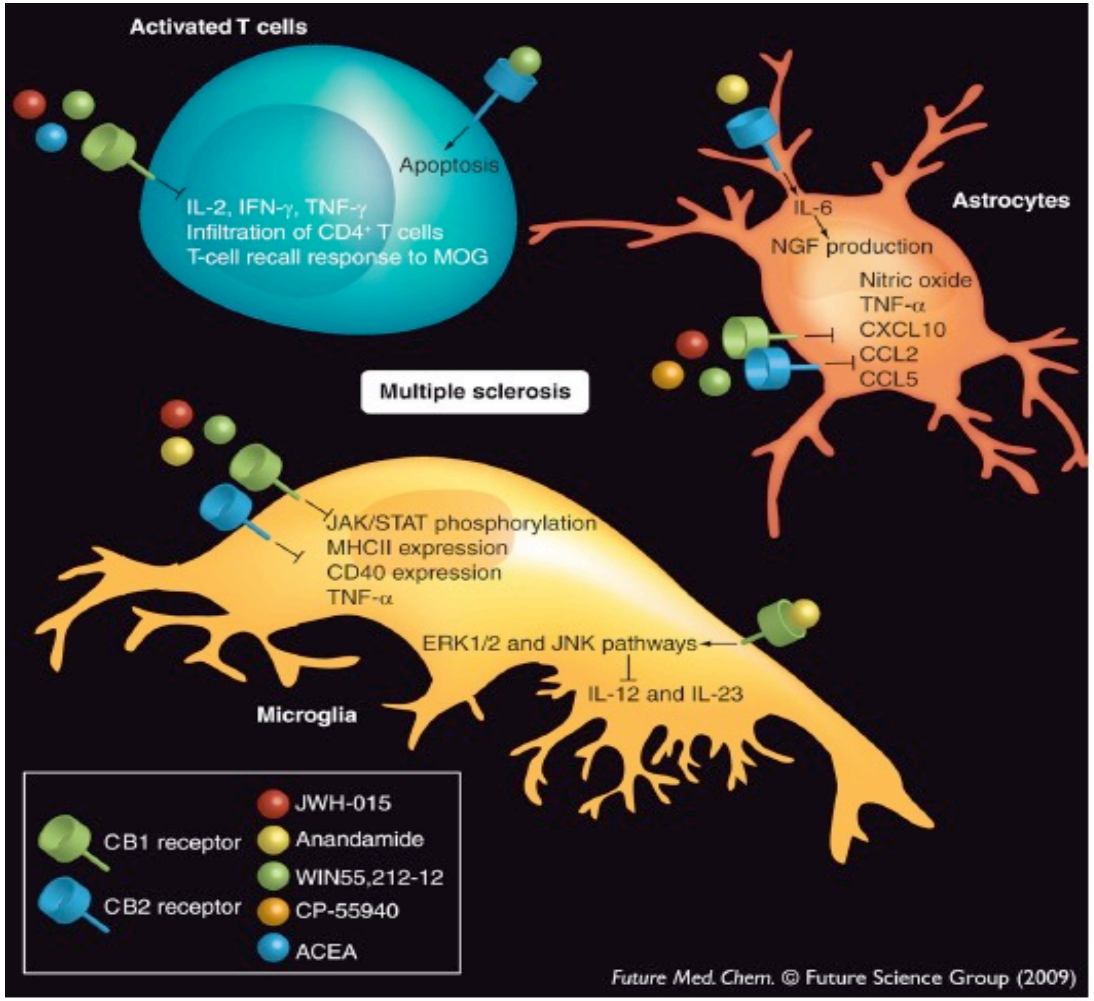
- Endocannabinoids facilitate survival against multiple insults
- Preserve
- Rescue
- Repair,
  - and/or
- Replace neurons, and Glial cells

Cannabinoid-based drugs as anti-inflammatory therapeutics Klein TJ *Nature Rev Immunology* **vol 5**, pages400–411 2005

- Cannabinoids …have been shown to either suppress or increase the production of pro-inflammatory cytokines — TNF, interleukin-1β (IL-1β) and IL-6 — in both patients and animal models, … modulate pro-inflammatory mediators.
- Cannabinoids and endocannabinoids regulate some of the inflammatory aspects of brain injury, inhibiting NMDA receptors,
  - functioning as antioxidants a
  - reducing the levels of pro-inflammatory cytokines in the brain
- Cannabinoids regulate the tissue response to inflammation in the colon
- Plant-derived cannabinoids and synthetic derivatives are anti-inflammatory and immunosuppressive in animal models of arthritis

Cannabinoids as novel anti-inflammatory drugs

Prakash Nagarkatti, Future Med Chem. 2009 October ; 1(7): 1333–1349



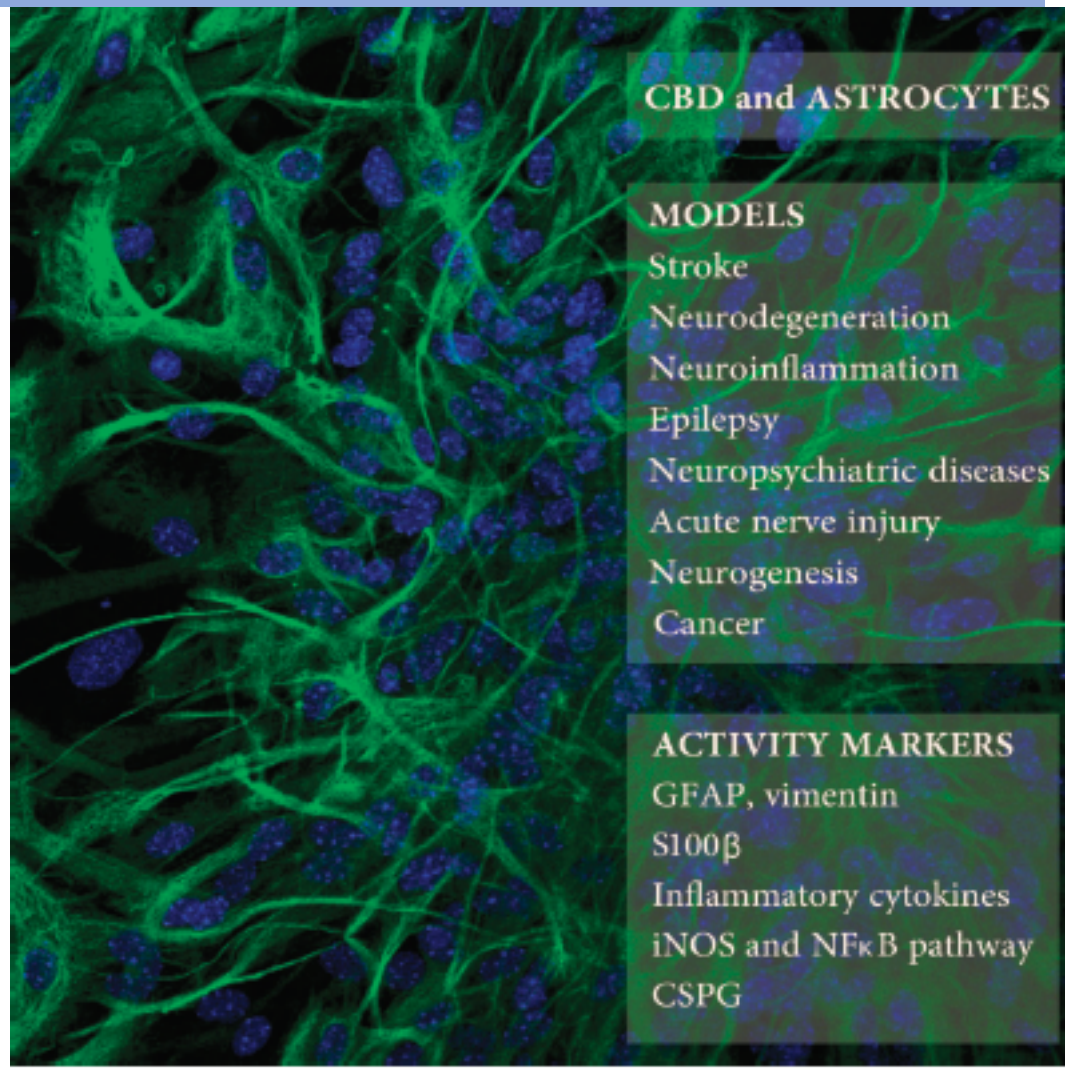
ure 1. Cannabinoids and multiple sclerosis

- Exogenous cannabinoids suppress T-cell-mediated immune responses
  - inducing apoptosis
  - suppressing inflammatory cytokines and chemokines.
- Cannabinoids have been tested in models of autoimmune disorders
  - MS, RA, colitis and hepatitis and cancers …
- protecting the host from the pathogenesis through induction of multiple anti-inflammatory pathways.

Modulation of Astrocyte Activity by Cannabidiol, a Nonpsychoactive Cannabinoid. Kozela E, Int Jour of Molec Sci 2017

- Astrocytes are the most numerous cells populating the central nervous system (CNS).
- astrocytes regulate neuronal growth and synapse formation and pruning, support neuro-signaling involved in acute injury,
- Involved in neurodegeneration; neuroplasticity, learning and memory;
- accompany neuropsychiatric disorders,
- drug addiction and dependence

- **CBDs modulate protective astrocyte activity**



Pharmacology of CBD in treatment of neurodegenerative disorders (Russo)

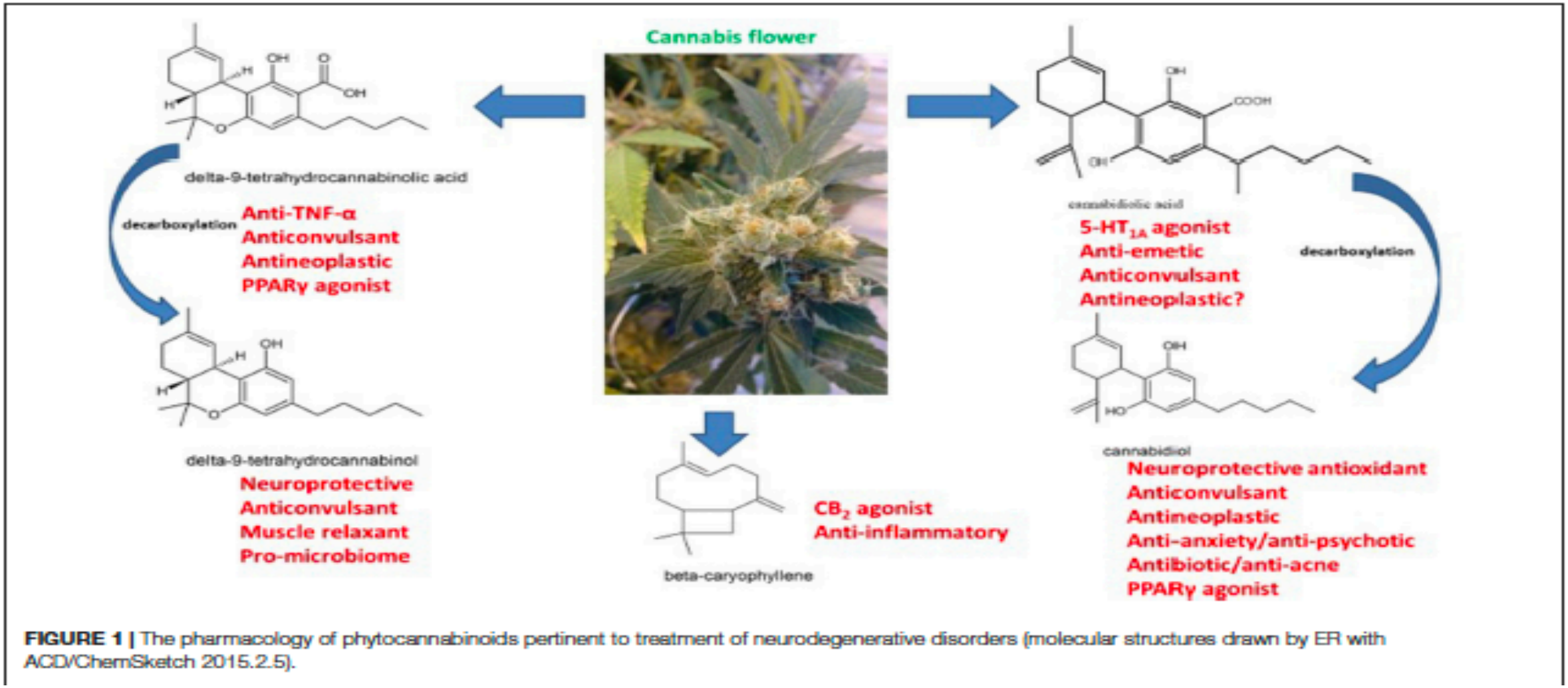


FIGURE 1 | The pharmacology of phytocannabinoids pertinent to treatment of neurodegenerative disorders (molecular structures drawn by ER with ACD/ChemSketch 2015.2.5).

National Acad of Sciences Comm on the Health Effects of Marijuana: Evidenced based review and research agenda 2017

Report Conclusions[5]

Chapter 4 Conclusions—Therapeutic Effects of Cannabis and Cannabinoids

There is conclusive or substantial evidence that cannabis or cannabinoids are effective:

- For the treatment of chronic pain in adults (cannabis) (4-1)
- As antiemetics in the treatment of chemotherapy-induced nausea and vomiting (oral cannabinoids) (4-3)
- For improving patient-reported multiple sclerosis spasticity symptoms (oral cannabinoids) (4-7a)

There is moderate evidence that cannabis or cannabinoids are effective for:

- Improving short-term sleep outcomes in individuals with sleep disturbance associated with obstructive sleep apnea syndrome, fibromyalgia, chronic pain, and multiple sclerosis (cannabinoids, primarily nabiximols) (4-19)

There is limited evidence that cannabis or cannabinoids are effective for:

- Increasing appetite and decreasing weight loss associated with HIV/AIDS (cannabis and oral cannabinoids) (4-4a)
- Improving clinician-measured multiple sclerosis spasticity symptoms (oral cannabinoids) (4-7a)
- Improving symptoms of Tourette syndrome (THC capsules) (4-8)
- Improving anxiety symptoms, as assessed by a public speaking test, in individuals with social anxiety disorders (cannabidiol) (4-17)
- Improving symptoms of posttraumatic stress disorder (nabilone; a single, small fair-quality trial) (4-20)

Therapeutic effects of Cannabis and cannabinoids:

- There is conclusive or substantial evidence that cannabis...is effective:
  - For the treatment of chronic pain in adults
  - As antiemetic in chemotherapy
  - For improving MS spasticity symptoms

Clinical studies with cannabinoids in chronic pain

- Whiting, Cannabinoids for medical use: A systematic review and meta-analysis. *JAMA* 2015, 313(24):2456–2473
  - 28 randomized trials in patients with chronic pain (2,454 participants)
  - Plants and synthetics, placebo controlled
  - Studied neuropathy (17 trials); cancer pain, multiple sclerosis, rheumatoid arthritis, musculoskeletal issues, and chemotherapy-induced pain
  - plant-derived cannabinoids increase the odds for improvement of pain by approximately 40 percent versus the control condition
- Wallace et al.Journal of Pain 2015
  - dose-dependent effect of vaporized cannabis flower on spontaneous pain, with the high dose (7 percent THC) showing the strongest effect

- **CONCLUSION There is substantial evidence that cannabis is an effective treatment for chronic pain in adults.**
- NAS

Cannabinoid Receptors and Pain Pathways

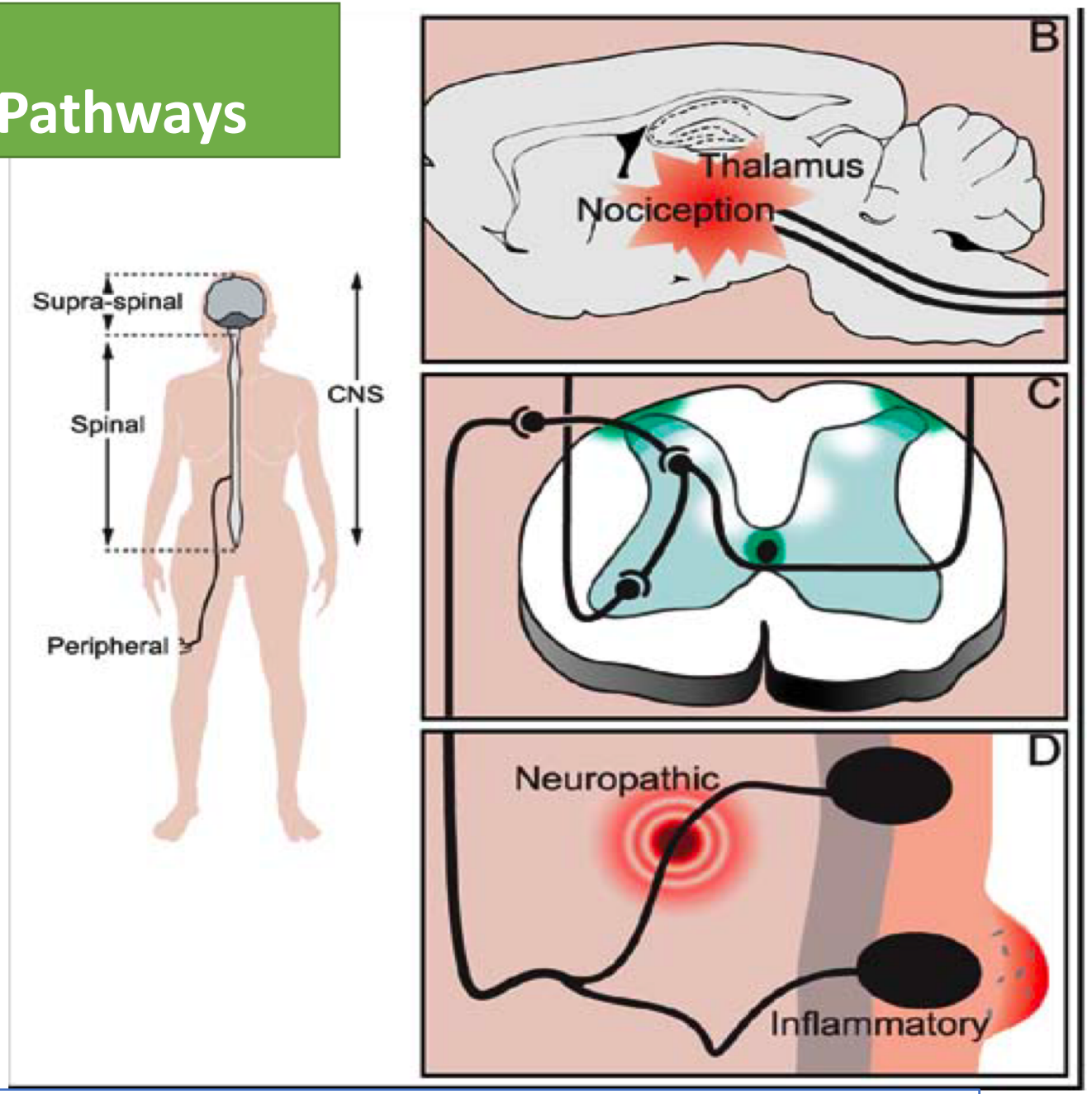
A: Cannabinoid receptors are present at the peripheral and central (spinal and supraspinal) levels.

B: Supraspinal CB1 receptors of the brain and brainstem nuclei involved in nociceptive perception as thalamus, amygdala, and periaqueductal grey matter.

C: The highest abundance of spinal CB1 receptors are found in the dorsolateral funiculus, in the surroundings of the central canal and in the superficial dorsal horn.

D: CB1 receptors in the peripheral sensory nerve endings,

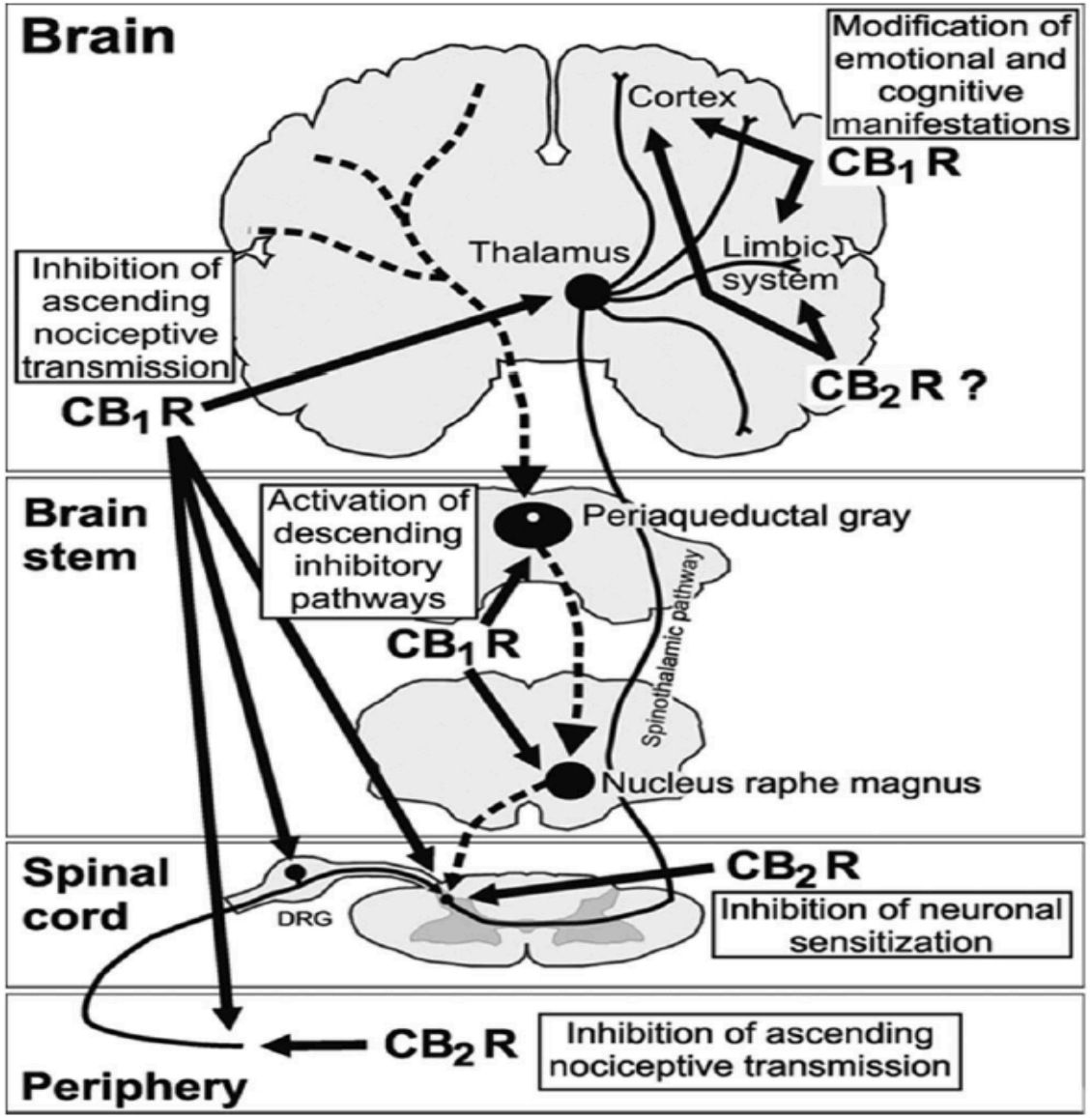
CB1 and CB2 receptors- non-neuronal cells participating in immune and inflammatory processes in the proximity of the primary afferent neurons nerve terminals.



J. Manzanares, Role of the Cannabinoid System in Pain Control…Current Neuropharmacology, 2006, Vol. 4, No. 3

Neuropathic pain

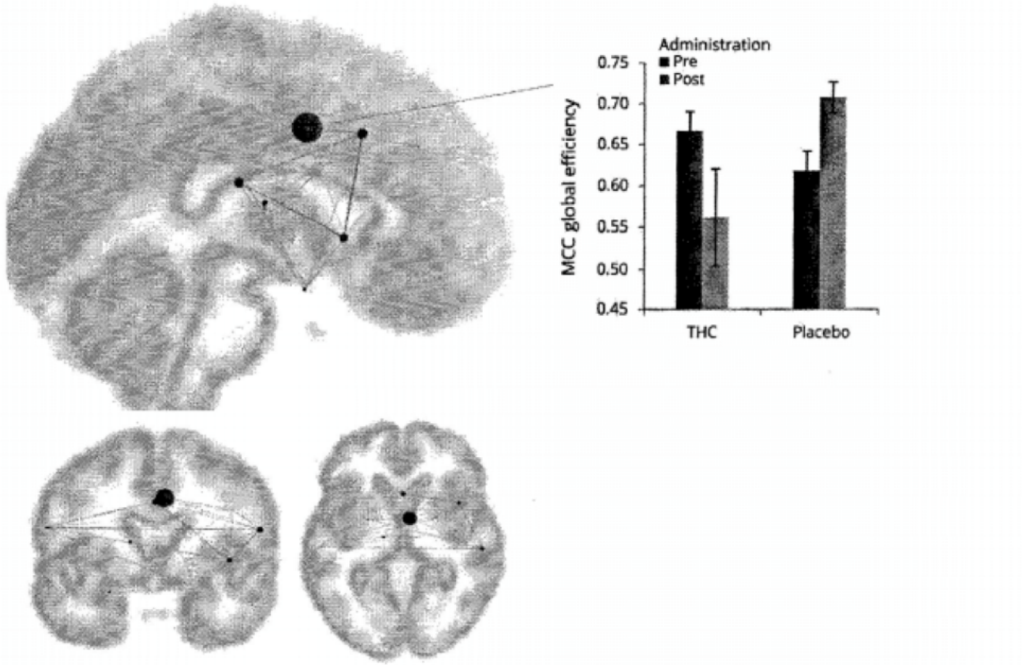
- Cannabinoids have been studied in various types of neuropathic pain including nerve injury, chemotherapy-induced, diabetic neuropathy, etc.
- CB-1 receptors have been found to be upregulated in the thalamus and the spinal cord [35] after nerve injury in rat models of NP
- **CBs have modest effect on NP in this analysis offset by side effects**



The endocannabinoid system and neuropathic pain
Rafael Maldonado*, Pain Feb 2016 V 157

Cannabis analgesia in chronic neuropathic pain is associated with altered brain connectivity.

Figure 5 Global efficiency change in middle cingulate cortex (MCC) after δ-9-tetrahydrocannabinol (THC)/placebo administration



MCC global efficiency changed significantly after THC administration (interaction effect $F_{1,14} = 3.05$; p-FDR = 0.0477). Each red circle represents a cluster within the network and its size represents the effect change. The bar graph demonstrates the interaction effect of THC and placebo. Error bars represent SEM.

- **Conclusion** … ACC and DLPFC, 2 major cognitive-emotional modulation areas, and their connections to somatosensory areas, are functionally involved in the analgesic effect of THC in chronic pain.
- …mediated through imbalance or functional disconnection between regulatory high-order affective regions and the sensorimotor cortex.
- THC analgesia is mediated through brain areas involved in supraspinal affective processing of pain

Weizman L. Neurology 2018;91:e 1285-1294

Cannabidiol (CB2) as a Potential Treatment for Anxiety Disorders. Blessing EM Neurotherapeutics 2015

- Preclinical evidence conclusively demonstrates CBD's efficacy in reducing anxiety behaviors relevant to multiple disorders
- PTSD, GAD, PD, OCD, and SAD
- with a notable lack of anxiogenic effects.

- Anxiety is a core behavioral element of **addiction** that often triggers cravings and promotes relapses.
- Neurobiology of **anxiety and addiction** are highly influenced by THC/CBD

CBD reduces anxiety in public speaking

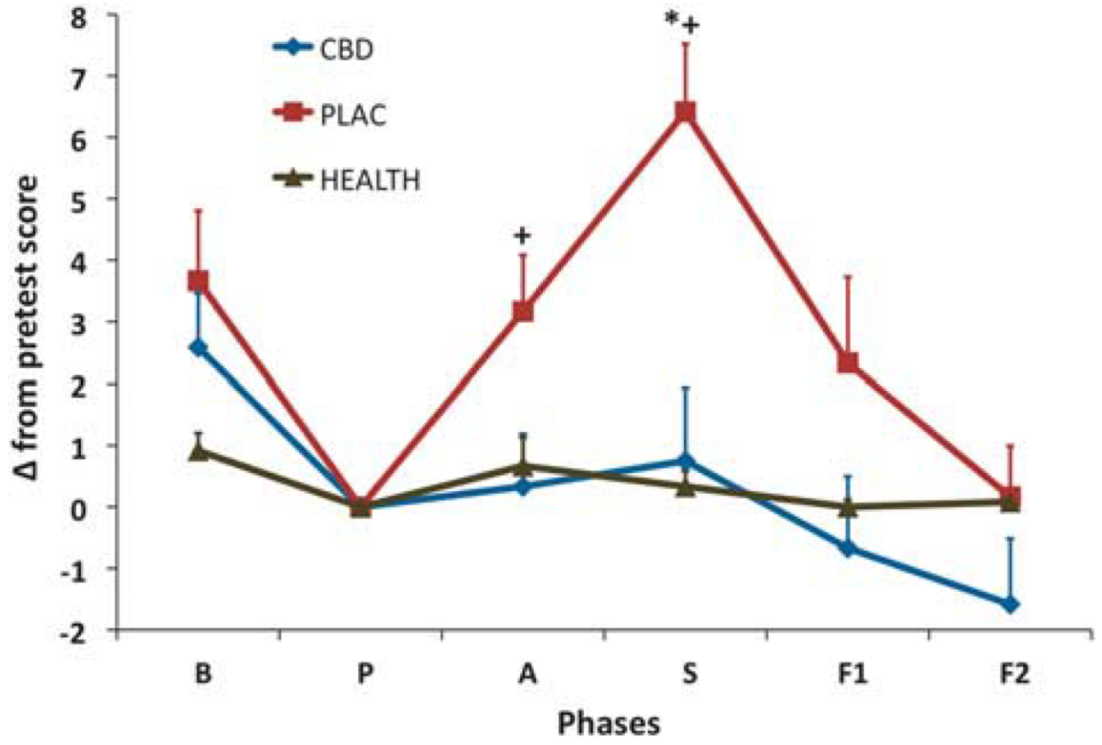


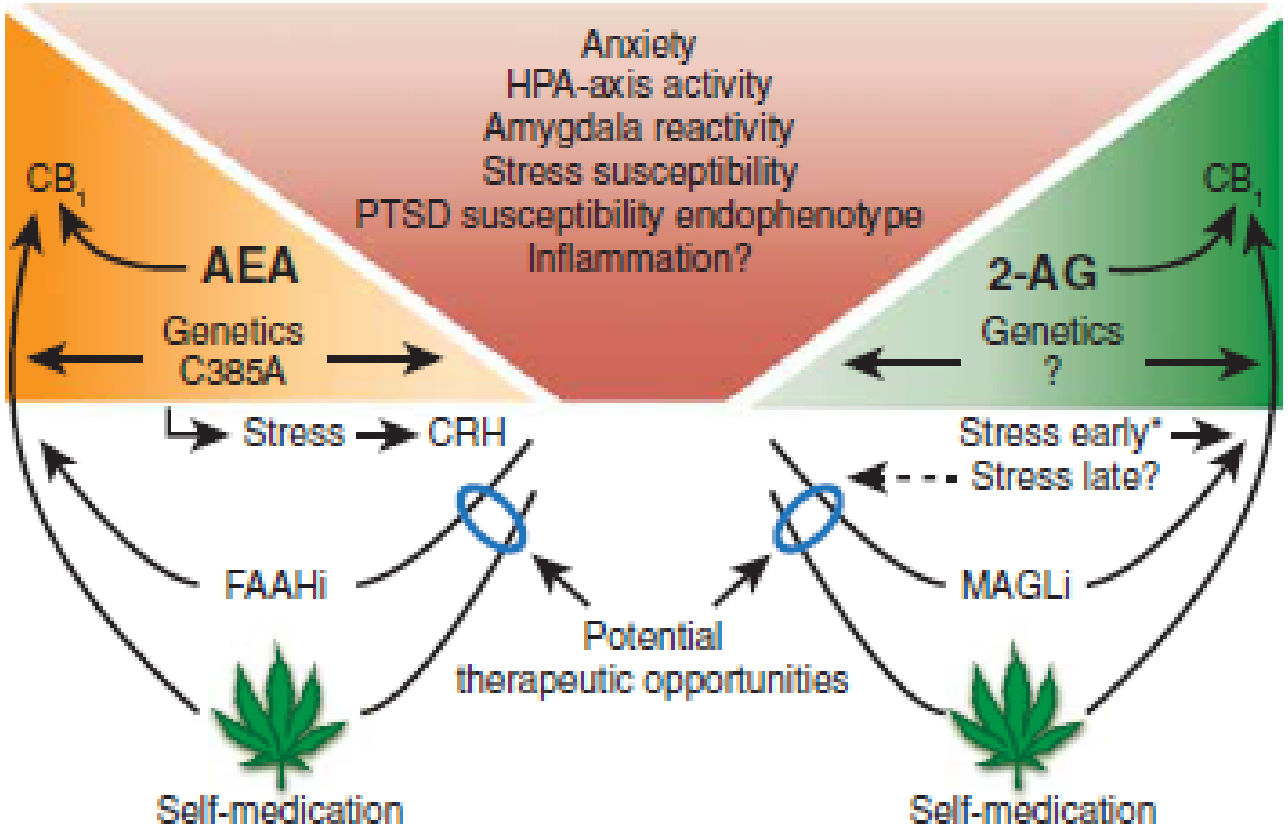
Figure 2 Changes in SSPS-N scores induced by simulated public speaking test (SPST). Other specifications are in the legend of Figure 1. *Indicates significant differences from healthy control and + from social anxiety patients who received cannabidiol

- blunted the flight-or-fight response, measured by increases in heart rate, blood pressure and skin conductivity, prompted by having to address others. These were small studies, and the amount of CBD involved, which was 600 milligrams in the social-phobia study,

Integrating Endocannabinoid (eCB) Signaling and Cannabinoids into the Biology and Treatment of Posttraumatic Stress Disorder

Matthew N Hill Neuropsychopharmacology REVIEWS (2018) 43, 80–102

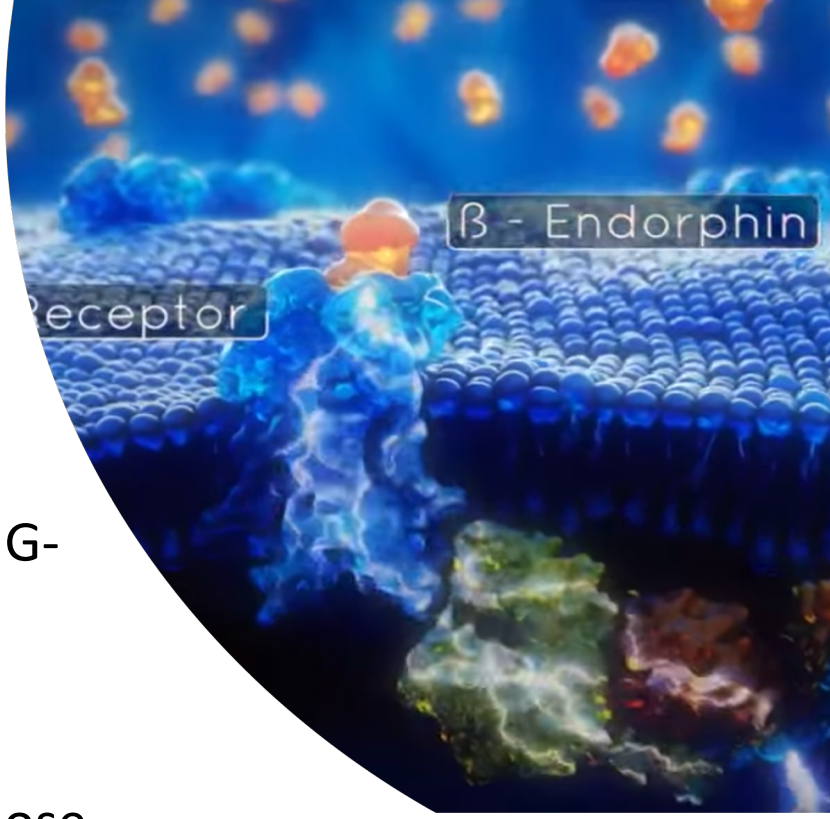
- PTSD represents a disturbance in neuronal, hormonal and inflammatory systems
- eCB system impairment could be a substrate for the etiology of PTSD
- eCBs are a target for the development of a novel class of drugs used to treat PTSD



Safety data re CBD ?

- Mechoulam and Carlini in 1978 and found no apparent toxic effects of CBD with epilepsy for a 3-month trial period.
- Safety profile of CBD demonstrated…up to 300 mg of CBD was administered daily to patients with epilepsy and healthy volunteers for up to 4.5 months (Cunha –Pharm 1980)
- CBD may induce a biphasic response in the immune system, with:
- higher doses potentially associated with inhibitory responses and
- lower doses potentially resulting in stimulatory process
- Rec: caution with CBD in immunosuppressed pts.

Synergism with opioids a) Experimental studies



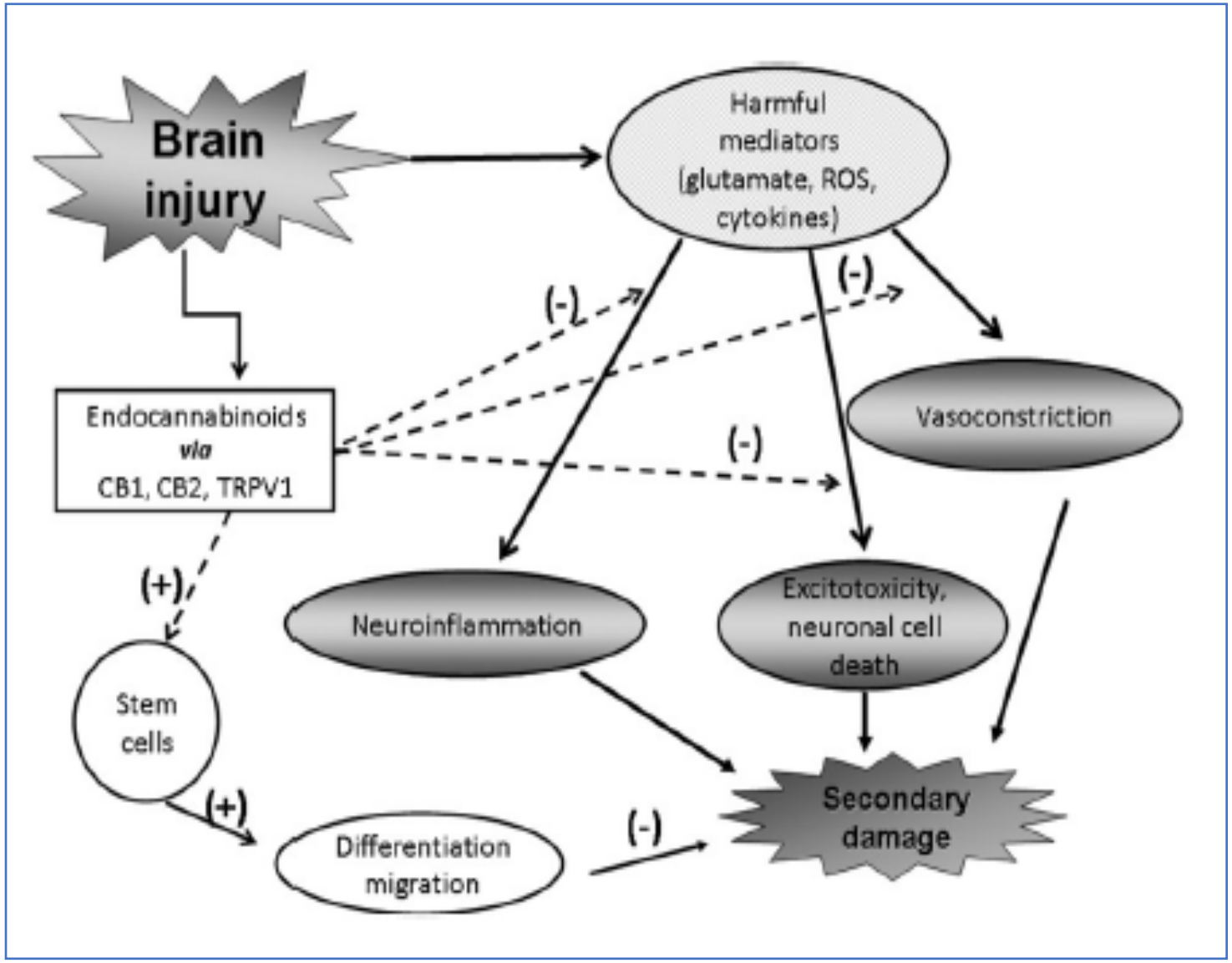
- Opioids and cannabinoids both provide antinociception through G-protein coupled mechanisms, and many studies have explored synergistic interactions
- A study using sq Morphine (MS) and intraperitoneal THC in rats showed equivalent antinociception using high dose MS or high dose THC or a low dose combination
- combination was shown to circumvent the development of tolerance when compared to either drug alone
- These data support the harmonious and even supportive use of cannabinoids in conjunction with opioids.
- Clinical studies support the experimental data on combined and/or simultaneous use of opioids and cannabinoids to treat pain.

Cannabinoids and brain injury: therapeutic implications.

Mechoulam R

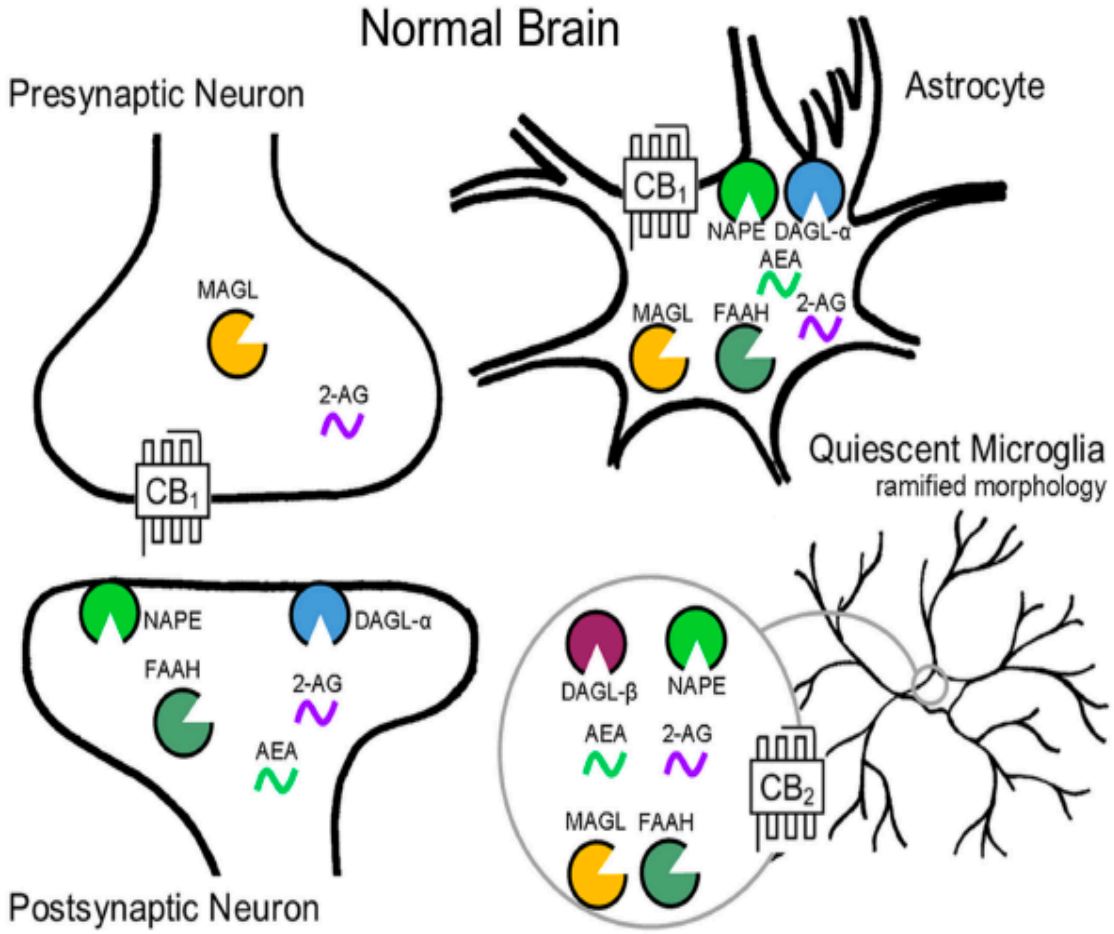
Trends in Mol Med 8:2, 2002

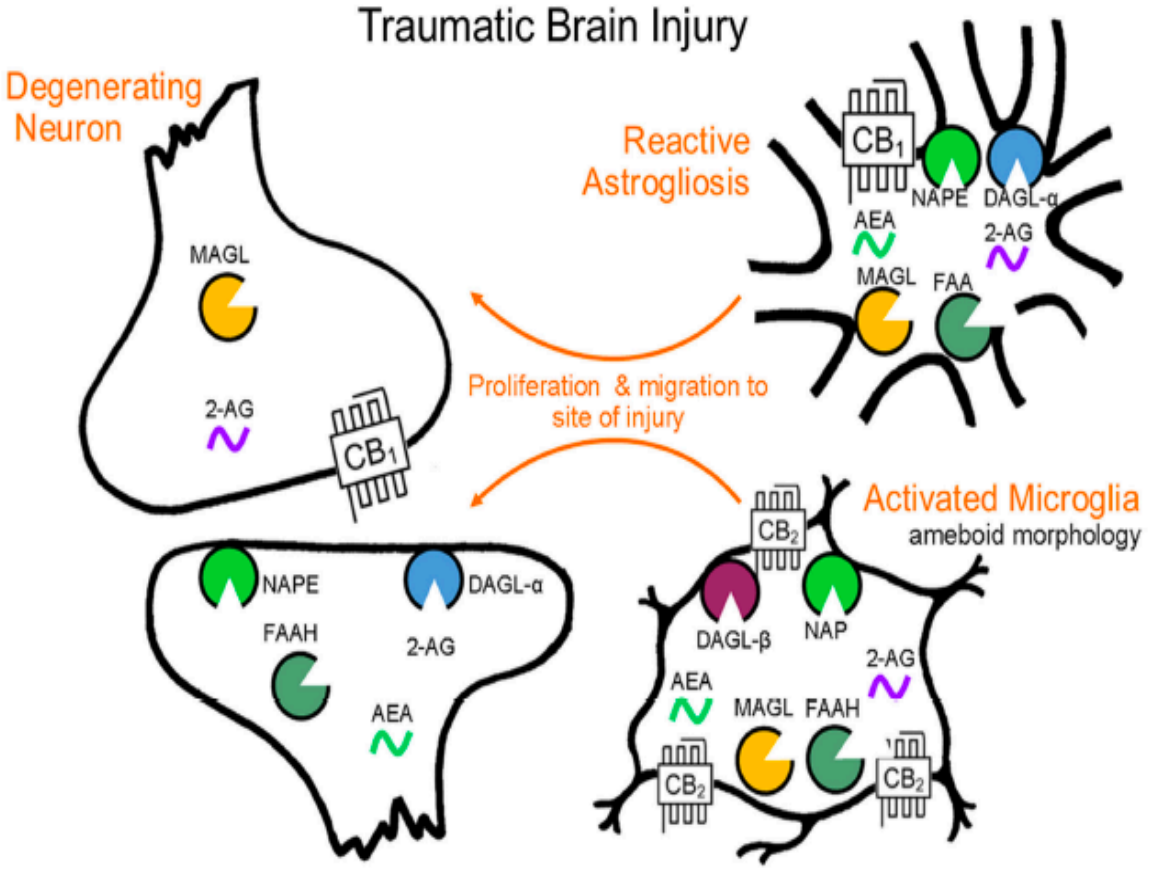
- endocannabinoids anandamide (AEA) and 2-arachidonoyl glycerol (2AG) some plant and synthetic cannabinoids, have neuroprotective effects following brain injury.
- The formation of the endocannabinoids AEA and 2AG is strongly enhanced after brain injury
- these endogenous compounds reduce the secondary damage incurred in brain injury/ischemia



Endocannabinoids: A Promising Impact for Traumatic Brain Injury.

Schurman L Frontiers in Pharmacology 2017 Vol 8





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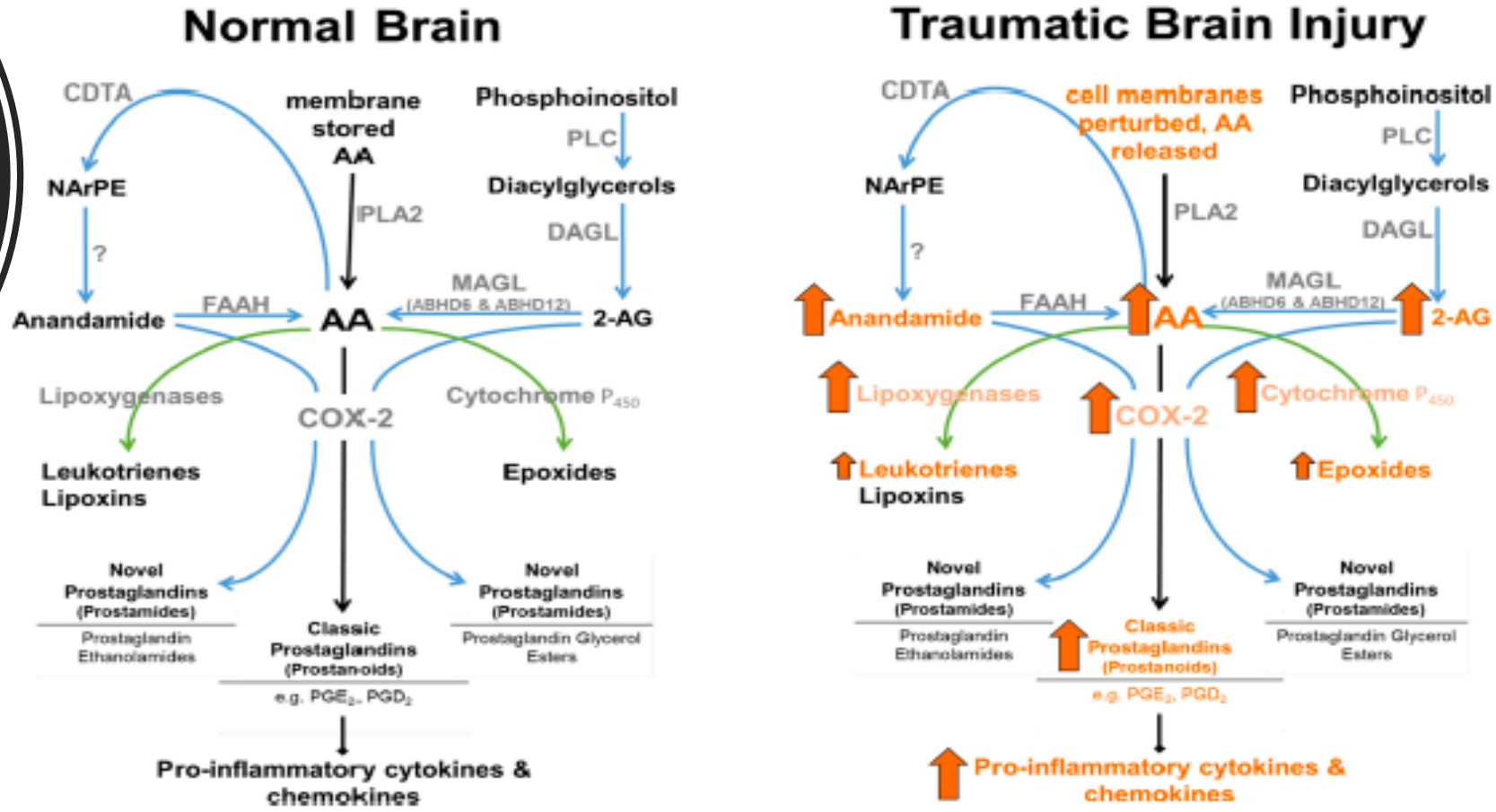


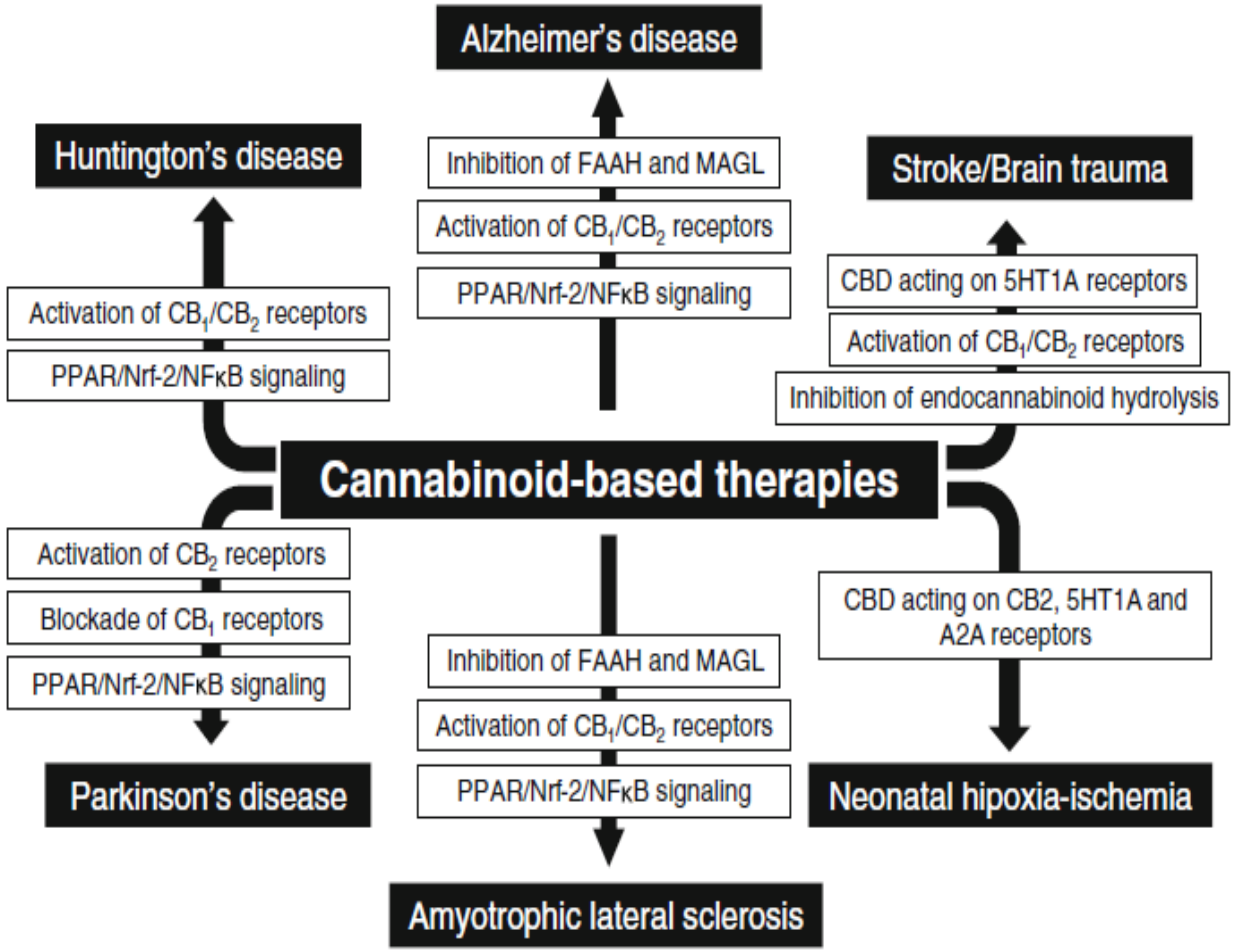
FIGURE 2 | Enzymatic regulation of anandamide and 2-AG in normal brain, and following TBI. 2-AG levels are approximately 1,000-fold higher than anandamide levels in brain. MAGL plays a rate-limited role in the production of AA in brain, lung, and liver (Nomura et al., 2008). Arrows represent known TBI-induced changes in eCBs, catabolic and downstream enzymes, and their metabolic products (arrow size has no relation to magnitude of change).

Overall, the abundant and growing pre-clinical research suggests that the eCB system possesses many promising targets for new and existing drugs that may ameliorate diverse TBI pathology.

Cannabinoids in Neurodegenerative Disorders and Stroke/Brain Trauma: From Preclinical Models to Clinical Applications

Fernández-Ruiz J, Neurotherapeutics (2015) 12:793–806

- Cannabinoid compounds may be neuroprotective in:
- Adult and neonatal ischemia,
- Brain trauma,
- Alzheimer's disease,
- Parkinson's disease,
- Huntington's chorea
- Amyotrophic Lateral Sclerosis



Cannabis Therapeutics and the Future of Neurology.

Ethan B. Russo, Frontiers in Integrative Neuroscience | October 2018 | Volume 12 | Article 51

- 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 (Russo, 2011; Russo and Marcu, 2017)+ THC
- Neuroprotection: CBD, THC
- Reduced Ab plaque formation: THC, CBD, THCA

Condition	Preparation	Level of evidence	Type of evidence
Multiple sclerosis (MS) spasticity	Nabiximols	Conclusive	Phase III RCTs, Regulatory approval
Epilepsy (Dravet and Lennox-Gastaut syndromes)	Cannabidiol (Epidiolex®)	Conclusive	Phase III RCTs, Regulatory approval
Chronic pain	THC, nabiximols	Substantial	Phase II RCTs
Schizophrenia, positive and negative symptoms	CBD	Substantial	Phase II RCTs
Sleep disturbance secondary to neurological symptoms	THC, nabilone, nabiximols	Moderate	Phase II–III RCTs
Glaucoma	THC, cannabis	Moderate	Phase II RCTs
Lower urinary tract symptoms (LUTS) in MS	Nabiximols	Moderate	Phase II RCTs
Tourette syndrome	THC, cannabis	Moderate	Phase II RCTs, observational studies
Dementia with agitation	THC, cannabis	Limited	Observational studies
Parkinson disease symptoms	THC, CBD, cannabis	Limited	Observational studies
Post-traumatic stress disorder	Cannabis	Limited	Observational studies
Social anxiety	CBD	Limited	Phase II RCT, observational studies

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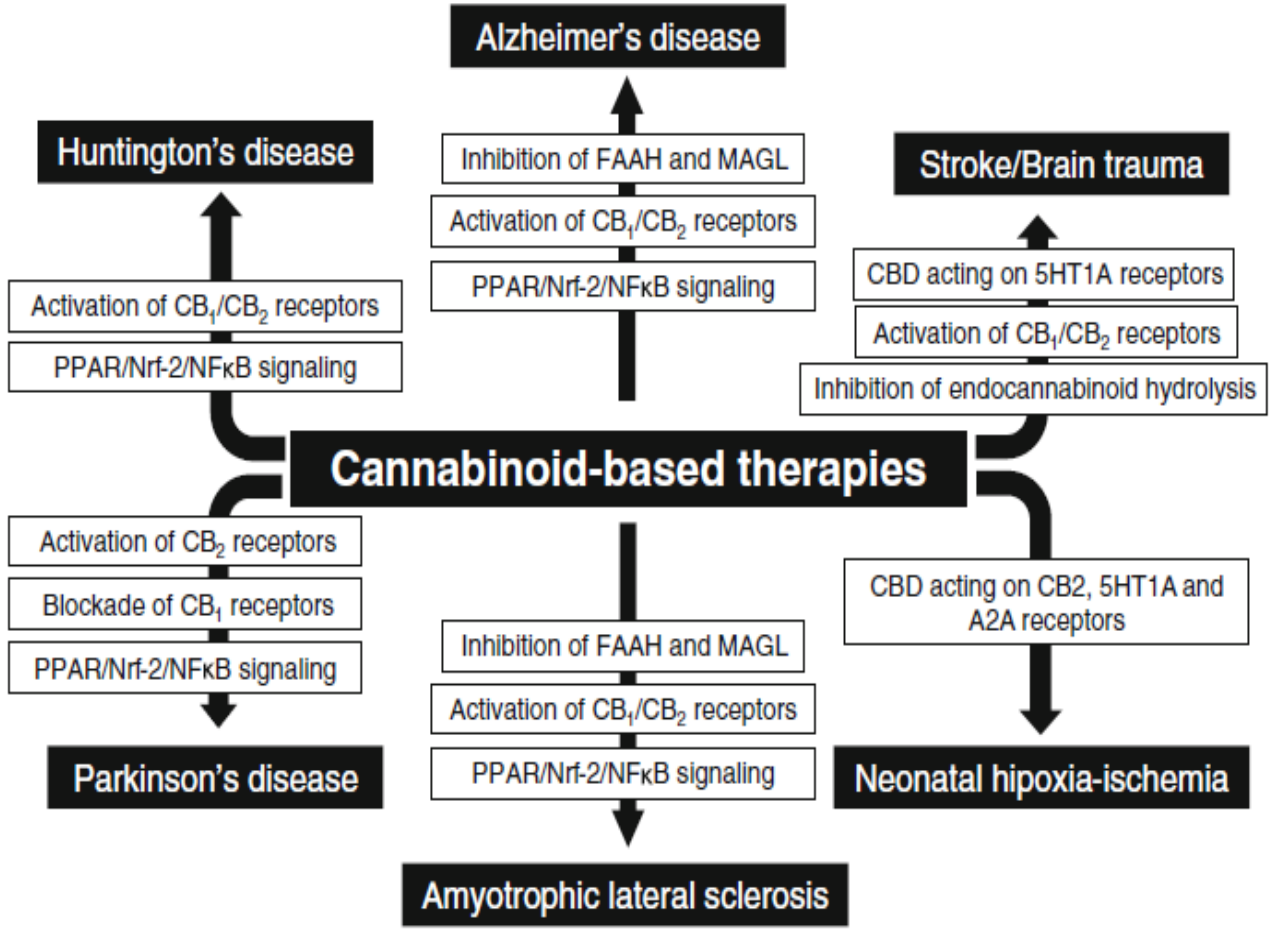


Cannabinoids in HIV/AIDS

Whiting, JAMA 2015

- Many HIV infected patients smoke marijuana for a variety of reasons, including symptom relief and reducing symptom frequency; the users report improvement:
  - in appetite (97%),
  - muscle pain (94%),
  - nausea (93%),
  - anxiety (93%),
  - nerve pain (90%), depression (86%), and paraesthesia (85%).
- However, many cannabis users (47%) also reported associated memory deterioration.
- **Conclusions:**
- **There is limited evidence that cannabis and oral cannabinoids are effective in increasing appetite and decreasing weight loss associated with HIV/AIDS.**

Cannabinoids In Multiple sclerosis (Ms)

National Acad of Sci. 2017
Koppel, Systematic review: Efficacy and safety of medical marijuana in selected neurologic disorders. *Neurology* 2014, 82(17):1556–1563
Whiting, JAMA 2015

- 11 studies that included patients with MS and 3 that included patients with paraplegia caused by spinal cord injury.
- Patients with multiple sclerosis have diverse types of pain:
  - dysesthesias, back pain, muscle pain, etc; and each type of pain needs to be managed differently
- Cannabinoids have a role in relieving pain, spasticity, tremor, nocturia and improving general well being in MS
  - nabiximols and orally administered THC are “probably effective” for reducing patient-reported spasticity scores
  - oral cannabis extract is “established as effective for reducing patient-reported scores” for spasticity

(**Negative**) Effect of cannabis use in people with **chronic non-cancer pain** prescribed opioids: findings from a 4-year prospective cohort study

Campbell, LANCET VOL 3, ISSUE 7, PE341-E350, JULY 01, 2018

At 4-year follow-up (2012-2016, n=1514) compared with people with no cannabis use:

- cannabis users had a greater pain severity score
- greater pain interference score
- lower pain self-efficacy scores
- greater generalised anxiety disorder severity scores

- “We found no evidence of a temporal relationship between cannabis use and pain severity or pain interference, and no evidence that cannabis use reduced prescribed opioid use or increased rates of opioid discontinuation”.

Adverse Health Effects of Marijuana Use

Nora D. Volkow NEJM 2014 June 5

Table 1. Adverse Effects of Short-Term Use and Long-Term or Heavy Use of Marijuana.

Effects of short-term use
Impaired short-term memory, making it difficult to learn and to retain information
Impaired motor coordination, interfering with driving skills and increasing the risk of injuries
Altered judgment, increasing the risk of sexual behaviors that facilitate the transmission of sexually transmitted diseases
In high doses, paranoia and psychosis
Effects of long-term or heavy use
Addiction (in about 9% of users overall, 17% of those who begin use in adolescence, and 25 to 50% of those who are daily users)*
Altered brain development*
Poor educational outcome, with increased likelihood of dropping out of school*
Cognitive impairment, with lower IQ among those who were frequent users during adolescence*
Diminished life satisfaction and achievement (determined on the basis of subjective and objective measures as compared with such ratings in the general population)*
Symptoms of chronic bronchitis
Increased risk of chronic psychosis disorders (including schizophrenia) in persons with a predisposition to such disorders

* The effect is strongly associated with initial marijuana use early in adolescence.

Cardiovascular, Cerebrovascular, and Peripheral Vascular effects of Smoked Marijuana

- Thomas and colleagues (2014- Am J Card) identified an association between marijuana inhalation and higher rates of acute myocardial infarction and increased cardiovascular mortality.
- In addition, they described published case reports that identify a safety signal between cannabis use and stroke.
- Of considerable concern are data indicating diminution of the volumes of the hippocampus, amygdala, and cerebellum in adult and adolescent heavy users compared with healthy controls
  - Matochik D&A Depend 2005, Yucel J Psych NeuroSci 2010

February 1, 2019

Should Physicians Recommend Replacing Opioids With Cannabis?

Keith Humphreys, PhD[1,2]; Richard Saitz, MD, MPH[3,4,5]

JAMA. 2019;321(7):639-640. doi:10.1001/jama.2019.0077

- Substituting cannabis for opioids is not the same as initiating opioid therapy.
- There are no randomized clinical trials of substituting cannabis for opioids in patients taking or misusing opioids for treatment of pain, or in patients with opioid addiction treated with methadone or buprenorphine.
- 4-year cohort study of 1514 patients with chronic pain who had been prescribed opioids. Cannabis use was associated with more subsequent pain, less self-efficacy for managing pain, and no reductions in prescribed opioid use.

frontiers in Psychiatry

Front Psychiatry. 2019; 10: 63.
Published online 2019 Feb 19. doi: 10.3389/fpsyt.2019.00063

PMCID: PMC6390812
PMID: 30837904

The Endocannabinoid System and Cannabidiol's Promise for the Treatment of Substance Use Disorder

Yann Chye,[1,*] Erynn Christensen,[1] Nadia Solowij,[2,3] and Murat Yücel[1]

▸ Author information ▸ Article notes ▸ Copyright and License information Disclaimer

Abstract

Go to:

Substance use disorder is characterized by repeated use of a substance, leading to clinically significant distress, making it a serious public health concern. The endocannabinoid system plays an important role in common neurobiological processes underlying substance use disorder, in particular by mediating the rewarding and motivational effects of substances and substance-related cues. In turn, a number of cannabinoid drugs (e.g., rimonabant, nabiximols) have been suggested for potential pharmacological

Conclusions re: MMJ and cognitive function

- Controversial in most reviews.
- + changes were accompanied by:
- Improved task performance
- Positive changes in ratings of clinical state,
  - Impulsivity,
  - Sleep
  - Quality of life.
- Further, patients reported notable decreases in conventional medications, including opioids.
- Patients utilizing MMJ appear to use products with different cannabinoid profiles (i.e., high CBD) relative to recreational users,
- Observed changes may also be related to secondary or more indirect effects, including:
  - the reduction of clinical symptoms
  - improved sleep,
  - decreased use of conventional medications

An Evidence Based Review of Acute and Long-Term Effects of Cannabis Use on Executive Cognitive Functions.

Crean R., J Addict Med. 2011 March 1; 5(1): 1–8.

TABLE 2

A Summary of Research Findings on the Effects of Cannabis on Executive Functions

Executive Function Measured	Acute Effects	Residual Effects	Long-Term Effects
Attention/Concentration	Impaired (light users) Normal (heavy users)	Mixed findings	Largely normal
Decision Making & Risk Taking	Mixed findings	Impaired	Impaired
Inhibition/Impulsivity	Impaired	Mixed findings	Mixed findings
Working Memory	Impaired	Normal	Normal
Verbal Fluency	Normal	Mixed findings	Mixed findings

Note: Acute Effects denotes 0–6 hours after last cannabis use; Residual Effects denotes 7 hours to 20 days after last cannabis use; Long-Term Effects denotes 3 weeks or longer after last cannabis use.

Effect of Marijuana Use on Outcomes in Traumatic Brain Injury

BRIAN M. NGUYEN, M.D. THE AMERICAN SURGEON October 2014,vol 80

- 446/538 TBI pts screened for illicit drugs (83%)
- 18.4% tested positive for THC
- THC+/THC- 75% m>f, mean age 32 vs 54 yo, more likely ETOH +
- Abbreviated Injury Score (Head AIS), and Injury SeverityScore (ISS) no sig difference
- +THC screen was associated with a decrease in mortality in adult pts sustaining TBI

TABLE 3. *Comparison of THC(+) versus THC(–) in Patients with TBI (n = 446)*

Variable	THC(+) (82 [18.4%])	THC(–) (364 [81.6%])	*P* Value
Gender (male)	75 (91.5%)	274 (75.3%)	0.001
Mean age (years)	32.3 (± 13.8)	53.2 (± 21.3)	<0.001
Ethnicity			
Hispanic	26 (31.7%)	113 (31.0%)	<0.001
White	22 (26.8%)	127 (34.9%)	
Black	32 (39.0%)	66 (18.1%)	
Asian/other	2 (2.4%)	58 (15.9%)	
Mechanism of injury			
Blunt assault	9 (11.0%)	40 (11.0%)	<0.001
Fall	28 (34.1%)	191 (52.5%)	
Motorcycle collision	7 (8.5%)	10 (2.7%)	
Motor vehicle collision	15 (18.3%)	45 (12.4%)	
Pedestrian/bicyclist *vs* MVC	13 (15.9%)	68 (18.7%)	
Gunshot wound	10 (12.2%)	10 (2.7%)	
ETOH (> 0.08%)	44 (53.7%)	102 (28.0%)	<0.001
Mean ISS	22.3 (± 11.6)	20.4 (± 10.7)	0.160
AIS Head ≥ 4	48 (58.5%)	190 (52.2%)	0.299
Craniotomy	7 (8.5%)	44 (12.1%)	0.361
Disposition			
Home without services	53 (64.6%)	187 (51.4%)	0.024
Acute care facility	5 (6.1%)	36 (9.9%)	
Rehabilitation center	8 (9.8%)	34 (9.3%)	
Skilled nursing facility	3 (3.7%)	29 (8.0%)	
Disability			
Temporary handicap	69 (84.1%)	259 (71.2%)	0.042
Permanent handicap	9 (11.0%)	45 (12.4%)	
Preinjury capacity	2 (2.4%)	18 (4.9%)	
Mortality	2 (2.4%)	42 (11.5%)	0.012

THC, tetrahydrocannabinol; TBI, traumatic brain injury; MVC, motor vehicle crash; ETOH, alcohol; ISS, Injury Severity Score; AIS, Abbreviated Injury Score.

Practical considerations in medical cannabis administration and dosing: *MacCallum 2018*

Cannabis sativa

- Dose and tolerance depend on prior experience “start low go slow”
- For medical pts. use CBD predominant strains –low THC
- 2.5-5mg THC is a decent starting threshold
- 10mg THC –strong effect for naïve pts
- Doses > 20-30mg/d risk psychoactive effect and AEs
- CBD + terpinoids may extend value
- Psychoactivity ≠ Efficacy
- Correct dose = lowest dose w efficacy

Comprehensive Interventions for Reducing Cannabis Use

Tirado-Muñoz; Curr OpinPsychiatry. 2018;31(4):315-323.

- Interventions: Behaviour therapy, Brief advice, Brief intervention, Cognitive-behavioural therapy, Comprehensive, Computerized, Contingency management, Drug counselling and/or education, Education, e-health, Intervention, Mindfulness-based meditation, Motivational enhancement therapy, Motivational interviewing,
- Multidimensional Family Therapy, Network therapy, Online, Pharmacological treatment, Pharmacotherapies, Prevention, Problem-solving training, Program evaluation, Psychoeducation, Real-time intervention, Rehabilitation, Relapse prevention, Social support, Telephone, Treatment, Web-based therapy

Medical Marijuana Education Lagging Behind Clinical Needs *Drug Alcohol Depend* 2017;180:151-155

- 9% of medical schools teach students about medical marijuana, new graduates are ill-equipped to prescribe and field questions on the topic
- 85% of residents and fellows said they had not received education on medical marijuana
- 31% of residents and fellows whose home states had legalized marijuana said they had received education on the topic, compared with 8.5% of those in states without legalized medical marijuana,

Chronic Pain/TBI Neuromatrix (Melzac):

Bio-psychosocial Systems Perspective

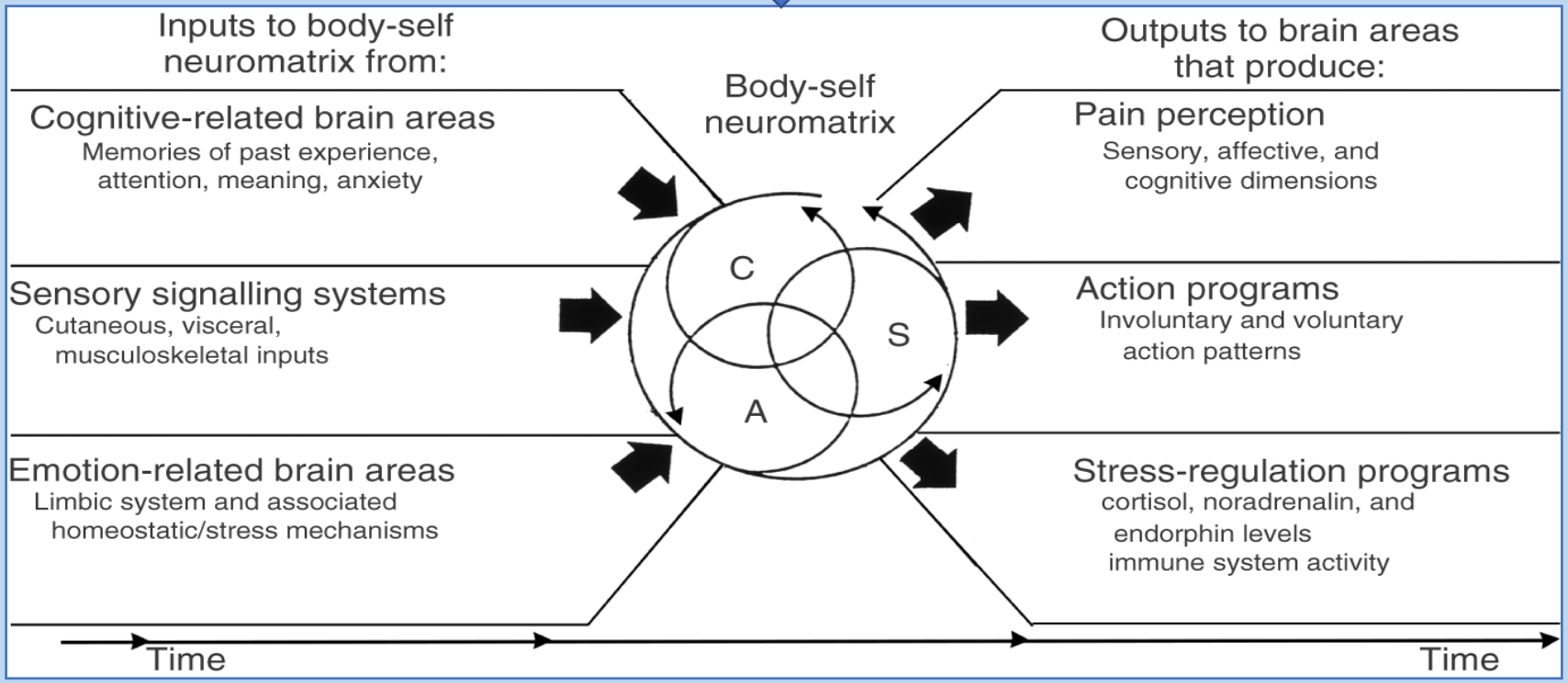
Opioids

Endorphin Systems

Interaction=Yes
Interchangeable =No

Cannabinoids

Endocannabinoid Systems



Can Cannabinoids play a role in TBI and mitigating the opioid crisis?

Current cannabinoid pharmacology and medical use is in its infancy re:

- dosing per condition,
- delivery systems,
- strain(s),
- reproducibility of botanicals,
- mastering pharmacokinetics,
- quantitative analysis of effects,
- objective changes in function,
- Adverse effect (s) / mitigation of AEs
- synergism with opioids/adjunctive agents,
- political hurdles,
- cultural expectations and acceptance.