Emerging Therapies and Evidence-Based Practice with CBD

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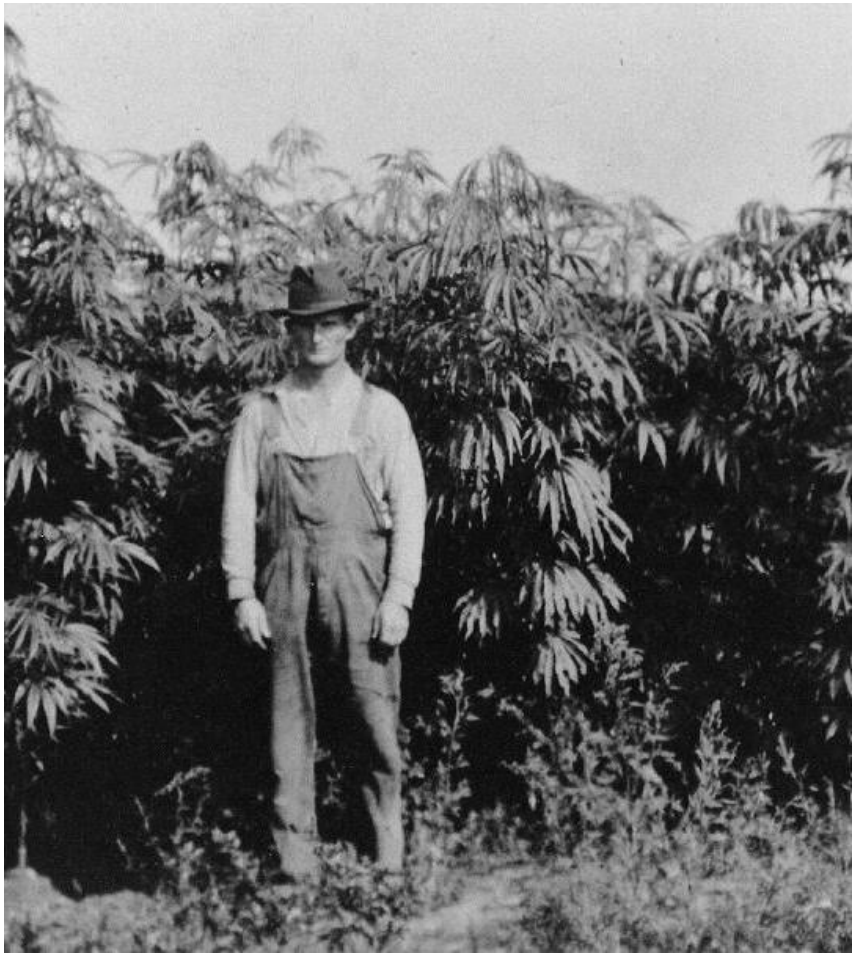
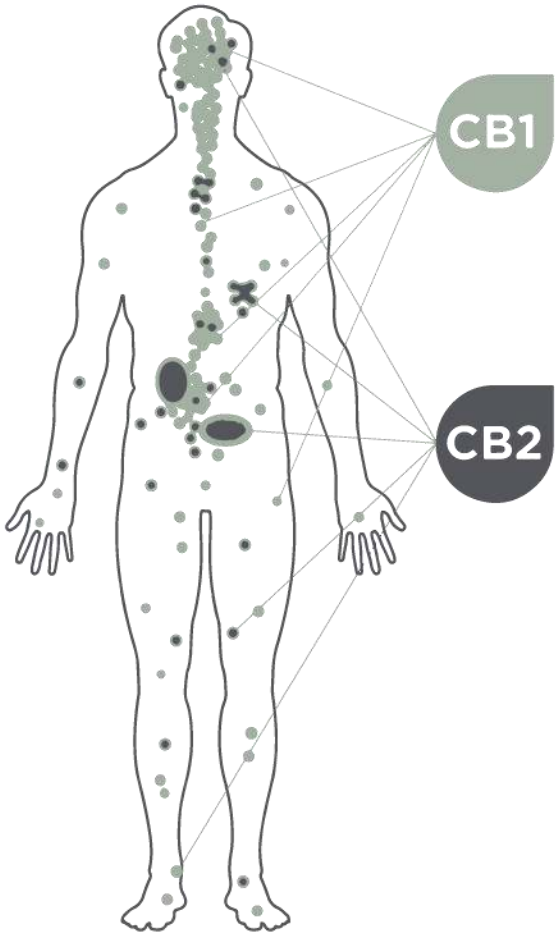
- ✓ The Endocannabinoid System
- ✓ CBD, THC, & Cannabinoids
- ✓ Hemp vs. MJ
- ✓ Full-Spectrum vs. Isolate
- ✓ History & controversy
- ✓ Current landscape

Quick Review



THE ENDOCANNABINOID SYSTEM



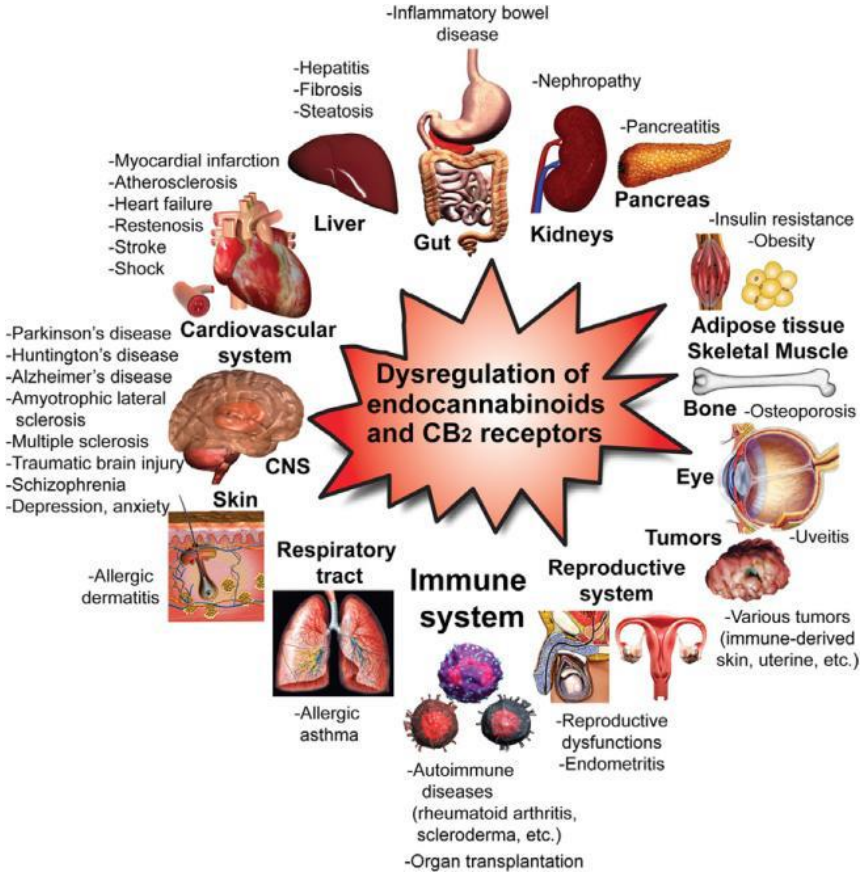
THE ECS HELPS IN REGULATING:

- Anxiety
- Appetite/Hunger
- Depression
- Digestion
- Immune Function
- Memory
- Mood
- Motor Control
- Pain
- Pleasure & Reward
- Reproduction & Fertility
- Sleep
- Temperature Regulation

CANNABINOIDS & THE ECS

- Endogenous cannabinoids
  - Anandamide, 2-AG
- Exogenous Cannabinoids
  - Plant derived
  - CBD, THC, CBG, CBN, THCV, etc.

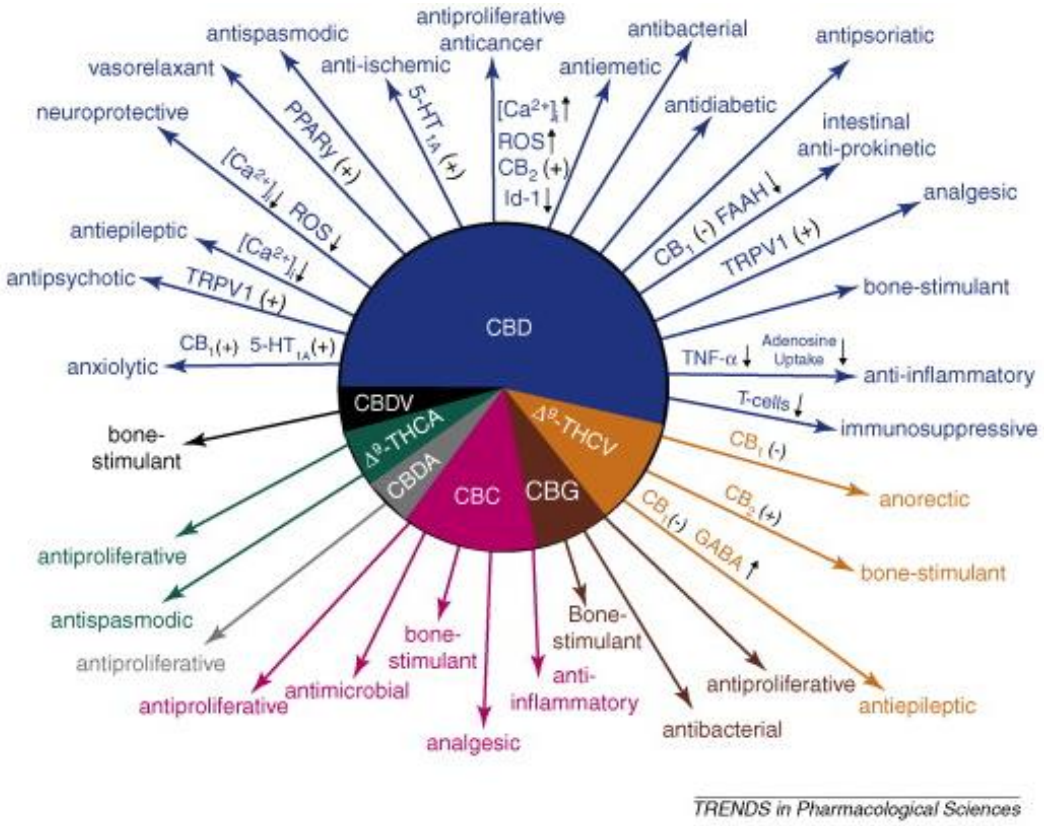
Dysregulation of the ECS



Cannabis and phytocannabinoids

- Phytocannabinoids are a specific chemical class found in Cannabis sativa
- There are over 100 related chemicals called “cannabinoids” in the plant
- Found throughout the plant, highest concentration in the resin secreted by female plants
- Most abundant CBs found in Cannabis Sativa
  - THC
  - Cannabidiol (CBD)
  - Cannabinol (CBN)
  - Cannabichromene (CBC)
  - Cannabigerol (CBG)
  - Cannabivarin (CBV)
  - Cannabidivarin (CBDV)
  - THCA and CBDA
- Cannot ignore pharmacologically active flavonoids, terpenes, etc…

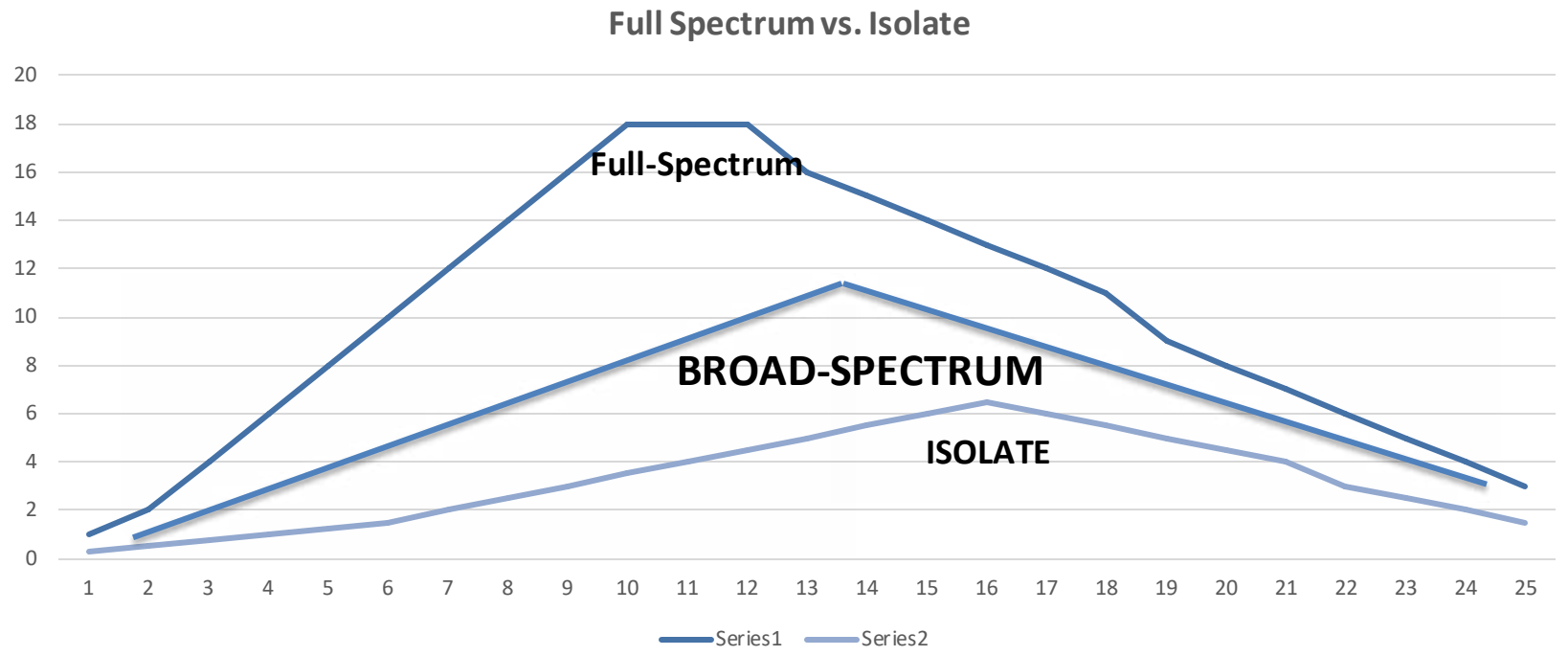
THE ENTOURAGE EFFECT: IT'S NOT <u>ONLY</u> ABOUT CBD!



The Entourage Effect:
Full-Spectrum vs. Isolate vs. Synthetic

Terpenes

Dose Response Curve

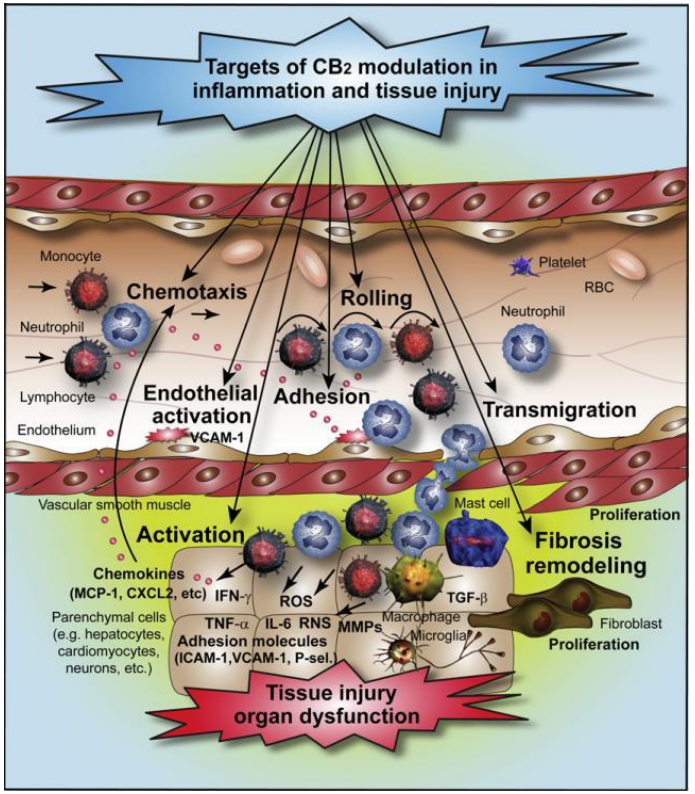


ɔwer doses = Lower risks!

EVIDENCE-BASED USES OF CBD HEMP EXTRACT

PAIN, SLEEP, MOOD, SEXUAL HEALTH, INFLAMMATION*

INFLAMMATION

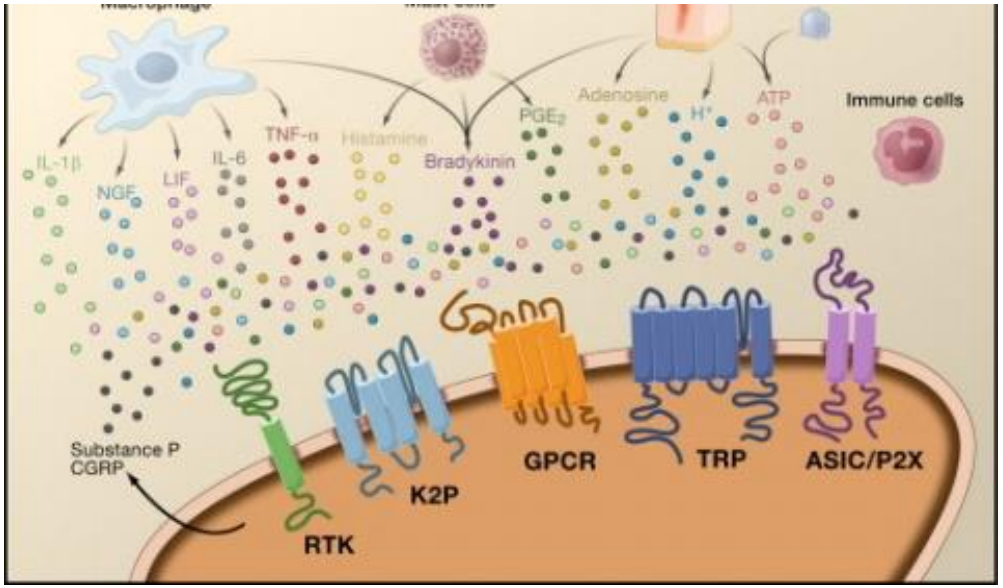


Clinical Trials in Humans

Dementia

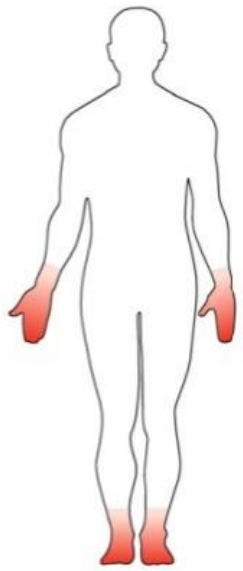
- 100 participants, all etiologies & ages
- Double-blind, placebo-controlled crossover
- Intervention: 15-30mg dose via 15mg softgels bid
- 6 weeks intervention
- 2 week washout
- Subjective: Caregiver survey for participant
- Objective: Wearables
- Additional: Caregiver assessment

- **Mild Cognitive Decline**
- 100 participants
  - Very different patient population
- Double-blind, placebo controlled, RCT
- Intervention: 15-30mg dose via 15mg softgels bid
- Volumetric MRIs at baseline and 12 month follow-up



CBD, Pain, and inflammation

- Chemicals released around the site of disease contribute to chronic pain conditions (histamine, bradykinin, serotonin, ATP, *prostaglandins*, *cytokines, chemokines* etc…)
- Phytocannabinoids generallyandn CBD specifically suppress this inflammatory response through multiple mechanisms



Chemotherapy Induced Neuropathic Pain (CIPN)

- **Debilitating peripheral neuropathy**
  - **Treatment limiting**
  - **Incidence up to 80%**
  - **No FDA approved medications**

- **Mechanisms**
  - Oxidative stress
  - Mitochondrial dysfunction
  - Changes in ion channel expression
  - Glial activation
  - Peripheral and central sensitization

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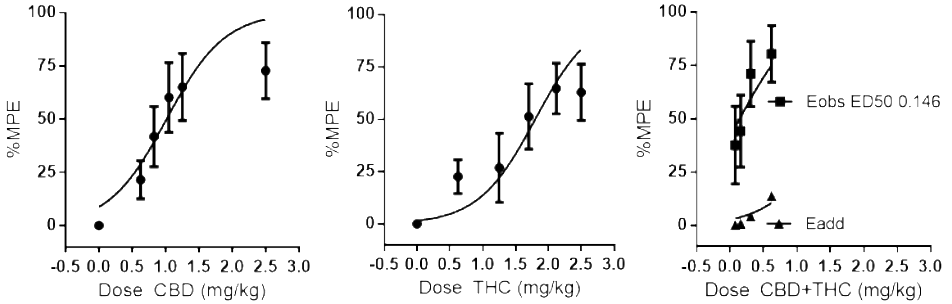

King et al British Journal of Pharmacology 2017

The dose required of CBD alone is 10X higher than when in combination with THC

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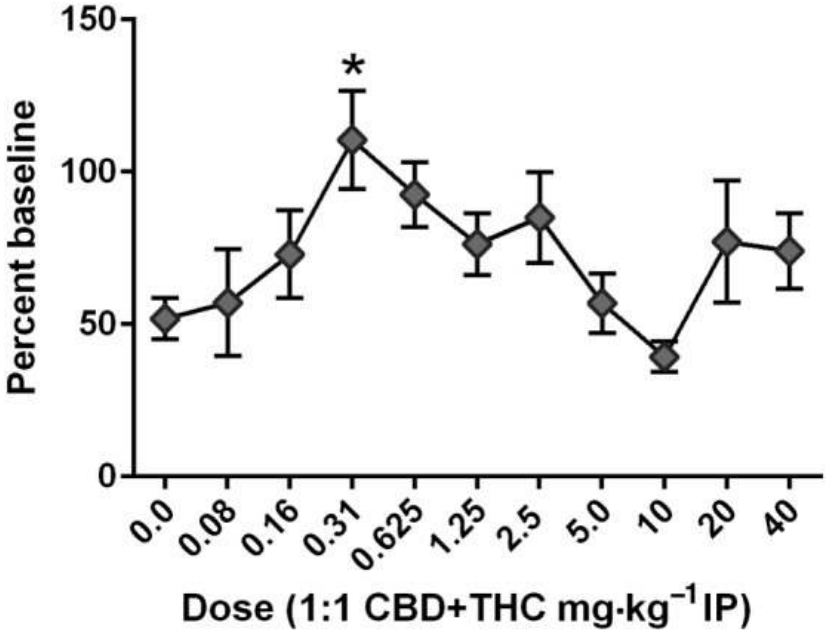

This synergistic combination effect shows the inverted U shape dose response curve

Clinical Trial: CIPN in Humans

- 100 participants
- 45mg dose tid
  - 15mg softgels
- Prevention vs. Treatment
- Survey Study*

BREASTCANCER.ORG

Opioid Reduction: Why CBD?

- Efficacy
- Safety
- Withdrawal
- Substitute or Treatment?

CANNABINIOIDS AND PAIN

JAMA's systematic review of cannabinoids analgesia.[1]

- 28 randomized clinical trials (RCTs) completed over 67 years.
- The review concluded that cannabis therapy for marked pain relief and spasticity reduction is supported by high-quality evidence.

Meta-Analysis from the National Academies of Science, Engineering & Medicine

- "Conclusive or substantial evidence" of cannabinoids' efficacy in pain relief, spasticity, seizures.
- Well tolerated

Petzke's Systematic Review on Cannabinoids & Pain

- 15 RCTs
- Conclusion: Cannabinoids effective for pain relief
- Side effects of intoxication with high THC*

CBD for Opioid Reduction: Withdrawal

- CBD & Fentanyl Pharmacokinetic Study
- No increased risk of respiratory depression
- No increased cardiovascular risk

SURVEY STUDY FROM 7 PAIN CLINICS
THE JOURNAL OF PAIN, 2019

- 63% report to have tried a CBD product (including products containing some THC)
- 37.30% of these answered that the used CBD product did NOT contain THC.
- Of these, the majority responded that CBD products:
  - have helped their condition (57.45%)
  - Reduced their pain medication (61.7%)
  - **including opioids (44.68%).**
- Among the pain conditions patients reported relieve were back pain (63.83%), nerve pain (38.30%), neck pain (38.30%), migraines (29.79%), limb pain (19.15%), fibromyalgia (19.15%), and other (19.15%).

Data Limitations

- Self-report
- Variable dosage
- Some may be using higher THC
  - "Microdose" of THC believed to be sufficient
  - Properties of CBD

OPIOID STUDY

ananda PROFESSIONAL

Evaluation of the Effects of CBD Hemp Extract on Opioid Use and Quality of Life Indicators in Chronic Pain Patients: A Prospective Cohort Study

Objectives: We aim to investigate the impact of full hemp extract cannabidiol (CBD) on opioid use and quality of life indicators among chronic pain patients.

Methods: An initial sample of 131 patients was recruited from a private pain management center's investigative population. Ninety-seven patients completed the 8-week study. The primary inclusion criteria included patients between 30 and 65 years old with chronic pain who have been on opioids for at least one year. Data was collected at three different time points: baseline, 4, and 8 weeks. Opioid and other medication use was evaluated via the medication and psychiatric treatment receipt. Improvement was evaluated using four indices: Pain Disability Index (PDI-4); Pittsburgh Sleep Quality Index (PSQI), Pain Intensity and Interference (PEG); and Patient Health Questionnaire (PHQ-4).

Results: Over half of chronic pain patients (53%) reduced or eliminated their opioids within eight weeks after adding CBD-rich hemp extract to their regimens. Almost all CBD users (94%) reported quality of life improvements. The results indicated a significant relationship between CBD and PSQI ($p=0.003$), and PEG ($p=0.006$). There was a trend towards improvement but no significant relationship between CBD use and PHQ and PDI.

Conclusion: CBD could significantly reduce opioid use and improve chronic pain and sleep quality among patients who are currently using opioids for pain management.

Figure Legends

Figure 1: Quality of life indices' change over study duration

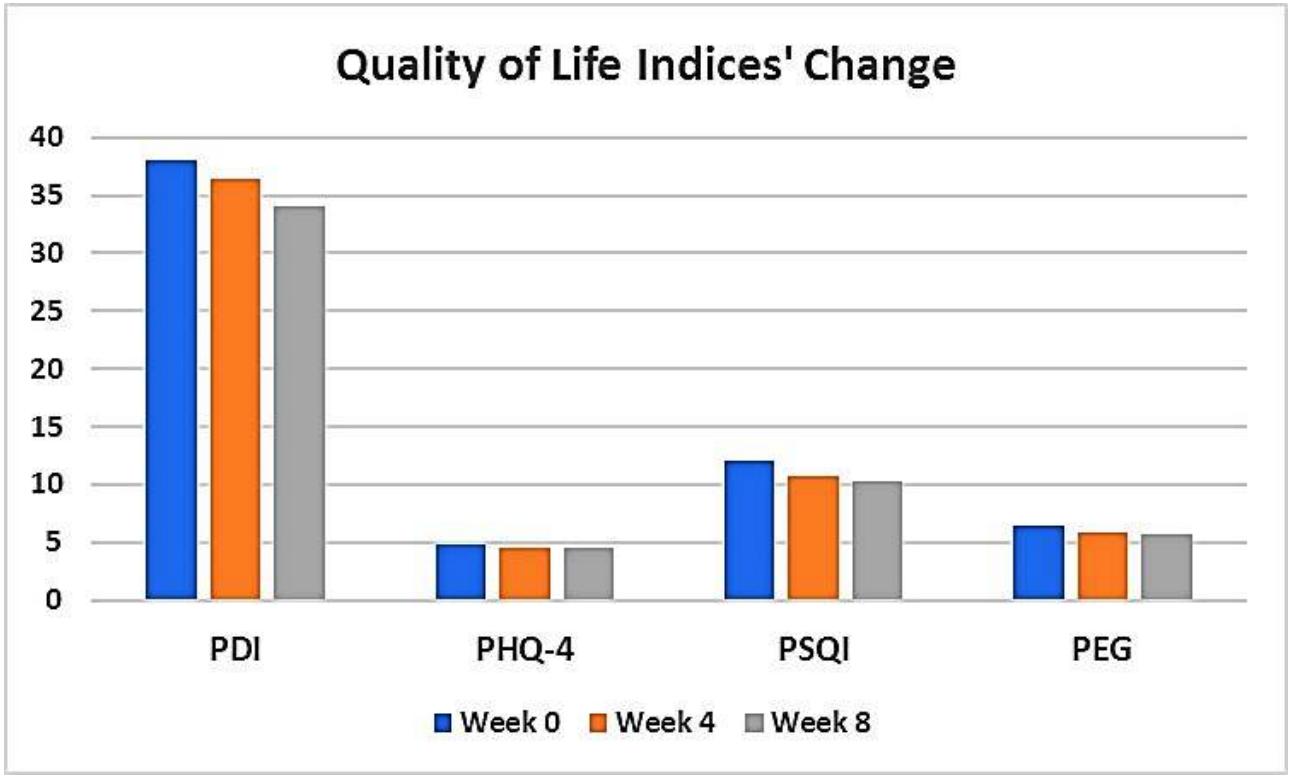

Table 1

Index/Scale	Baseline	Week 4	Week 8	P Value
PDI	38.02 ± 15.2	36.4 ± 12.4	34.1 ± 12.4	0.09
PHQ-4	4.8 ± 3.6	4.5 ± 3.1	4.5 ± 3.4	0.7
PSQI	12.09 ± 4.1	10.7 ± 3.9	10.3 ± 4.3	0.03*
PEG	6.5 ± 1.9	5.9 ± 1.9	5.7 ± 2	0.006*

Table 1: Quality of life indices' change over study duration

PDI: Pain disability index, PHQ-4: The 4-item patient health questionnaire, PSQI: Pittsburgh Sleep Quality Index, PEG: Pain Intensity and Interference.

Study Firsts

- Use of OTC hemp-derived CBD oil
- Outside of survey studies, this is the largest study on the topic to date (by a factor of 3 or more)
- Uniform product
- Low doses of CBD oil used
  - (average dose was 30mg)
  - All other studies use higher doses - 10x or more.
- identified dose, delivery, cannabinoid content, and product used.
- Consistency is key!

- CONCLUSIONS
- LIMITATIONS
- NEED FOR CLINICAL EDUCATION
- DRUG SCREENING ADAPTATION
- FUTURE RESEARCH

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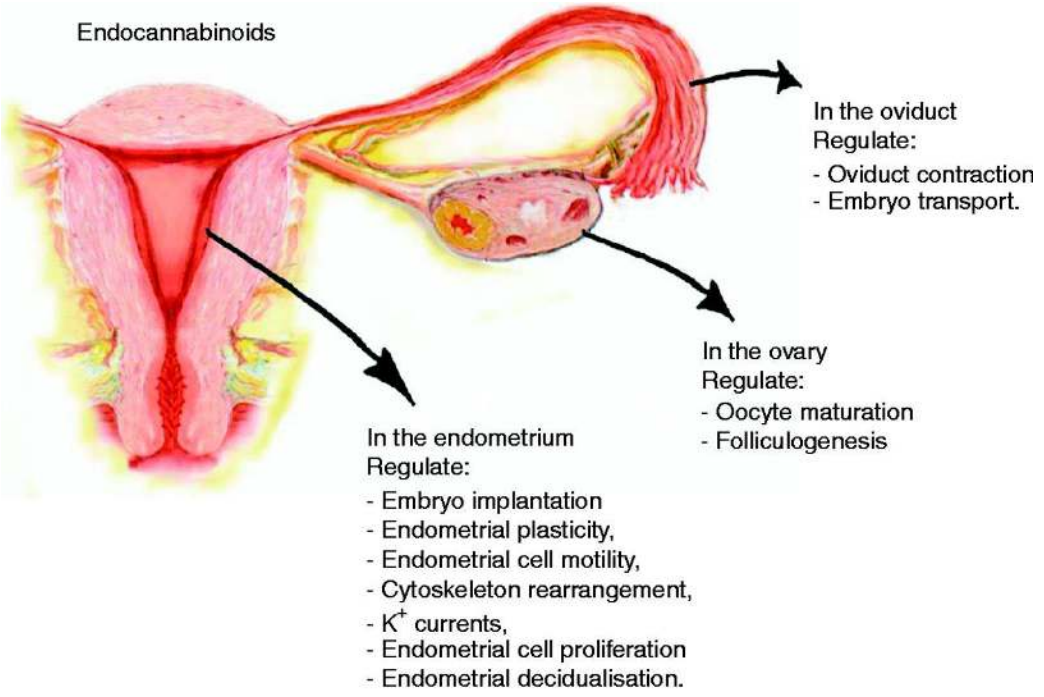
Murphy Pain Center

The Endocannabinoid System & Sexual Health:

- Abundance of CB2 receptors in female reproductive organs influencing…
  - Hormonal regulation (esp. HPA axis), libido, mood, vasodilation, inflammation, nociceptive pain, temperature control, sleep/wake cycle, etc.
  - Oocyte maturation, folliculogenesis, ovarian endocrine section, embryonic transport & implantation, steroid hormone production, placentation, endometrial proliferation, etc.
  - And Orgasm.

- O'Llenecia, S. W., Holloway, A. C., & Raha, S. (2019). The role of the endocannabinoid system in female reproductive tissues. *Journal of ovarian research*, *12*(1), 3.
- Karasu, T., Marczylo, T. H., Maccarrone, M., & Konje, J. C. (2011). The role of sex steroid hormones, cytokines and the endocannabinoid system in female fertility. *Human reproduction update*, *17*(3), 347-361.
- Komorowski, J., & Stepień, H. (2007). The role of the endocannabinoid system in the regulation of endocrine function and in the control of energy balance in humans. *Postepy higieny i medycyny doswiadczalnej (Online)*, *61*, 99-105.

Overview of biological activities of endocannabinoids in the female reproductive organs.



Di Blasio, A. M., Vignali, M., & Gentilini, D. (2013). The endocannabinoid pathway and the female reproductive organs. *J Mol Endocrinol*, *50*(1), R1-9.

Areas of Research

Endometriosis

- Cannabinoid agonists exert antiproliferative effects on deep infiltrating endometriosis (Leconte et al., 2010)
- The ECS "contributes to mechanisms underlying both the peripheral innervation of the abnormal growths and the pain associated with endometriosis," (Dmitrieva et al., 2010)
- Increased cannabinoid signalling may reduce proliferative capacity of endometriotic lesions, (DiBlasio et al., 2013).
- The ECS provides a novel therapeutic opportunity for pain management due to endometriosis (Bouaziz et al., 2017)

Libido & Sexual Satisfaction

- Endocannabinoids regulate sexual function & cannabinoid receptors influence multiple areas of the brain responsible for sexual function (Pfaus, 2009)
- Cannabinoids influence hormones and neurotransmitters that affect sexual behavior (Lopez, 2010)
- Masturbation to orgasm releases endogenous cannabinoid (Fuss et al., 2017)
- Survey of 373 women over 11 months (Lynn et al., 2019):
  - Cannabinoids before a sexual encounter more than doubled likelihood of satisfactory orgasm
  - Cannabinoids use resulted in increased libido, decreased pain with sex

Clinical Trials that Analyzed the Association Between Endocannabinoid System and Endometriosis-Associated Pain (Bouaziz et al., 2017)

n	Design study and patient characteristics	Molecules tested and doses	Mode of delivery and length	Results of the studies	References
220	RCT Primary dysmenorrhea Age 16–24 Not necessarily endometriosis but all etiology of dysmenorrhea	PEA 400 mg and Polydatin 40 mg versus placebo	Once a day. Ten days a month	Improvement of pelvic pain in 98.18% The combination of PEA and transpolydatin was more effective than placebo (p<0.001) No side effect	Tartaglia et al.[56]
56	Endometriosis CPP Quality of life Sexual health	PEA 300 mg and LA 300 mg	Twice daily for 9 months	Progressive reduction of the pain syndrome Improve the QoL Improve sexual life of women	Caruso et al.[48]
61	Endometriosis RCT Three groups after laparoscopy conservative treatment of endometriosis	Group A (n=21): PEA 400 mg + transpolydatin 40 mg Group B (n=20): placebo Group C (n=20): celecoxid 200 mg	Group A: twice a day for 3 months Group B: placebo 3 months Group C: twice a day for 7 consecutive days	All groups: decrease in dysmenorrhea, dyspareunia, and pelvic pain PEA + transpolydatin more effective than placebo (p<0.001) Celecoxid best decrease compared to placebo and PEA	Cobellis et al. [49]
24	Endometriosis CPP Evaluation of the use of associated pain killer	PEA 400 mg Polydatin 40 mg	Twice a day for 90 days	Statistically significant improvement of pelvic pain, dysmenorrhea, and dyspareunia Improvement in QOL Not statistically significant for dysuria and dyschezia Decrease assumption of NSAIDs	Lo Monte et al.[50]

n, No. of patients included in the study; CPP, chronic pelvic pain; NSAID, nonsteroidal anti-inflammatory drug; PEA, *N*-palmitoylethanolamine; QOL, quality of life; RCT, randomized control study.

Bouaziz, J., Bar On, A., Seidman, D. S., & Soriano, D. (2017). The clinical significance of endocannabinoids in endometriosis pain management. *Cannabis and cannabinoid research*, *2*(1), 72-80.

FAQs:
What you need to know

- Dosing
- Delivery
- Interactions
- Monitoring
- Side effects
- Tolerability
- Risks
- Product Selection
- Etc.

Dosing and Delivery

Find the peak

Sublingual vs. Oral vs. Topical

Starting dose: 10mg sublingual, 15mg oral
Topical: Apply to affected area as needed

DRUG/ DRUG INTERACTIONS

CBD INTERACTS WITH CYP 450

- Potential inhibition at CYP3A4, CYP2C9, CYP2C19, CYP2D6*

THINK GRAPEFRUIT JUICE BUT…

CLINICALLY SIGNIFICANT?

- Dose dependent
- 20mg/kg/day**
- Case study of Warfarin at 10mg/kg
- Typical Doses much, much lower

FOLLOW UP & COUNSELING

RISKS & ADVERSE EFFECTS

LIVER TOXICITY

SIDE EFFECTS

TOLERABILITY

VULNERABLE POPULATIONS

- **-PEDIATRICS**
- **-CANCER**
- **-HIV+**
- **-OTHER IMMUNOCOMPROMISED**

But Will I Fail a Drug Test?

- **Full-Spectrum products (0.3% THC)**
  - **Unlikely, but possible.**
- **Broad- Spectrum, THC-free products & Isolate products**
  - **No chance of a TRUE positive**
  - **Cross-reactivity an issue**
- **SAMSHA recommendations**
  - **Confirmation serum test**
  - **15ng/ml**

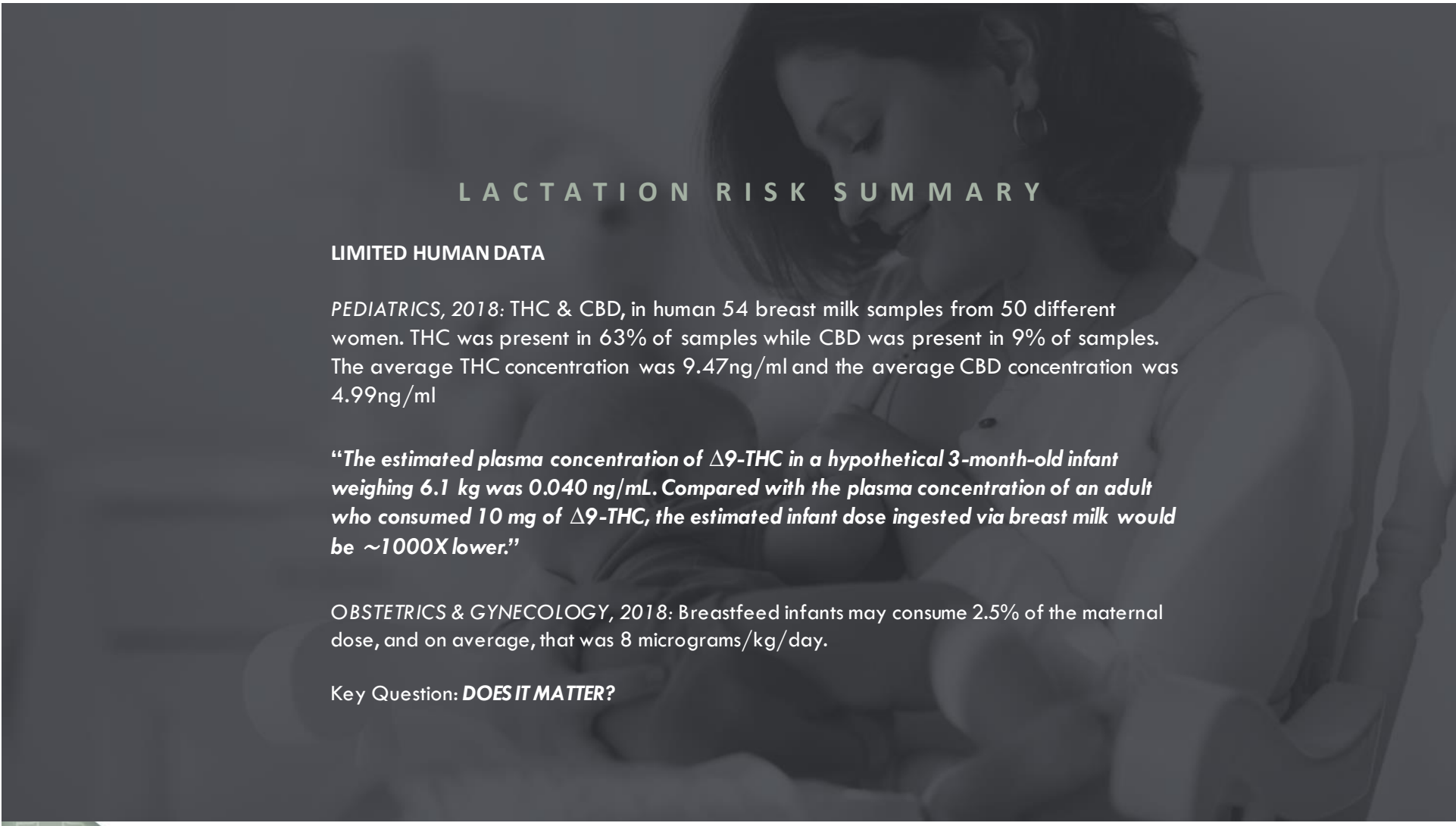
Use in Pregnancy & Breastfeeding

- **Animal Data:**
- Oral administration of cannabidiol (0, 75, 150, or 250 mg/kg/day) to pregnant rats throughout the period of organogenesis resulted in embryofetal mortality at the highest dose tested. There were no other drug-related maternal or developmental effects. The highest no-effect dose for embryofetal toxicity in rats was associated with maternal plasma cannabidiol exposures (AUC) approximately 16 times that in humans at the recommended human dose (RHD) of 20 mg/kg/day.

- Oral administration of cannabidiol (0, 50, 80, or 125 mg/kg/day) to pregnant rabbits throughout organogenesis resulted in decreased fetal body weights and increased fetal structural variations at the highest dose tested, which was also associated with maternal toxicity. Maternal plasma cannabidiol exposures at the no-effect level for embryofetal developmental toxicity in rabbits were less than that in humans at the RHD.

- When cannabidiol (75, 150, or 250 mg/kg/day) was orally administered to rats throughout pregnancy and lactation, decreased growth, delayed sexual maturation, neurobehavioral changes (decreased activity), and adverse effects on male reproductive organ development (small testes in adult offspring) and fertility were observed in the offspring at the mid and high dose. These effects occurred in the absence of maternal toxicity. The no-effect dose for pre- and postnatal developmental toxicity in rats was associated with maternal plasma cannabidiol exposures approximately 9 times that in humans at the RHD. 8.2

- **Lactation Risk Summary** There are no data on the presence of cannabidiol or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for EPIDIOLEX and any potential adverse effects on the breastfed infant from EPIDIOLEX or from the underlying maternal condition.



LACTATION RISK SUMMARY

LIMITED HUMAN DATA

PEDIATRICS, 2018: THC & CBD, in human 54 breast milk samples from 50 different women. THC was present in 63% of samples while CBD was present in 9% of samples. The average THC concentration was 9.47ng/ml and the average CBD concentration was 4.99ng/ml

"The estimated plasma concentration of ∆9-THC in a hypothetical 3-month-old infant weighing 6.1 kg was 0.040 ng/mL. Compared with the plasma concentration of an adult who consumed 10 mg of ∆9-THC, the estimated infant dose ingested via breast milk would be ~1000X lower."

OBSTETRICS & GYNECOLOGY, 2018: Breastfeed infants may consume 2.5% of the maternal dose, and on average, that was 8 micrograms/kg/day.

Key Question: ***DOES IT MATTER?***

NAVIGATING THE WILD WEST OF THE CBD MARKET

Certificate of Analysis

Should:

- Be done by an ISO certified, third party lab
- Include cannabinoid content
- Include tests for pesticides, microbes, chemicals
- Be lot specific

QUESTIONS?

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