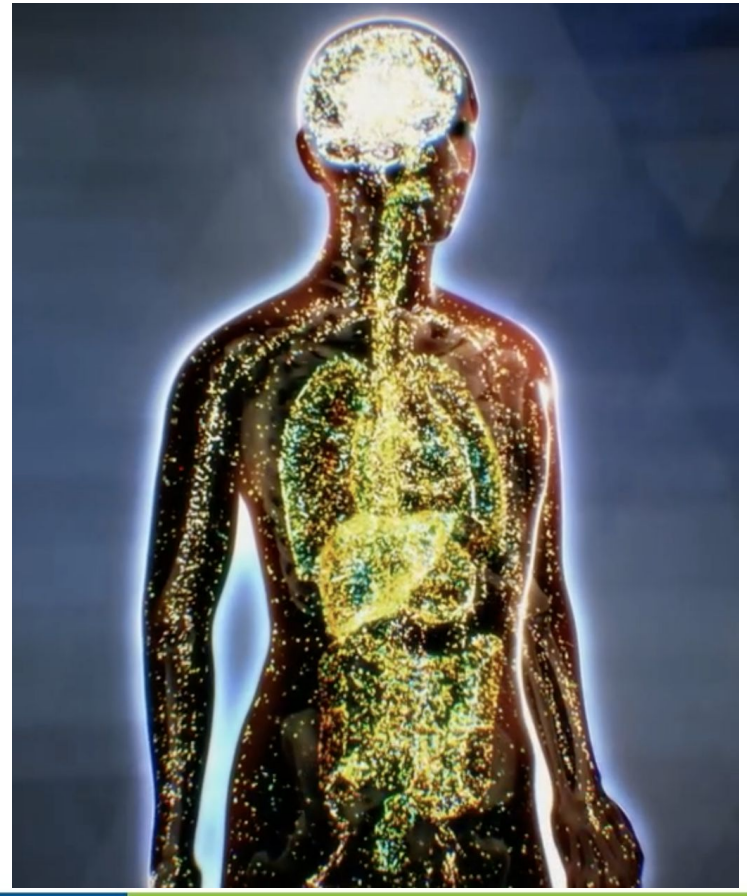
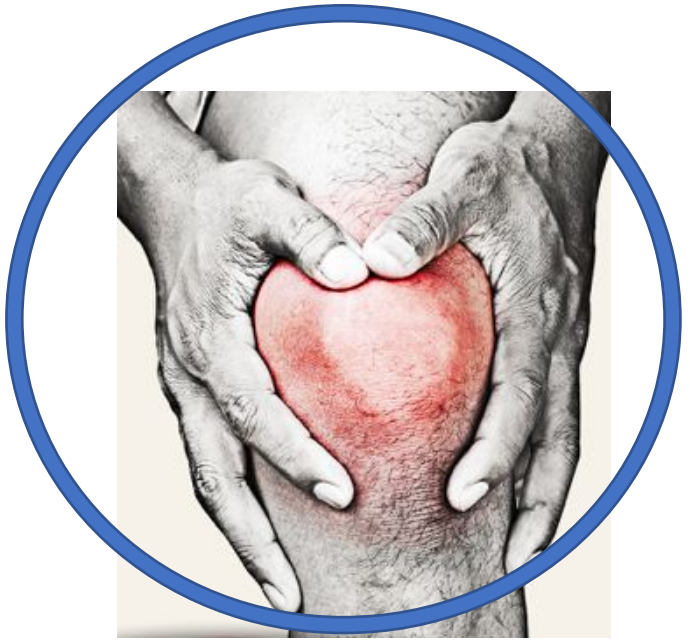
The Endocannabinoid System in Pain & Inflammation: A Primer for Surgeons

Thomas Meade, MD-*Chief of Knee Arthroplasty*
Coordinated Health/Lehigh Valley Network, Allentown Pennsylvania.



- Why am I here?
- What Is the Endocannabinoid System?
- Why do we need to know about it?
- How can it help my patients?

Cannabis Is Coming!
Does It Have Any Role In Pain Control For The Total Knee Patient

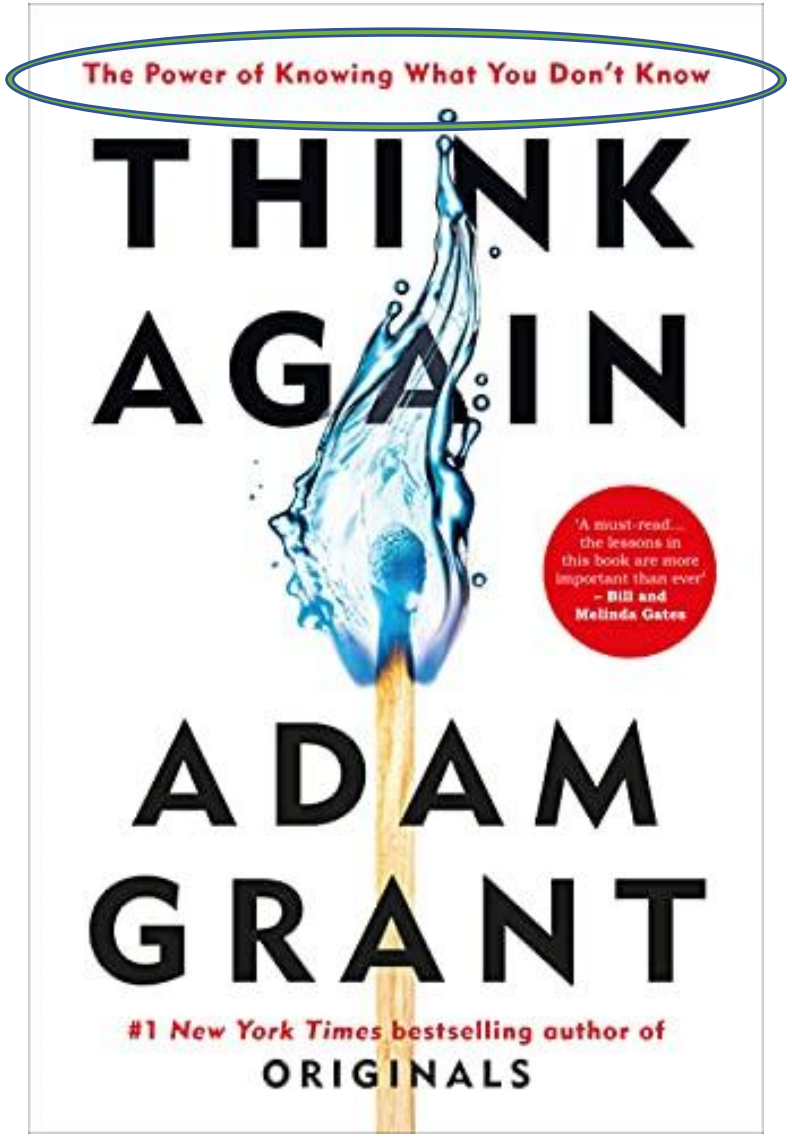


I Have Tried It & It Seems To Help-
Tom Meade MD

You Really Are Nuts!
Let's Stick To The True & Tried Pain Management Systems---Michael A. Kelly, MD

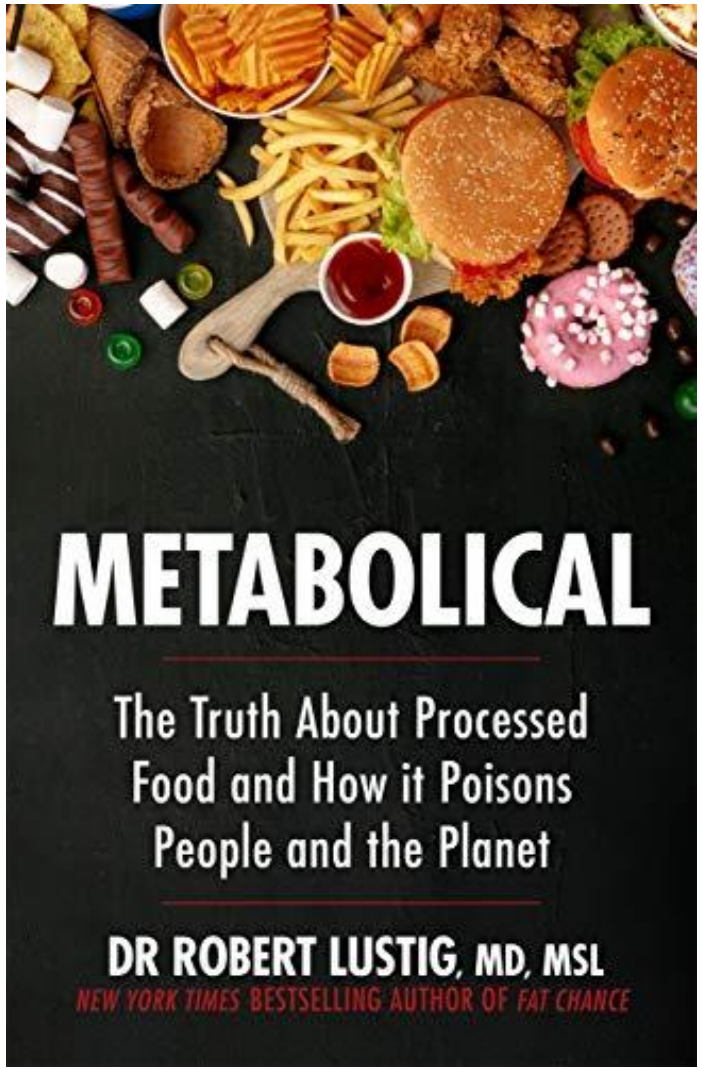
Tried and True Pain Management

- Narcotics
  - Opioid Crisis- 700,000 deaths
  - 60% post op side effects
  - Excess Rx: 90 pills/TKA
  - Ortho residents –rarely trained
- NSAIDS
  - >20,000 ANNUAL DEATHS
  - CV,GI, RENAL SE
- ACETAMINOPHEN
  - Main cause acute liver failure in US & UK



- Part of the problem is **cognitive laziness**.
- We often prefer the **ease of hanging on to old views** over the difficulty of grappling with new ones.
- It requires us
  - to **admit that the facts may have changed**,
  - What was **once right may now be wrong**.

- ……. knowing **when it's time to abandon some of your most treasured tools**—and most cherished parts of your identity.



- Last 50 yrs medicine has taught us
  - that we **physicians have a whole lot to unlearn**

- —**except nutrition,** … can't **unlearn** what you were never taught

- Same is true **for endocannabinoid System**
  - Discovered in early 90's's
  - Still taught in few Med Schools-13%

INFORMATION ON CANNABIS SAFETY

- **No** known case of **lethal overdose (**HHS)
- Marijuana in its natural form is one of **the safest therapeutically active substances** known to man.(DEA Chief Law Judge)
- **LD50- none known**, had to be estimated on basis of animals
- Of lethal to effective dose at 40,000 to 1 vs 4-10:1 ETOH
- BUT-Powerful chemical with variety of effects

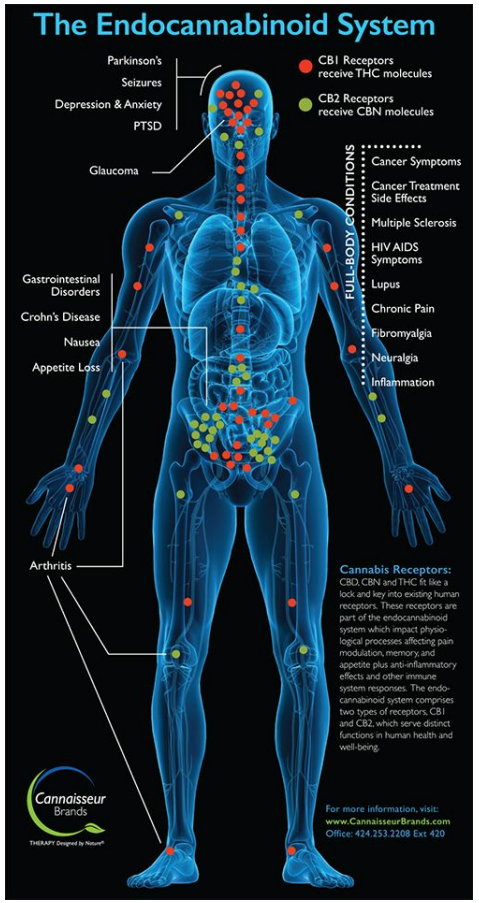
University of Kentucky fraternity member dies of 'presumed alcohol toxicity'

The University of Kentucky has suspended all activities at FarmHouse Fraternity following...

Cleveland.com
2 days ago

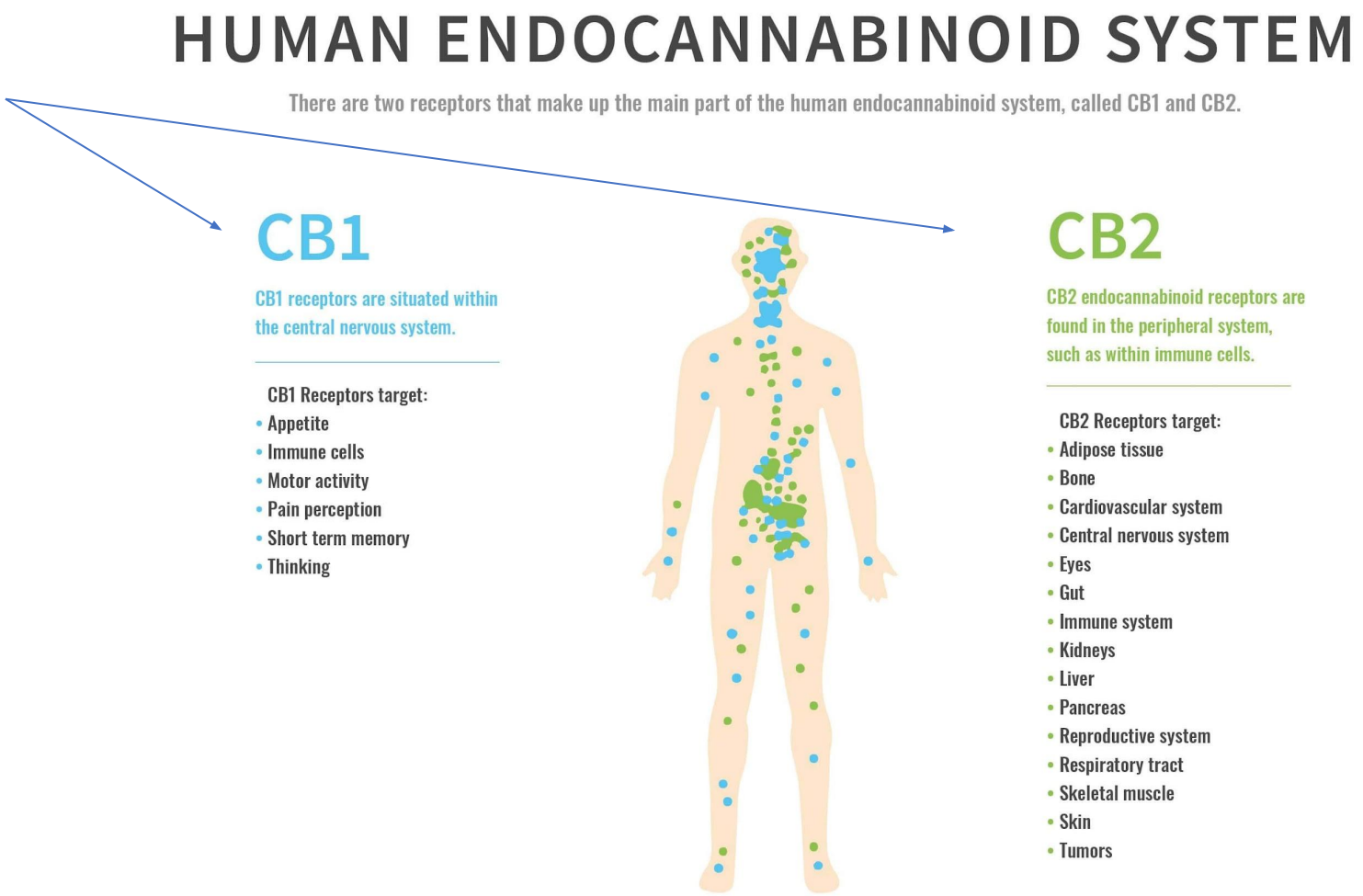
What Is The ECS?

- **Simple Terms**: Ubiquitous system of neurotransmitters & receptors throughout the CNS and peripheral NS- infancy of understanding
- **600 M yrs old**
- Receptors in brain & every major organ (except brainstem)
- Our **most important physiologic system**- for cellular homeostasis
  - "supercomputer that regulates homeostasis in body"
- Regulate temperature, sleep, cognition, pain, inflammation, nausea, tissue healing, appetite, mood, bone remodeling, nerve function, learning , memory, fertility…….



Simple: 3 Major Components

1. ECS- Receptors CB1 CB2
2. Endogenous Cannabinoids
    1. Discovered 90's
        1. Anandamide (AEA)-1992
        2. 2-AG- 1995
3. Phytocannabinoids- CBD, THC



Medical ,Political & Legal History

- 5000's yr's humans cultivated cannabis: fiber, seeds & medicinal properties
- Used for **Pain Relief** Chinese medicine – 581 AD
- Dozens countries used it in Dark & Middle ages
- 1621- Jamestown Colonists were ordered to grow 100 hemp plants by King James 1st-fiber exports (3rd cash crop tobacco, lumber)
- 1842 American pharmacies selling medical preparations cannabis
  - analgesic, sedative, anti-inflammatory, antispasmodic and anticonvulsant effects.
- Cannabis plant on 10 dollar bill as late 1914, Printed on Hemp

Beginning of Marijuana Prohibition

- 1910 Prohibition sentiment- many states outlawed
- 1937- Marijuanna Tax Act prohibited cannabis use –Hemp included so THC, CBD illegal
  - Corporate hit Job
    - John D Rockefeller Jr
      - Competed w Petroleum & Opium [Opium Cartel, Bayer (heroin)]
    - Hearst Paper Empire
    - DuPont- Nylon
  - AMA protested - used for >100yrs of 'substantial medical value'

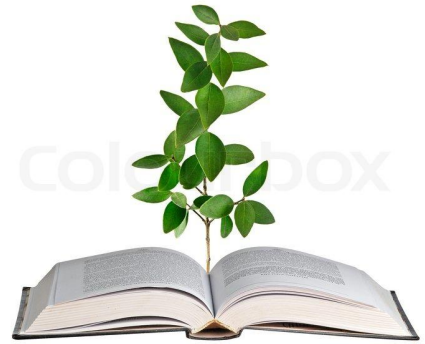
- 1970 Controlled Substance Act classified Cannabis & Hemp Schedule 1 drug
  - (no medical value) Heroin, LSD, Meth, Crack -highly addictive
- 1996-California- Medical Marijuanna legal (now 36 states)
- 2014 –Colorado Recreational use (now 21)
- 2018-Hemp Farm Bill –Legalized Hemp (THC <0.3%)
  - DEA oversight USDA & States
  - BUT CBD still remains a Schedule 1 substance and 'illegal' under federal law
  - Handcuffs loans, some research- still gray area

Under U.S. federal law, marijuana is defined as **having no medical use.**
So it might come as a surprise to hear that the **government owns one of the only patents on marijuana as a medicine.**

The patent (**6630507)** is titled "Cannabinoids as antioxidants and neuroprotectants" and was awarded to the Department of Health and Human Services (HHS) in October 2003.

Science History
Israel Ground Zero
Med-Marijuanna Movement

- 1964- Dr Raphael Mechoulam- Father of Cannabinoid Medicine
  - Morphine, Cocaine isolated 150 yr ago
  - **Discovered THC-** active ingredient cannabis not known!!
  - 25 yrs thought was no receptor
  - No concept of endocanabinoids for 30 yrs



- 1988 Dr Howlett--Brain receptor discovered responded to cannabis-**CB1**
  - thus named 'cannabinoid' receptors- turn out most abundant neurotransmitter in brain
  - -Thus must be a natural 'THC'- went hunting for endogenous compound
- 1992 'Anandamide'-natural cannabinoid (means- Bliss, Delight, Supreme Joy) a neurotransmitter,
  - 1993 2nd ECS receptor discovered **CB2**
- 1995 another 2-AG discovered a few yrs later-1995
  - NIH: **ECS involved in essentially every human disease**

Basic Science Facts- Endocannabinoid System

- Humans and animals synthesize endocannabinoids- same receptors as exogenous plant bases CBD/THC
- Crucial for bioregulation and unique/ubiqutous cell signaling: PAIN-Acute, Chronic Inflammatory, Neuropathic
- Anti- inflammatory effects of most species –mediated thru CB2 receptors
- Derived from FFA in cell membranes-similar to Omega 3/6
- May help normalize sleep, improve appetite (common PO TJA SE)
- **U Dept HHS-** owns patent (2003) on use CBD as Anti-Ox & Neuroprotectants
- Significant ‘cross-talk’ betwn opioid & EC receptors- dec dose response curve

More Basic Science Facts: Endocannabinoid System

Ibuprofen, Ketorolac, Acetaminophen,Cox-2 –all have a cannabinoid MOA for analgesia

Surgical site of an injury

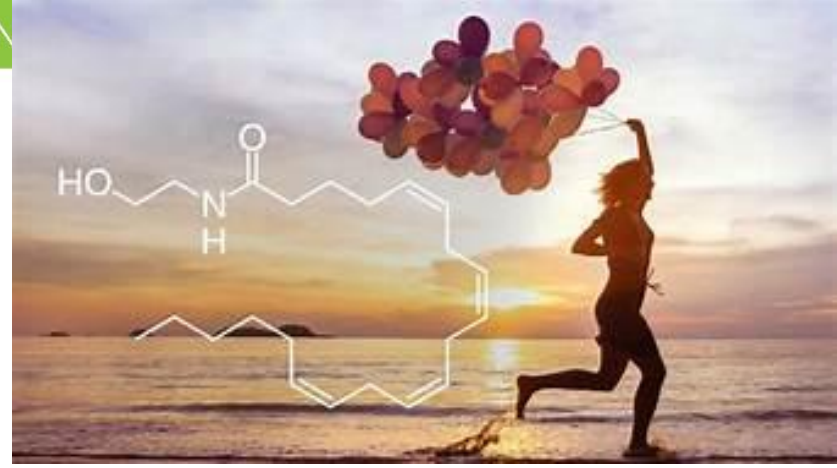
decreasing the release of pro-inflammatory activators

stabilizing the nerve cell firing

.

Endogenous Cannabinoids
Anandamide

(AEA) (N-arachidonoyl ethanolamine)



- Anandamide (Sanskrit - joy, bliss delight)
  - Fatty acid Neurotransmitter,
    - partial agonists to CB1 (CB2 little)
  - Derived from cell membrane-
    - Omega-6 PUFA derivative (Arachidonic acid, phospholipase A2)
    - Synthesized on demand (sec to mins)
  - Degraded by FAAH enzyme (inhibitors –therapeutic research)
  - CB1 –"CB1 is the **psychoactive, neuro-modulatory, and analgesic receptor**"
    - CNS: Eating, **sleep & pain relief**, pleasure, memory, concentration, movement, coordination, sensory and time perception
    - Responsible for 'Runners high'
  - CB2 –an **anti-inflammatory immunomodulatory** receptor

Acetaminophen

- Metabolites (basically inhibit FAAH enzyme)
- Weak CB1 agonist (Central CNS)
- Inhibits Anandamide reuptake---> analgesic effect
- Black Pepper- inhibits anandamide reuptake- analgesic

Case Report--2019

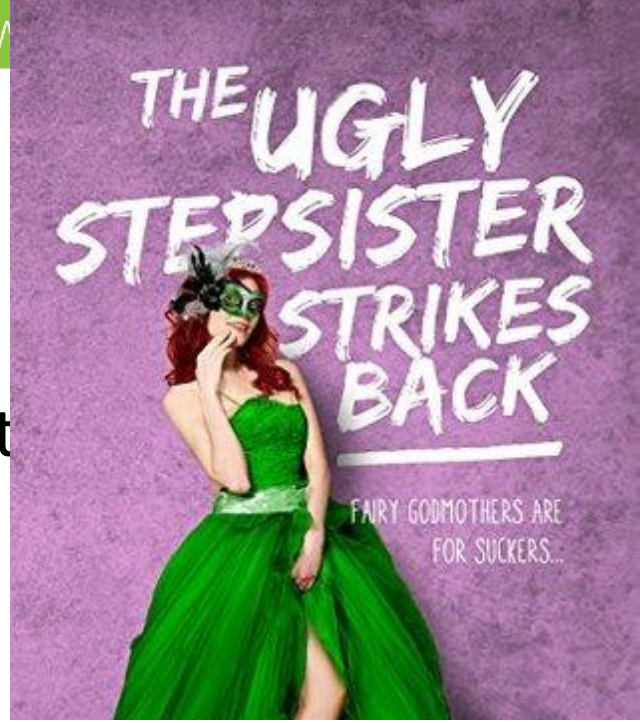
- Scottish woman with a rare genetic mutation in her FAAH gene
  - elevated anandamide levels was reported to be
  - immune to anxiety,
  - unable to experience fear
  - insensitive to pain.
  - The frequent burns and cuts she suffered due to her hypoalgesia healed more rapidly than was expected.

^ Murphy, Heather (28 March 2019). "At 71, She's Never Felt Pain or Anxiety. Now Scientists Know Why". *The New York Times*. Retrieved 29 March 2019.

2-AG

(2-arachidonoyl glycerol)-1995

- Not as sexy as THC & Anandamide- may be more import
- Most prevalent EDC in brain (1000X)
- Full CB1 CB2 agonist
- Critical Role: appetite, mood, anxiety
- Outsized Role: inflammatory & neuropathic pain

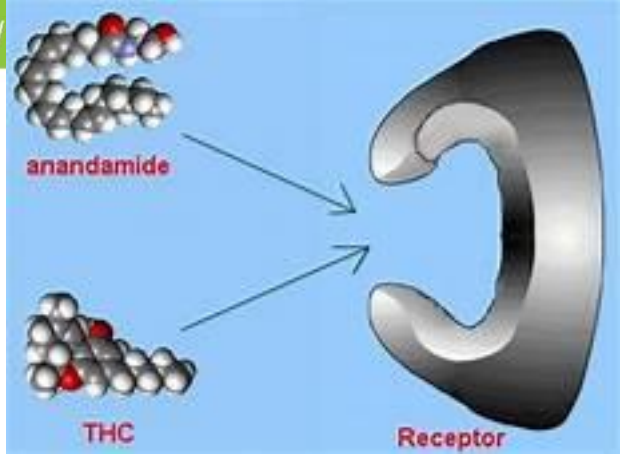


Cannabis Components

- Cannabinoids (~100) THC, CBD, CBG, CBN etc
  - Only THC psychoactive CB1 no other bind to CB1
  - CBD –anti inflammatory, counteracts THC
  - CBD –Has no side effects!!, completely non-toxic metabolically-NIH research
  - CBD & THC has anti epileptic properties- but CBD can be given in hi doses- no SE

- Terpenes-aromatic molecules (100) Scent, flavor, relaxation, stress relief, pain, anti-oxidant, anti-bacterial, anti-fungal, anti-cancer, (Pepper, tea, cloves, spices)
- Combination : Entourage effect

Phytocannabinoids

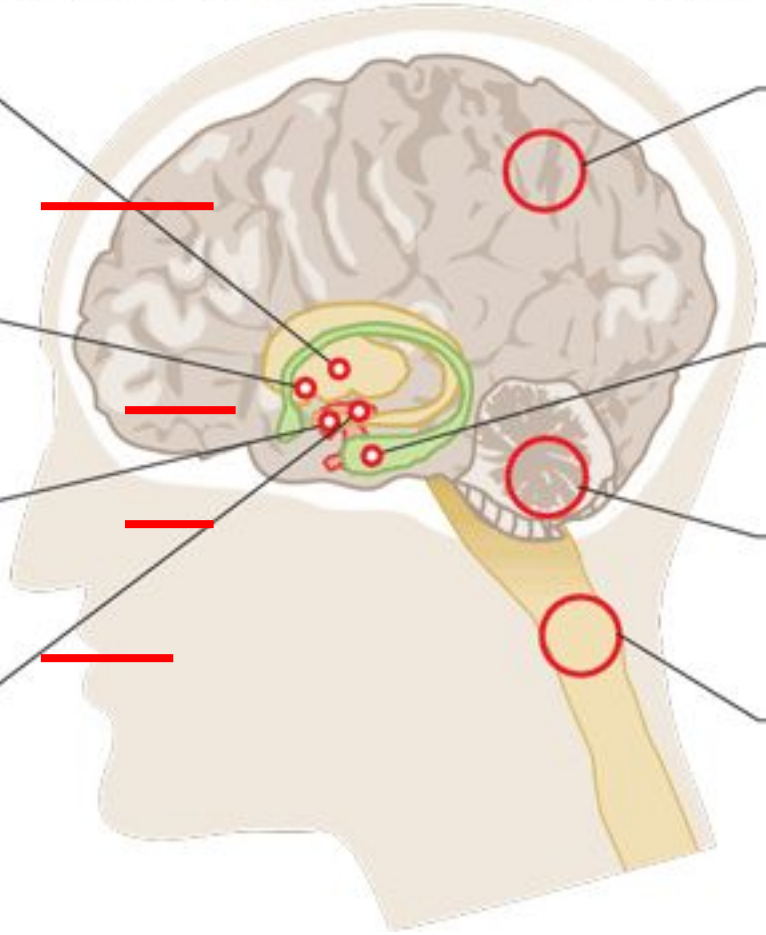


- THC- Simple- CB1 partial agonist
  - Euphoria, relaxation, heighten sensory perception, altered time perception, inc appetite
  - Dramatic personal differences- others fear, distrust, panic, hallucinations
  - Smoking immediate effect
    - Oral 60-90 min
  - Effects last 3-24 hrs; long half life,
    - blood 30 days
  - But no receptors in brainstem- thus no resp depression
  - SE: **tachycardias, disorientation, lack of physical coordination**

Pairs CB1 receptor location and effects

THC and the brain

Tetrahydrocannabinol (THC), the psychoactive substance found in cannabis, produces its effects on the body when marijuana is smoked or otherwise ingested. Found throughout the body, cannabinoid receptors are found in greatest quantity in the brain, particularly in areas that govern coordination, judgment, learning and memory. Some of the areas THC affects:



Basal ganglia
Associated with behavioral decision-making, learning and motor control

Ventral striatum
Associated with the process of predicting and feeling reward

Amygdala
Associated with anxiety, emotion and fear

Hypothalamus
Controls appetite, the body's temperature, hunger and thirst, sleep and sexual behavior

Neocortex
Controls higher cognitive functions; interprets sensory information

Hippocampus
Controls memory and learning

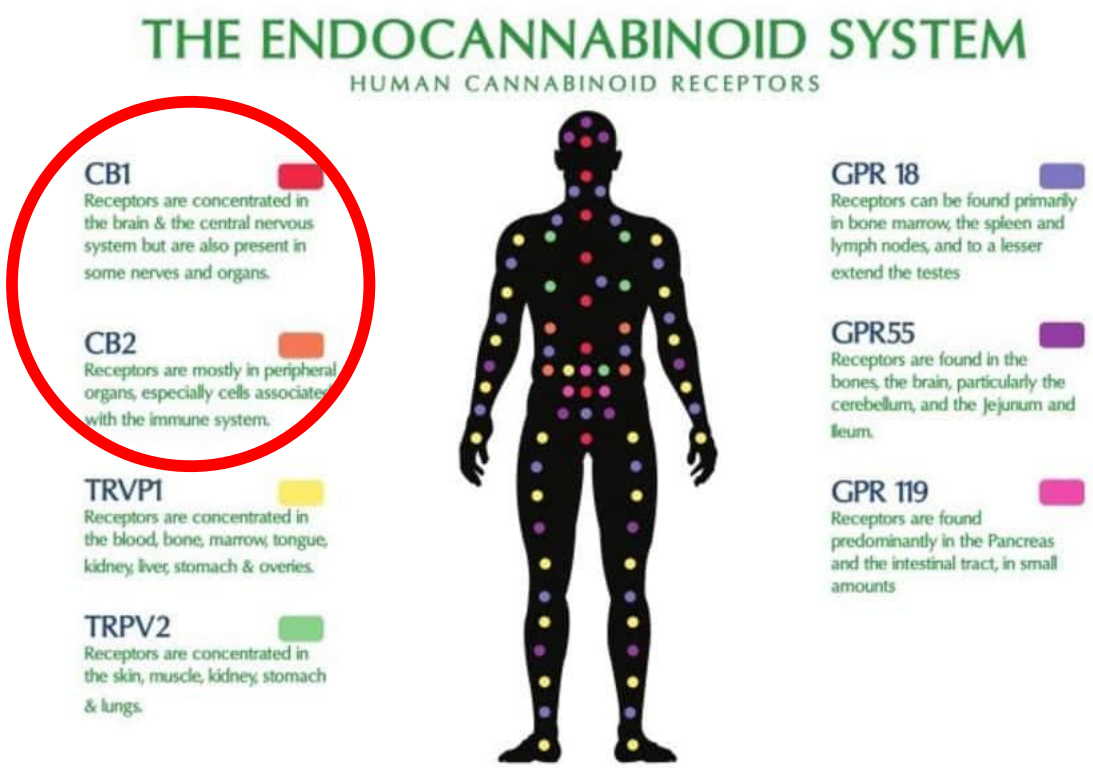
Cerebellum
Controls coordination and motor control

Brain stem and spinal cord
Controls vomiting reflex and the transmission of pain signals

Source: Scientific American

The Register

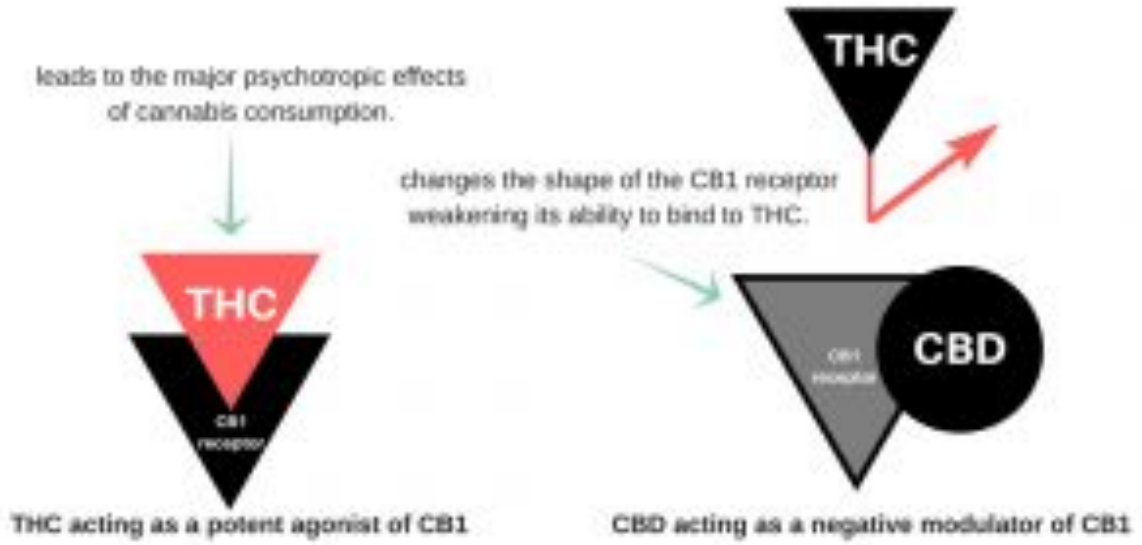
Just to confuse – CBD interacts MANY other ECS receptors- Less understood



CBD (Cannabidiol)

- CBD- More complex
  - **CB2**- Antagonist
    - Broad anti-inflammatory effects throughout body
    - expressed in osteoblasts and osteoclasts, stimulates bone formation, and inhibits bone resorption
  - **CB1** Delays reuptake AG-2 & Anandamide-
    - enhancing natural EC in brain-
    - Neuroprotective against seizures- (Epidiolex)
  - **Serotonin receptors**: anti-anxiety
  - **G coupled protein receptor**:
    - appetite, sleep, pain perception, n/v
  - **Vanilloid Receptors**:
    - TRPV1-pain perception (Capsaicin)
  - GPR55, PPARS:
    - osteoclasts, bone density, tumor regression, amyloid degradation

CBD dampens effect of THC



Unifying Law of Pain

‘The Origin of All Pain is Inflammation & Inflammatory Response’

Irrespective of type of pain: Acute, chronic, peripheral, central, nociceptive or neuropathic-Underlying origin is inflammation and inflammatory response

Activation of pain receptors, transmission and modulation of pain signals, neuro plasticity & central sensitization are all one continuum of inflammation and inflammatory response

Mediators of pain: Eicosanoids, Cytokines, Neuropeptides, Growth Factors, Neurotransmitters

Open Access Rambam Maimonides Medical Journal
CANNABINOIDS AND PAIN
Special Issue on Pain
Guest Editors: Elon Eisenberg and Simon Vulfsons

The Endocannabinoid System, Cannabinoids, and Pain

Perry G. Fine, M.D.[1]* and Mark J. Rosenfeld, M.S., Ph.D.[2]

[1]Professor of Anesthesiology, Pain Research and Management Centers, Department of Anesthesiology, School of Medicine, University of Utah, Salt Lake City, Utah, USA; and [2]Chief Executive Officer, ISA Scientific, Draper, Utah, USA

- Cannabinoids Analgesic similar to weak opiods
- Improvement of the pain symptoms in patients with chronic musculo-skeletal inflammation
- Cannabinoids analgesic effect, it is more likely to occur in hyperalgesic and inflammatory states
- Anandamide & THC have similar antinociceptive effects at CB1 receptors
- CBD activity at CB2 receptors seems to account for its anti-inflammatory properties

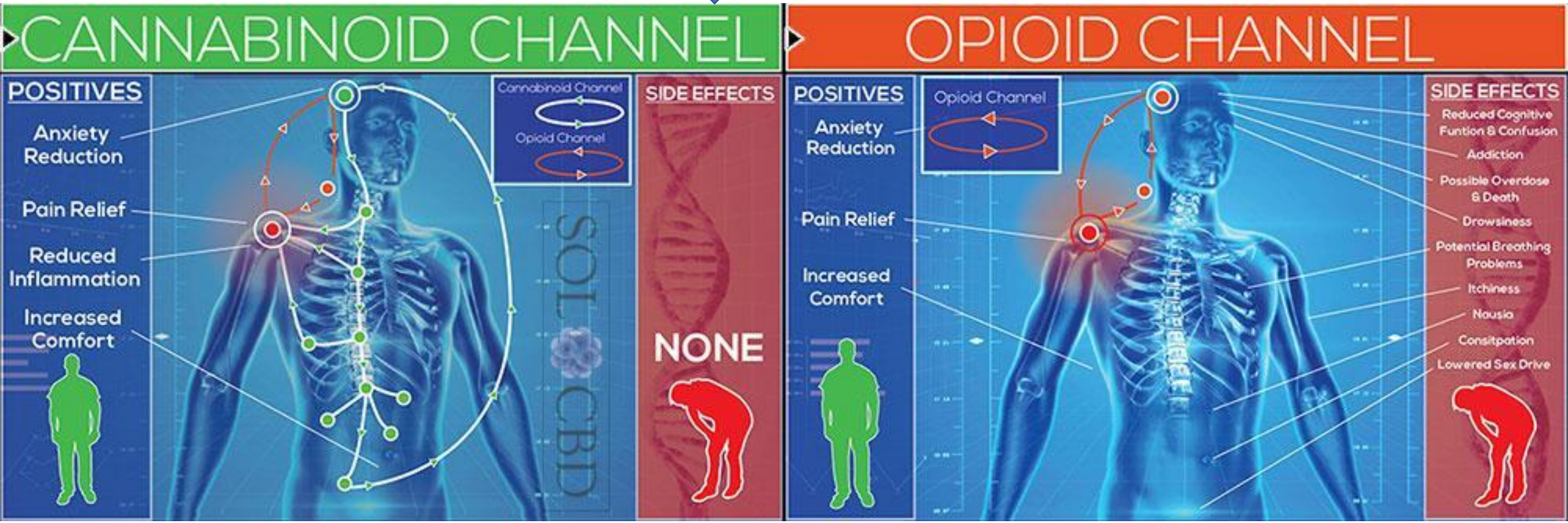
Cannabinoids & NSAIDs

1. **NSAIDs & Cannabinoids May Synergistically Reduce Pain**
2. **NSAIDs**
    1. **Can Inhibit Endocannabinoid Degradation**
    2. **May Reduce Some Side Effects of THC**
3. **Phytocannabinoids Also Inhibit COX-2**

Cross talk opioid receptors

- Mounting evidence that endogenous and exogenous cannabinoids exert some influence on opioid receptors
- Peripheral pain control: CB2 receptor agonists can evoke analgesia by triggering the release of beta-endorphin

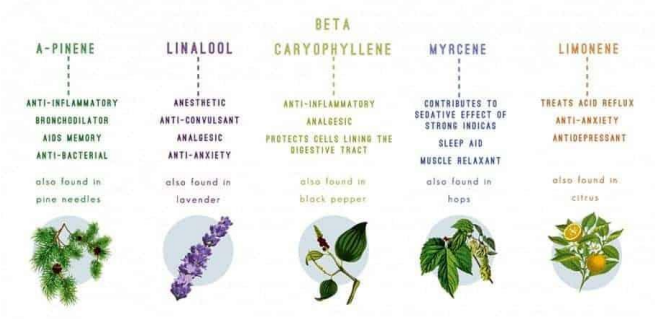
Hi Safety Profile



Entourage effect & Terpenes

- **The Entourage Effect**: Combined enhanced synergistic effect –compounds working together

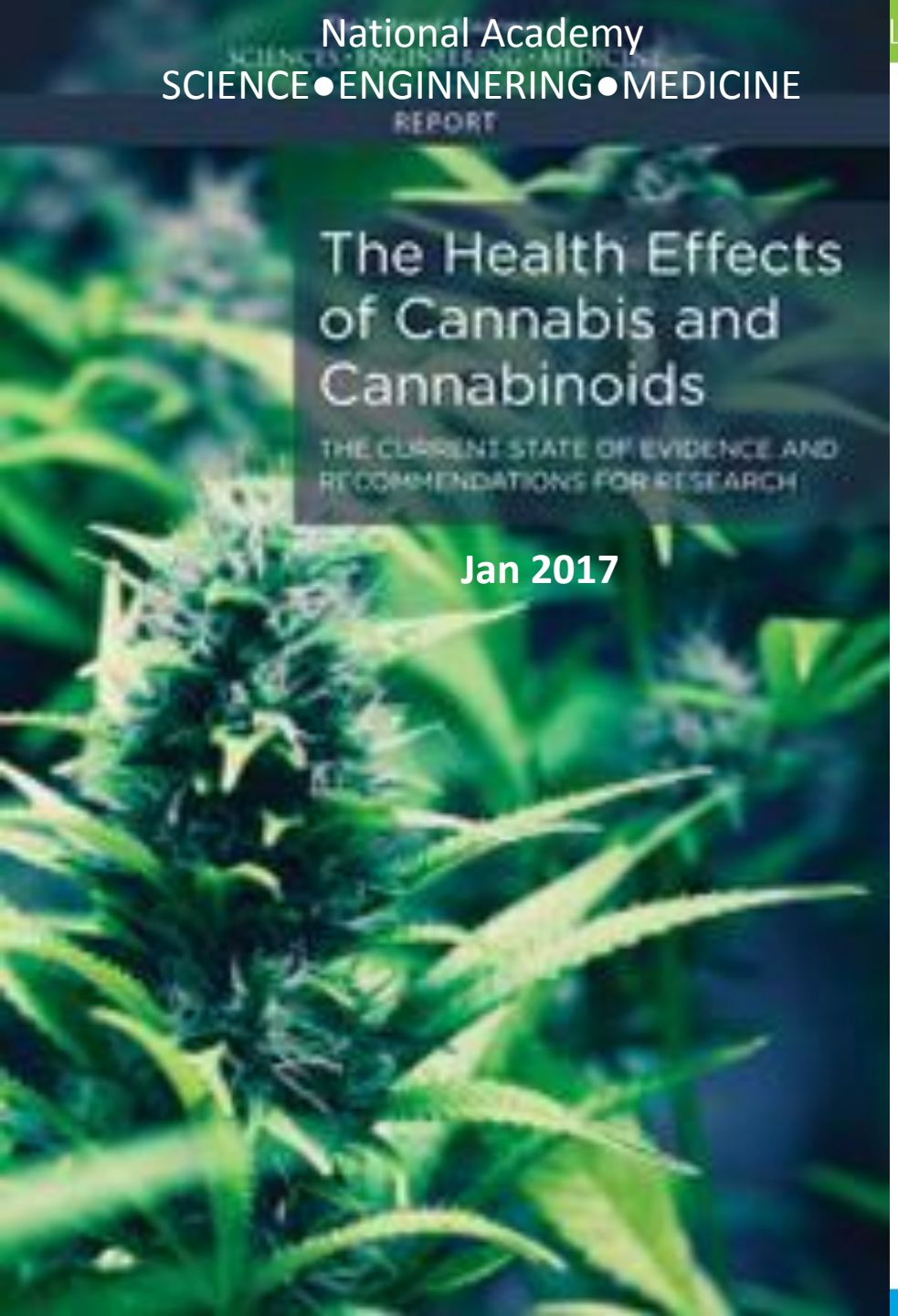
- Terpenes: Another important cannabis chemical class (~100)
  - aromatic molecules that help give plants a particular taste or smell.
- “generally recognized as safe” (GRAS) by the USDA
- The terpene .-caryophyllene is in black pepper, cinnamon, clove, and other spices.
- 2nd molecule selectively binds to the **CB2**
- Strong anti-inflammatory and analgesic effects effective at reducing neuropathic pain, sensitization, pain



Sleep & Pain

- Cannabinoids used for centuries as sleep aid
- Relaxing & sedative effects
- Normalized sleep improve pain relief
- Cannabinoids suppress sleep-related apnea.
- Opioid analgesics CNS depressants

  - Further research and clinical application both in sleep and pain medicine.



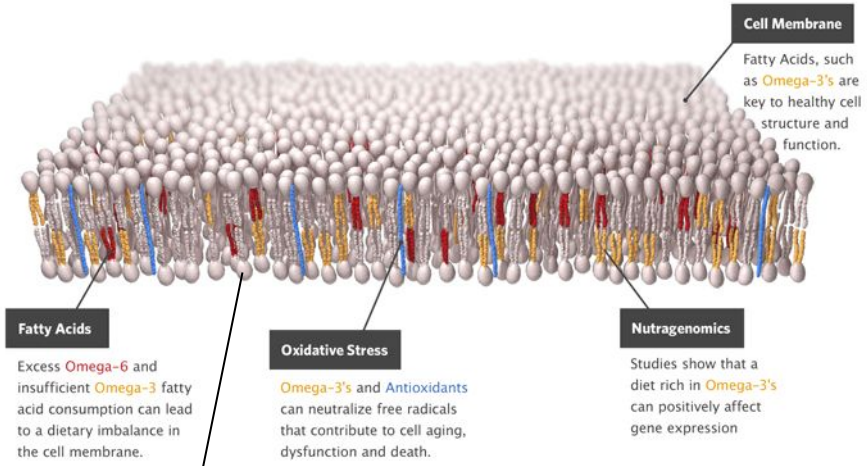
National Academy
SCIENCE●ENGINNERING●MEDICINE

- **CONCLUSIONS FOR: THERAPEUTIC EFFECTS**

10,000 Studies

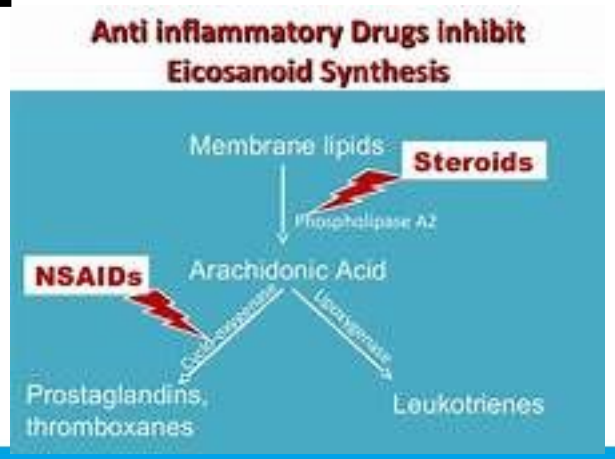
- Conclusive evidence that cannabis or cannabinoids are effective: **Treatment for chronic pain in adults**

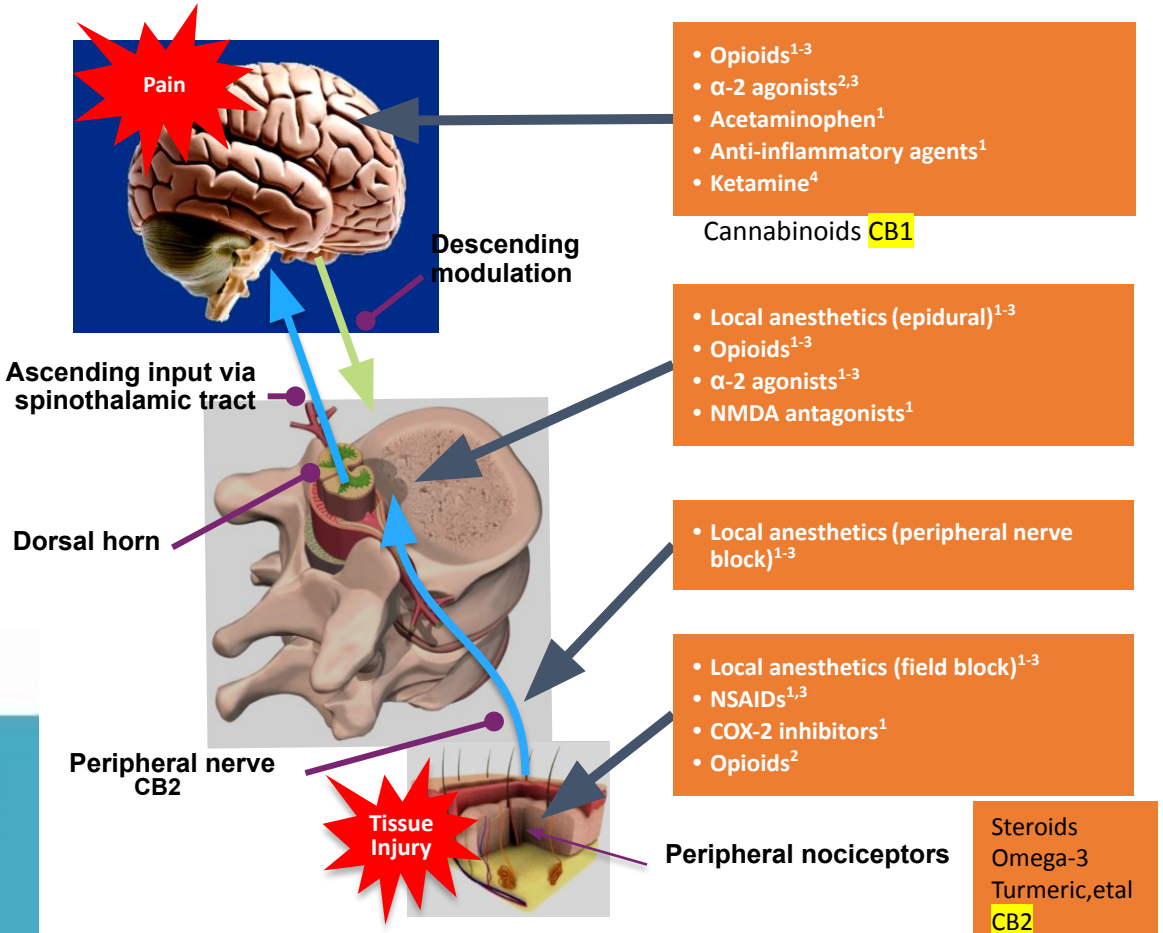
A Multimodal Approach Uses a Variety o Therapeutics That Work at Different Site



Endocannabinoids

Anandamide & 2AG





- Opioids[1-3]
- α-2 agonists[2,3]
- Acetaminophen[1]
- Anti-inflammatory agents[1]
- Ketamine[4]

Cannabinoids CB1

- Local anesthetics (epidural)[1-3]
- Opioids[1-3]
- α-2 agonists[1-3]
- NMDA antagonists[1]

- Local anesthetics (peripheral nerve block)[1-3]

- Local anesthetics (field block)[1-3]
- NSAIDs[1,3]
- COX-2 inhibitors[1]
- Opioids[2]

Steroids
Omega-3
Turmeric,etal
CB2

Evaluation of the effects of CBD hemp extract on opioid use and quality of life indicators in chronic pain patients: a prospective cohort study

Alex Capano[a,b], Richard Weaver[c] and Elisa Burkman[c]

[a]Ecofibre Ltd, Philadelphia, PA, USA; [b]Lambert Center for the Study of Medicinal Cannabis & Hemp Philadelphia, Philadelphia, PA, USA; [c]University of Louisville, Louisville, KY, USA

RESULTS

CBD-rich extract enabled our patients to reduce or eliminate opioids with significant improvement in their quality of life indices.

Conclusions 978 Studies on Cannabis for 184 Conditions From 1971 – 2018 (Pre-clinical & clinical- Pain & Inflammation)

- Downregulates GABA in Dorsal Horn- **decreasing pain**
- **Tissues injury**: activators **decrease hyperalgesia & allodynia**
- CR2 agonists **decrease inflammation & related hypersensitivity**
- **Modulates** supraspinal, spinal, and **peripheral pain** pathways
- **Anandamide, THC** block **acute pain** response
- **Anti-nociceptive: unequivocally** demonstrated in several different animal models of **inflammatory and neuropathic pain**.
- Robust evidence of the **opioid-sparing effect** of cannabinoids
- Endocannabinoid activation causes antinociceptive effects in the 3 major types of pain-acute, chronic inflammatory pain, and neuropathic pain.
- **THC** has also been shown to trigger the release of **endogenous opioids**,
- …..cannabinoids exert some influence on opioid receptors

Contents lists available at ScienceDirect

The Journal of Arthroplasty

journal homepage: www.arthroplastyjournal.org

Primary Arthroplasty

Should Cannabinoids Be Added to Multimodal Pain Regimens After Total Hip and Knee Arthroplasty?

Thomas R. Hickernell, MD, Akshay Lakra, MD *, Ari Berg, MD, Herbert J. Cooper, MD, Jeffrey A. Geller, MD, Roshan P. Shah, MD

Department of Orthopedic Surgery, Center for Hip and Knee Replacement, NewYork-Presbyterian Hospital/Columbia University Medical Center, New York, New York

Dronabinol

- Lower LOS
- Fewer ME's
- More studies

AAOS –Now-2019

- Cannabinoids Can Serve as Alternatives to Narcotic Pain Medication for Fracture Healing
  - Endorsed Dr Oz, Sanjay Gupta- mainstream Media
  - Pre-clinical science strong
  - CBD $1B
  - Starting dose 15-25 mg/day
  - Doses up to 600mg/day well tolerated
  - Rec: Buy 3rd party testing & COA
  - Best evidence: MSK pain OA, RA, Back, Nerve, Fibro, Anxiety
  - Basic science- helps bone regeneration, healing
  - More studies

archives
AAOS American Academy of Orthopaedic Surgeons
American Association of Orthopaedic Surgeons

AAOS-Now 2020

Cannabis use for management of chronic musculoskeletal pain increasing, new study shows

- N=629
- 20% use for managing pain
  - 90% effective reported
  - 40% decreased other pain meds
  - 57%- more effective than other pain meds
  - 39% used CBD
    - 60% ingested tinctures
  - Don't know formulations, dosages, routes of administration
  - 65% non-users were interested in using
- Conc: More work understanding role – managing chronic MSK pain

Journal of the AAOS®
AMERICAN ACADEMY OF ORTHOPAEDIC SURGEONS

REVIEW ARTICLE April 2020

Medicinal *Cannabis* in Orthopaedic Practice

Kleeman-Forsthuber, Lindsay T. MD; Dennis, Douglas A. MD; Jennings, Jason M. MD, DPT

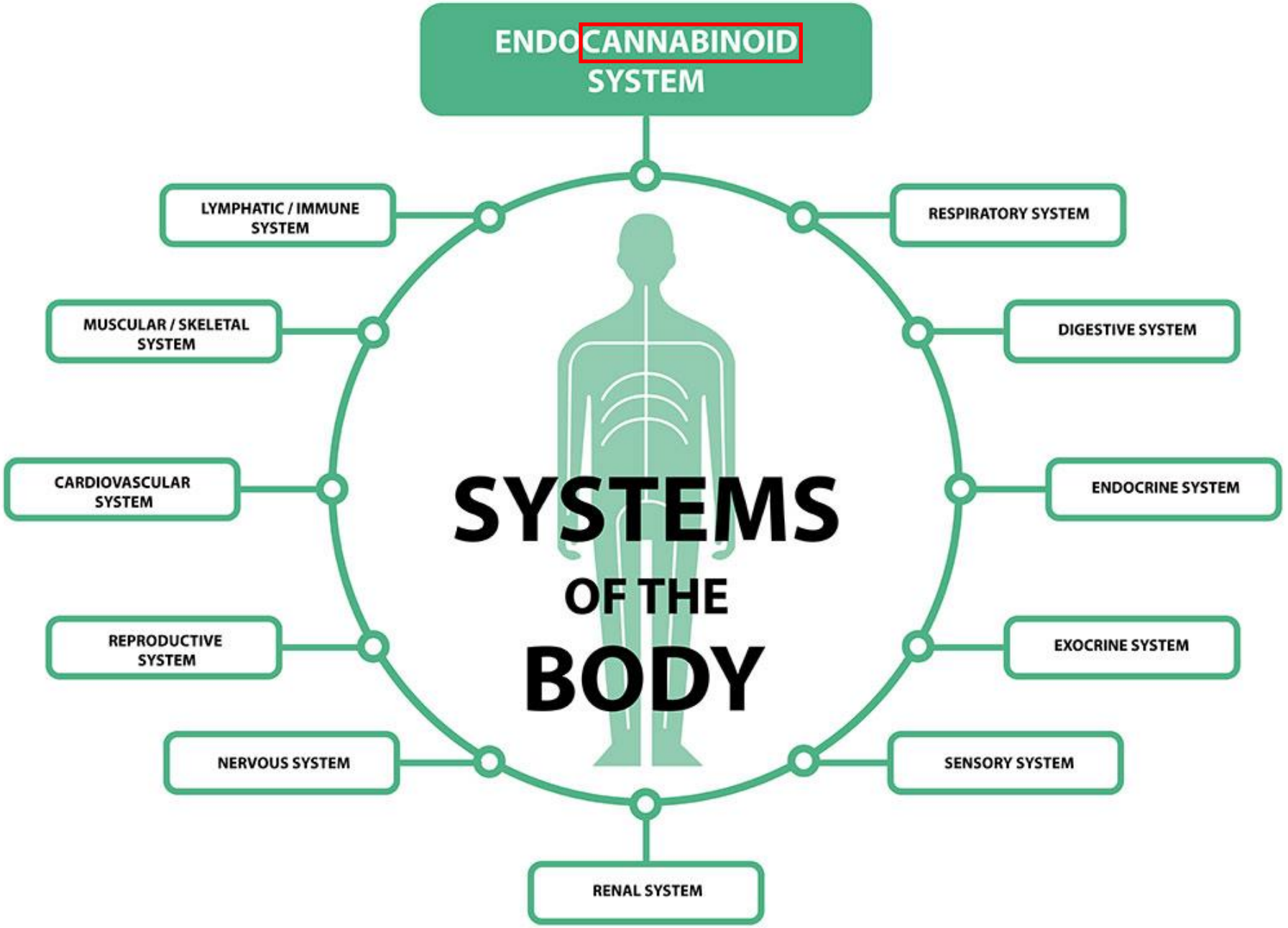
- ***Cannabis*** has emerged as a potential alternative or adjunct to opioids in management of pain related to MSK conditions
- Most orthopaedic surgeons have little knowledge on its medical applications or efficacy.[7–10]
- The endocannabinoid system play a role in decreasing the inflammatory cascade and enhancing pain management.
- Evidence to date is scant and precludes recommendations for its widespread use.
- Future research is warranted

As More Athletes Use Cannabis for Aches and Pain, There's More We Need to Know

journal *PLOS One 2019*

- 26% athletes surveyed – used cannabis –past 2 weeks
- 67% - in their lifetime
- 61% for Pain
  - 68% reported relief
  - Sleep, pain, calm down- most improvement
- Only 40% physicians discuss cannabis as alt treatment
- Little guidance for pts-- Physicians lack tools

Final Thoughts



10/27/2021

- 23% use past 30d 18-25 yo
- Rx meds bad SE
  - (wt gain, libido, insomnia)
- Chronic pain:
  - benefit better sleep, ↓anxiety
- Beware unregulated dispensaries


PERSONAL JOURNAL.

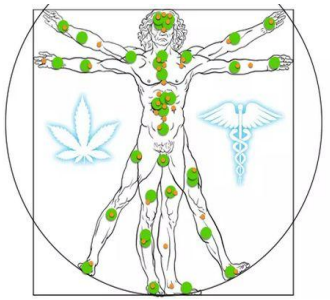
THE WALL STREET JOURNAL. Wednesday, October 27, 2021 | A13

Marijuana as a Mental-Health Treatment?

What do I tell my patients?

- **Buyer Beware-** Lots junk/scam artists in market
- Beware of **THC**-Psychoactive component only
  - Can help w chronic pain, dose limited by SE
- CBD- research exploding- most preclinical-stay tuned
- **Full spectrum Hemp Extract-** may be most beneficial due to **entourage** effect
- Buy **organic**, USA grown & processed, **COA-QR code** w ingredients, 3rd party tested- online
- **Start Low, Go Slow** (CBD 25-40mg/d) (THC 1mg)
- Become **educated consumer**
- Greatest potential in **chronic pain, nerve pain**, sleep, anxiety, tissue & bone healing
- "In humans, **CBD** exhibits no effects indicative of any **abuse or dependence potential . . .**
- To date, there is **no evidence of public health related problems** associated with the use of pure CBD."

Conclusion



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- ECS = (Biologic) Cryptocurrency
- Both Unknown a few decades ago
- Poorly understood by most
- Lack of trust- common denominator in explosive use
  - (FDA/DEA-& Dept Treasury/monetary policy)
- Used by many--dabble
- Many- don't know how either works but willing to try
- Know its not going away
- Waste a lot $$$ if not careful
- Time will tell-Eventually be proven to be the most important 'systems' controls our life (financially/biologically)

Q&A

THANK YOU