Clinical Use of the Cannabinoids with Case Reports & Discussion

The 49th Annual Conference of the

American Osteopathic Society of Rheumatic Diseases

and the

Integrative Health Alliance

Kenton Crowley, Pharm.D., FAARFM, ABAAHP

March 20 – March 21 , 2021

Faculty Disclosure

Faculty member Kenton Crowley discloses the following relationships:

Director of Research and Development, Silver State Trading, NV

Founder and COO, Trokie California Inc, CA

Founder and CMO, Palliative Care Corp, CA

Learning Objectives

At the conclusion of this program, the participant will be able to:

- List the most common medical indications that cannabis is used for today
- Discuss the importance of knowing why the formulation and route of administration impacts the onset and duration of action of phytocannabinoid therapy
- Discuss the value of cannabis as an alternative or adjunct treatment in chronic pain conditions with or without opiates

Goals of Presentation

- Go over important basic cannabis terminology
- Discuss general considerations when recommending a cannabis product/treatment
- List the most common real-world medicinal uses of cannabis today and share peer reviewed data to support the indications discussed
- Present case reports supporting the use of cannabis in those indications

Marijuana vs Hemp

- Both are *Cannabis sativa L.,* which describes the species
- Regulatory terms based on delta-9-tetrahydrocannabinol (THC) content
  - Marijuana: > 0.3mg/gm of THC in the dry weight of plant
    - Schedule 1 drug = No recognized medicinal value, highly addictive
  - Hemp: ≤ 0.3mg/gm of THC in the dry weight of plant
    - Amended Farm Bill of 2018
      - Agricultural commodity
      - Legal in states that have approved USDA programs
      - Federally legal by default as (program rolls out) in state approved programs

Cultivar vs Chemovar vs Strain

- **Cultivar** (strain) are phenotypically different plants named by the grower based on smell, appearance and physiological effects
  - Common terms (usually inaccurate):
    - **Sativa**: Taller plant, more energetic, “head high”
    - **Indica**: Shorter plant, more relaxing, “body high”
    - **Hybrid**: A mix of the two and >95% of the flower market
      - Varieties: Jack Herer, Blueberry, Cannatonic
- **Chemovar** is determined by terpene profile, cannabinoids, potency and quantity of standard biomolecules (i.e. lipids, waxes, flavonoids, proteins, phenols, sterols, etc.)
  - To better ensure reproducible cannabis experiences and effects

Hazekamp,A et al *Drug Testing and Analysis* 2012. Russo,E *Frontiers in Pharmacology* 2016

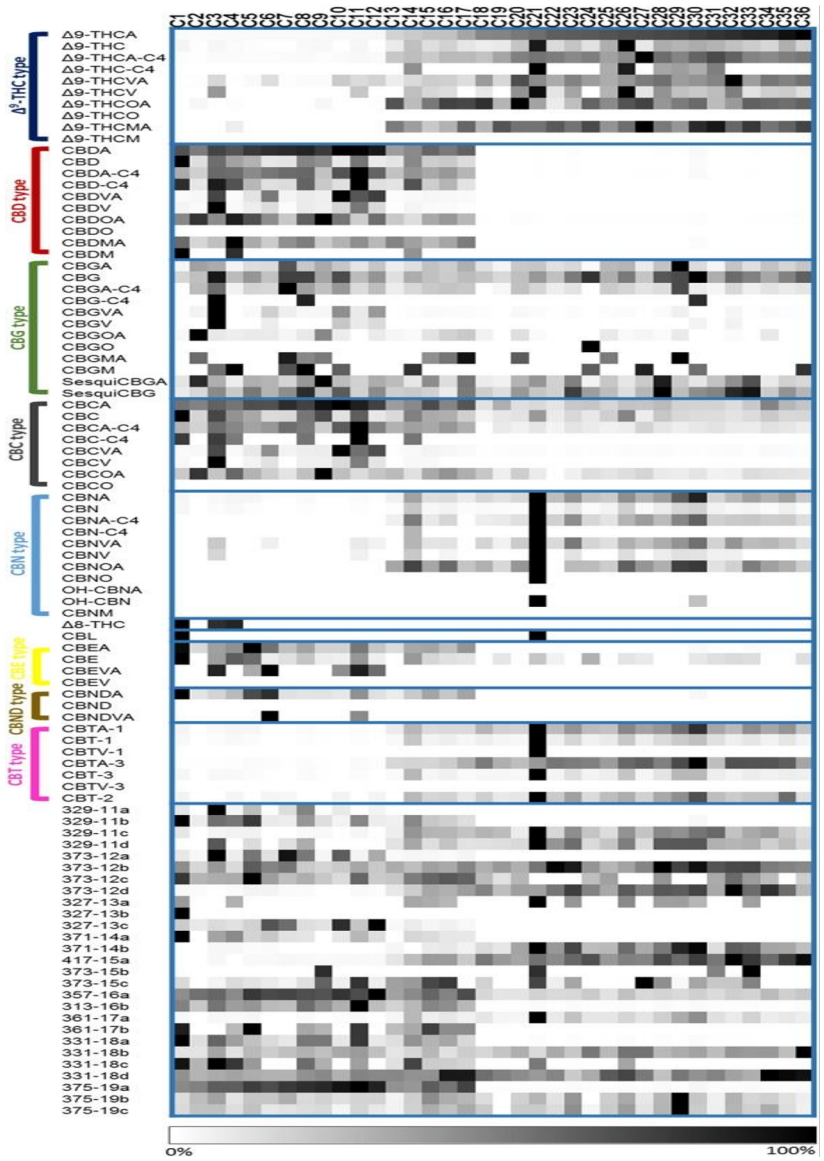
Sci Rep. 2018; 8: 14280.

Published online 2018 Sep 24. doi: 10.1038/s41598-018-32651-4

A new ESI-LC/MS approach for comprehensive metabolic profiling of phytocannabinoids in *Cannabis*

Paula Berman,1 Kate Futoran,1 Gil M. Lewitus,1 Dzmitry Mukha,1 Maya Benami,1 Tomer Shlomi,1,2 and David Meiri1

- 10 Δ^9-THC type
- 10 CBD type
- 12 CBG type
- 8 CBC type
- 11 CBN type
- 1 Δ^8-THC type
- 3 CBND type
- 7 CBT type



Extracts and Extraction Methods

- **Full Spectrum** Extracts: maintain the full profile of the cannabis plant that was processed
- **Broad Spectrum** Extracts: contain non-measurable "THC Potential" (THCA-A + delta-9-THC) and attempt to maintain the remainder of the full plant profile
- **Isolate** Extracts: Contain >99% of a single cannabinoid
- The method of extraction will determine what components of the plant are able to be removed and that content varies significantly
  - **CO2 Extraction**: Supercritical and Subcritical
  - **Light Hydrocarbon** Extraction: butane, propane, etc.
  - **Alcohol Extraction**: Ethanol, Isopropyl, Methanol, etc.
  - **Petroleum Hydrocarbon** Extraction: Heptane, Hexane, etc.
  - **Other**: Water, Steam Distillation, Cold-Press Extraction, etc.

Considerations Choosing Formulations

- Many routes of administration of cannabis (ROA)
- Challenges facing a practitioner recommending a ROA and formulations:
  - Products in a category can be very different
    - Formulation (base, diluents, excipients, surfactants, etc.)
    - Content of actives (source of API(s), extraction method, etc.)
    - Forms of API's (i.e. nano, non-nano, esterified, etc.)
    - Bioavailability (ROA huge impact)
    - Onset and duration of action; non-linear, biphasic PK's, dose dep.
    - Genomics of the individual
    - Sex
  - General Principles on ROA and ratios of major API's
  - Important not to categorize clinical outcomes based on the ROA or the product form

Case Study: Minor Cannabinoid Impact?

- Patient: Male, mid-30's, 8 seizures per day
- CBD/THC 3:1 SL, 40mg/mL, no terpenes, MCT oil, Diamond OG:
  - seizure-free for 9 weeks
- Next batch of 40mg/ml, 3:1 SL in MCT oil, Lemonade Haze:
  - seizures re-start in less than 24 hrs
- Actives came from two different cultivars: Diamond OG and Lemonade Haze

	CBD	THC	THCA	CBDA	CBN	CBG	THCV	CBGA	CBC
Diamond OG	300	100	15.3	0.00	0.66	1.76	0.73	**0.99**	**0.00**
Lemonade Haze	300	100	15.6	0.00	0.45	1.62	1.19	**0.00**	**1.06**

Cannabis Routes of Administration

- Combustion smoking (Flower or Bud)
- Vaporization (Bud, oil, wax, resin, etc.)
- Edible forms (food, candy & drinks, etc.)
- Orally (capsules & tablets)
- Sublingual & buccal (tinctures, troches, etc.)
- Transdermal patches
- Topicals (creams, roll-ons, lotions, balms, etc.)
- Suppositories

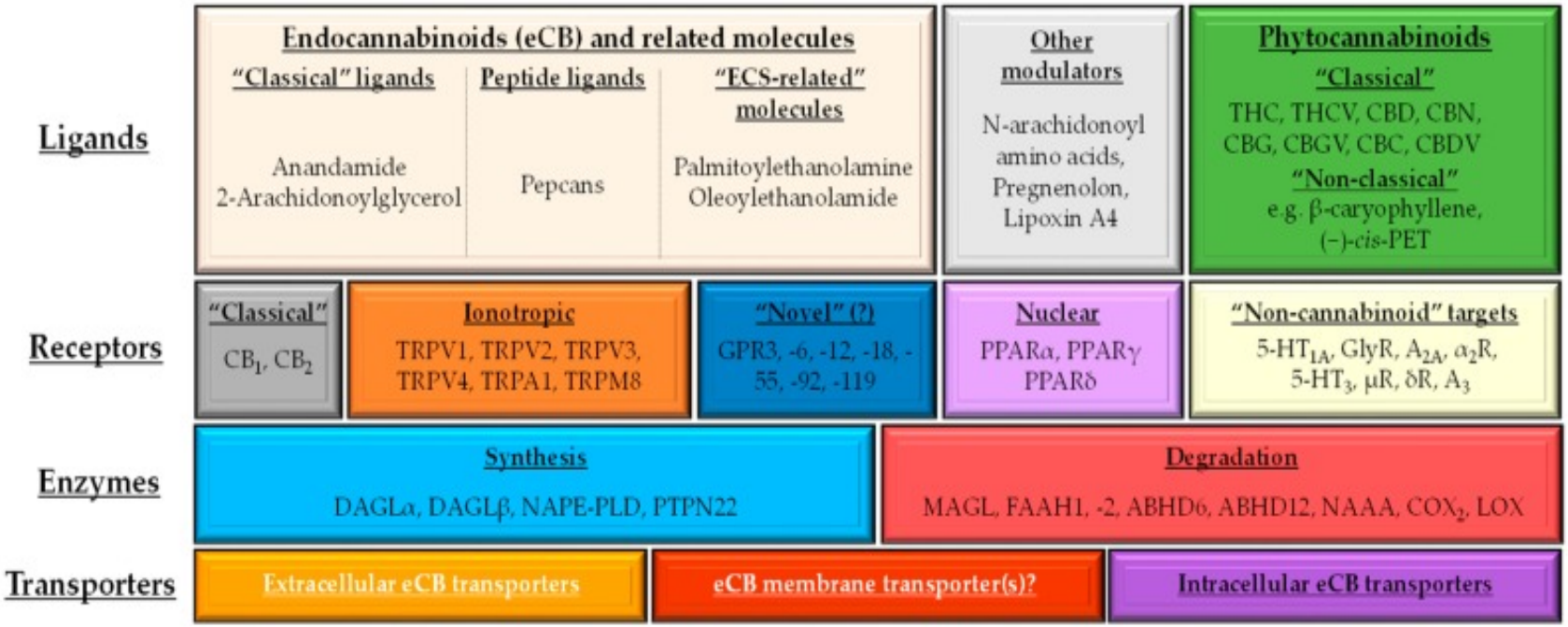
General Guidelines-Route of Administration

- **Inhalation**: Smoking/Vaping/MDI's
  - Onset of a less than a minute and duration of 1-3 hours
  - Not as anti-inflammatory as all other routes of administration
- **Edibles** (brownies, cookies, candy, gummies, drinks, infused foods, etc.)
  - 45 minutes to 4 hours onset and duration of 6 hrs to over 24 hours depending on dose taken and GI function
  - Dependent on what is in stomach at the time of administration
  - Unpredictable onset and duration for most people
- **Sublingual**: Tinctures, FA solutions (olive, coconut, MCT, etc.)
  - 15 to 45 minutes onset, variable based on how long held in mouth before swallowing AND solvent (ETOH, short-chain/long-chain FA's)
  - Misbranded (High Times pharmacopeia instead of the USP)
  - Formulations make a difference in onset and duration
- **Buccal** Absorption (between cheek/lip & gum): Troche, film, ODT, etc.
  - Least saliva production depending on placement within the mouth
  - 3 to 15 min onset, variable based on formulation, duration up to 8hrs

Reported Medical Applications for Cannabis

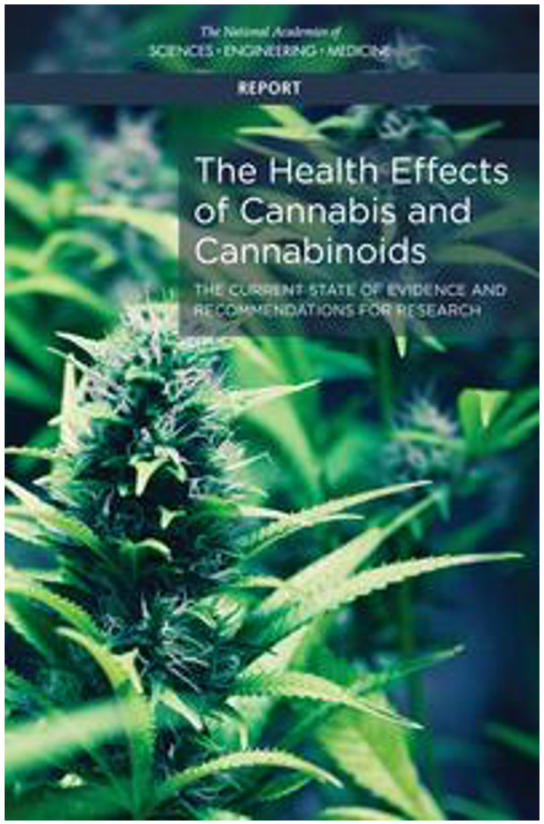
- ADHD
- Addiction/withdrawal
- AIDS/HIV
- Anorexia
- **Anxiety*****
- Arthritis
- Autism Spectrum Disorder***
- Autoimmune Disorders****
- Bipolar Disorder
- Cachexia
- Cancer****
- **Chronic Pain*****
- Crohn's Disease****
- Depression
- Epilepsy/Seizures**
- Fibromyalgia****
- Glaucoma
- Hypertension
- IBS/IBD****
- Meniere's Disease
- Multiple Sclerosis
- **Nausea/Emesis*****
- Neuropathic Pain
- OCD
- Parkinson's Disease
- PMS/PCOS
- PTSD
- Psychosis/Schizophrenia
- **Sleep Disorders*****
- Wellness/proactive medicine

ECS System Receptors Involved in Pain



Toth KF, et al. Molecules 2019 Mar 6;24(5):918

The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research

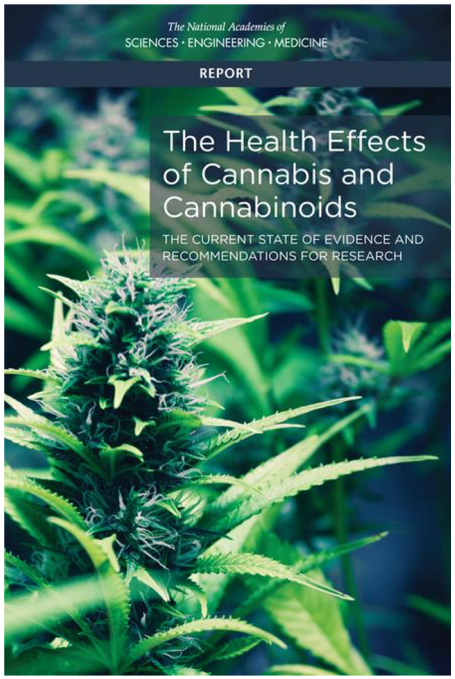


- The committee reached nearly 100 research conclusions based on consideration of more than 10,000 research articles
- The committee broke down the levels evidence:
  - Conclusive evidence of clinical efficacy
  - Substantial evidence of clinical efficacy
  - Moderate evidence of clinical efficacy
  - Limited evidence of a statistical association
  - Limited evidence of clinical inefficacy
  - Insufficient evidence to support or refute efficacy
  - Substantial evidence of statistical association

http://www.nationalacademies.org/hmd/Reports/2017/health-effects-of-cannabis-and-cannabinoids.aspx

Evidence of clinical efficacy

The National Academies of Sciences report on cannabis and cannabinoids



Conclusive evidence of clinical efficacy:

- Chronic pain in adults.[1]
- Antiemetics in the treatment of chemotherapy-induced nausea and vomiting.[2]
- Improving patient-reported multiple sclerosis spasticity.[2]

Moderate evidence of clinical efficacy :

- Improving short-term sleep outcomes in individuals with sleep disturbance associated with obstructive sleep apnea syndrome, fibromyalgia, chronic pain, and multiple sclerosis.[3]

[1]Cannabis; [2] Oral cannabinoids; [3] Sativex; [4] THC; [5] CBD; [6] Nabilone

Chronic Wounds

- WHO – Chronic Wounds are a “Major Global Public Health Crisis”
  - Affects up to 6% of population
  - Females have twice the Prevalence/Incidence of wounds than Males
  - USA spends up to 80 billion dollars annually
- Major drivers of serious deleterious Global Healthcare trends
  - Opioid Crisis
  - Proliferation of antibiotic “Superbugs”

Hellstrom A, et al. BMC Geriatrics 2016 Jan 21;16-25

Domigues E, et al. J Tissue Viability 2016 Aug;25(3):180-184

Nussbaum, SR, et al. Value in Health Care 2018 Jan;21(1):27-32

Chronic Wounds

- Outcomes
  - Poor healing rates
  - High recurrence rates
  - Rising amputation rates
  - High levels of suffering
  - Rising costs are leading all areas of Healthcare (7.5% per annum)
  - Wound-Related Pain continues to be poorly managed

Nussbaum, SR, et al. Value in Health Care 2018 Jan;21(1):27-32

Wound-Related Pain (WRP)

- Prevalence
  - 17-65% of patients with chronic wounds report pain
  - Pain intensity associated with multiplicity of wounds
  - NRS scores higher in females
  - Malignant Wounds & Perineal/Genital Wounds most painful
- Associated Symptoms
  - Sleep disturbance
  - Reduced QOL
  - Emotional Symptoms
    - Anxiety, Depression, Fear, Anger

Maida V, et al. J Pain Sympt Mangament 2009;37(2):2060211
Woo K, et al. Curr Opin Support Palliat Care 2013;7(1):86-94

Wound-Related Pain (WRP)

- WRP inhibits healing
- More than 70% of patients with chronic wounds use opioids
  - Opioids inhibit wound healing
- Problems with current treatment guidelines (analgesics)
  - Opioids (tolerance, constipation, N/V, etc.)
  - NSAID (GI bleeds, renal failure, etc.)
    - Inhibits wound healing
      - Inhibiting fibroblasts, angiogenesis & increase scaring
  - TCA (anticholinergic SE's, etc.)
  - SSRI/SNRI (decreased libido, dyspepsia, etc.)
  - APAP (N/V, anxiety, agitation, insomnia, etc.)
  - Lidocaine (dermatitis, erythema, pruritus, etc.)
- Current treatment guidelines do not address BTP

Shanmugan VK, et al. Wound Rep Reg 2017;25:120-130
Anderson K, et al. J AM College Wound Specialists 2014;4:84-91

Topical CBD Oil for Epidermolysis Bullosa

- Cases (n=3)
  - 6-month-old male
  - 3-year-old female
  - 10-year-old male
- “Self initiated and Self titrated”
- All 3 cases reported:
  - Analgesia
  - Reduced pruritus
  - Reduced blistering
  - Improved wound healing
- One case was completely weaned off opioids

Chelliah MP, et al. Paediatric Dermatology 2018;e224-e227

Received: 21 May 2020 | Revised: 30 July 2020 | Accepted: 31 July 2020
DOI: 10.1111/iwj.13484

ORIGINAL ARTICLE

IWJ WILEY

Topical cannabis-based medicines – A novel paradigm and treatment for non-uremic calciphylaxis leg ulcers: An open label trial

Vincent Maida[1,2] | **Runjie B. Shi**[1] | **Francesco G. T. Fazzari**[3] | **Lydia Zomparelli**[4]

[1]Division of Palliative Care, University of Toronto, Toronto, Ontario, Canada
[2]Division of Supportive & Palliative Care, William Osler Health System, Toronto, Ontario, Canada
[3]Faculty of Medicine, University of Ottawa, Ottawa, Ontario, Canada
[4]Faculty of Science, McMaster University, Hamilton, Ontario, Canada

Correspondence
Vincent Maida, MD, MSc, BSc, CCFP (PC), FRCP (cand), Division of Supportive & Palliative Care, William Osler Health System, 101 Humber College Boulevard, Toronto, Ontario, Canada, M9V 1R8.
Email: vincent.maida@utoronto.ca

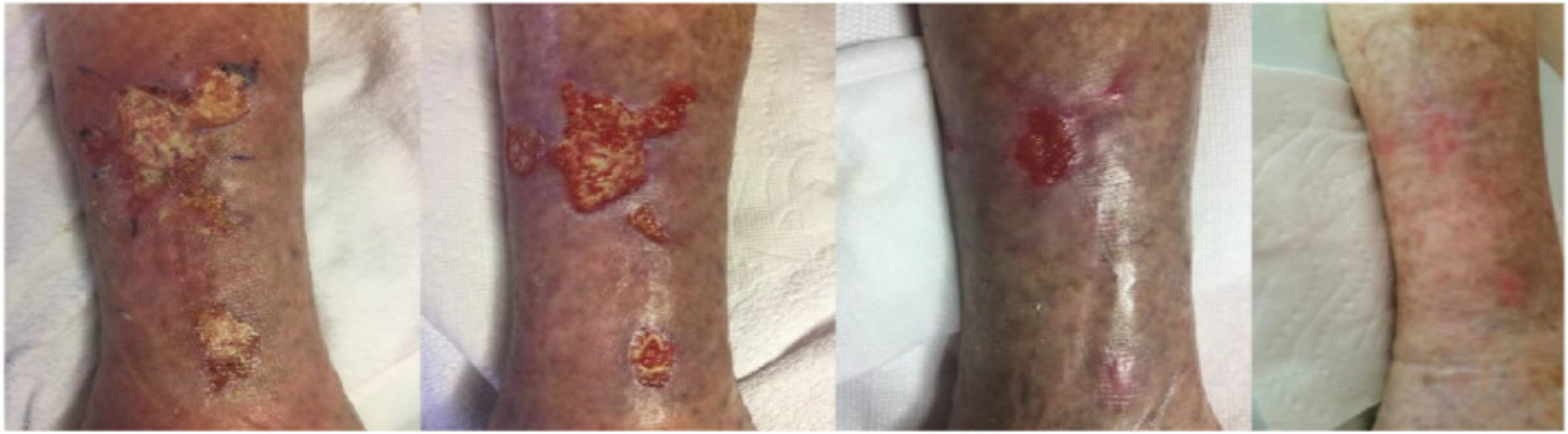
Abstract

Non-Uremic Calciphylaxis (NUC) is a rare condition that often manifests as intractable and painful integumentary wounds, afflicting patients with a high burden of co-morbidity. The Endocannabinoid System (ECS) is a ubiquitous signalling system that is theorised to be dysregulated within wound beds and associated peri-wound tissues. Preclinical research has shown that the dominant chemical classes derived from the cannabis plant, cannabinoids, terpenes, and flavonoids, interact with the integumentary ECS to promote wound closure and analgesia. This is a prospective open label cohort study involving two elderly Caucasian females with recalcitrant NUC leg ulcers of greater than 6 months duration. Topical Cannabis-Based Medicines (TCBM) composed of cannabinoids, terpenes, and flavonoids were applied daily to both the wound bed and peri-wound tissues until complete wound closure was achieved. Wounds were photographed regularly, and the digital images were subjected to planimetric analysis to objectively quantify the degree of granulation and epithelization. Analgesic utilisation, as a surrogate/proxy for pain scores, was also tracked. The cohort had a mean M3 multimorbidity index score of 3.31. Complete wound closure was achieved in a mean of 76.3 days. Additionally, no analgesics were required after a mean of 63 days. The treatments were well tolerated with no adverse reactions. The positive results demonstrated in very challenging wounds such as NUC, among highly complex patients, suggest that TCBM may have an even broader role within integumentary and wound management. This treatment paradigm warrants being trialled in other wound types and classes, and ultimately should be subjected to randomised controlled trials.

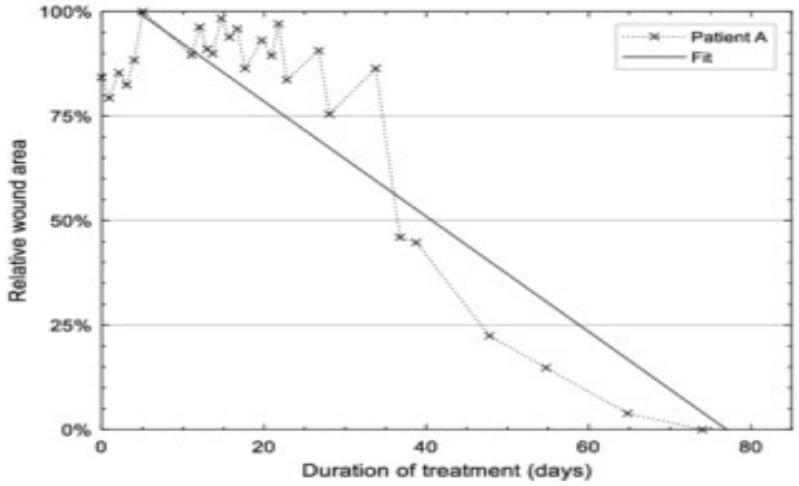
KEYWORDS
topical cannabis-based medicines, non-uremic Calciphylaxis, endocannabinoid system, wound closure, wound-related pain

- Cannabinoid extracts promote wound closure and analgesia
- NUC – very difficult, 45-80% one year mortality rate
- Poor response to current Tx
  - Costly and painful
- Study
  - Prospective open label (n=2)
  - Non-healing NUC > 6 months
  - VS-12 & VS-14 applied
  - Phytocannabinoids, terpenes, flavonoids, hyaluronic acid, aloe vera, quercetin, etc.
- Results
  - Complete closure 76.3 days
  - Relief of WRP
    - Clinically significant pain relief within 0.6 months
    - No analgesics at 2.1 months

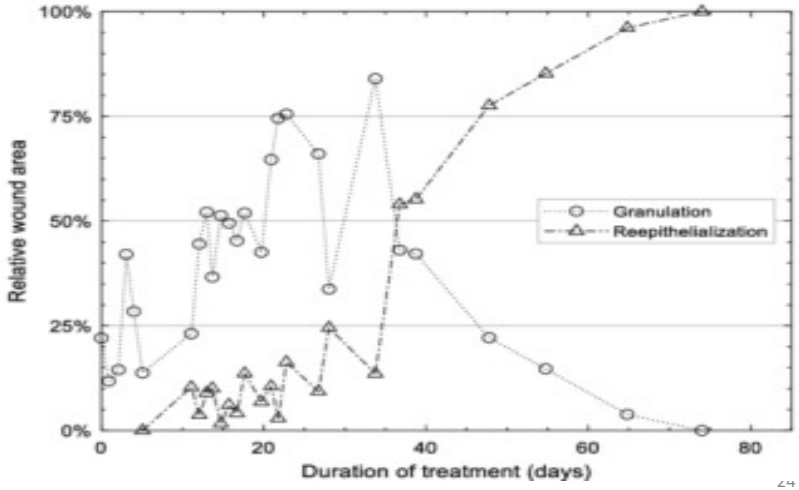
(A) Representative images



(B) Relative wound area analysis



(C) Relative wound composition analysis



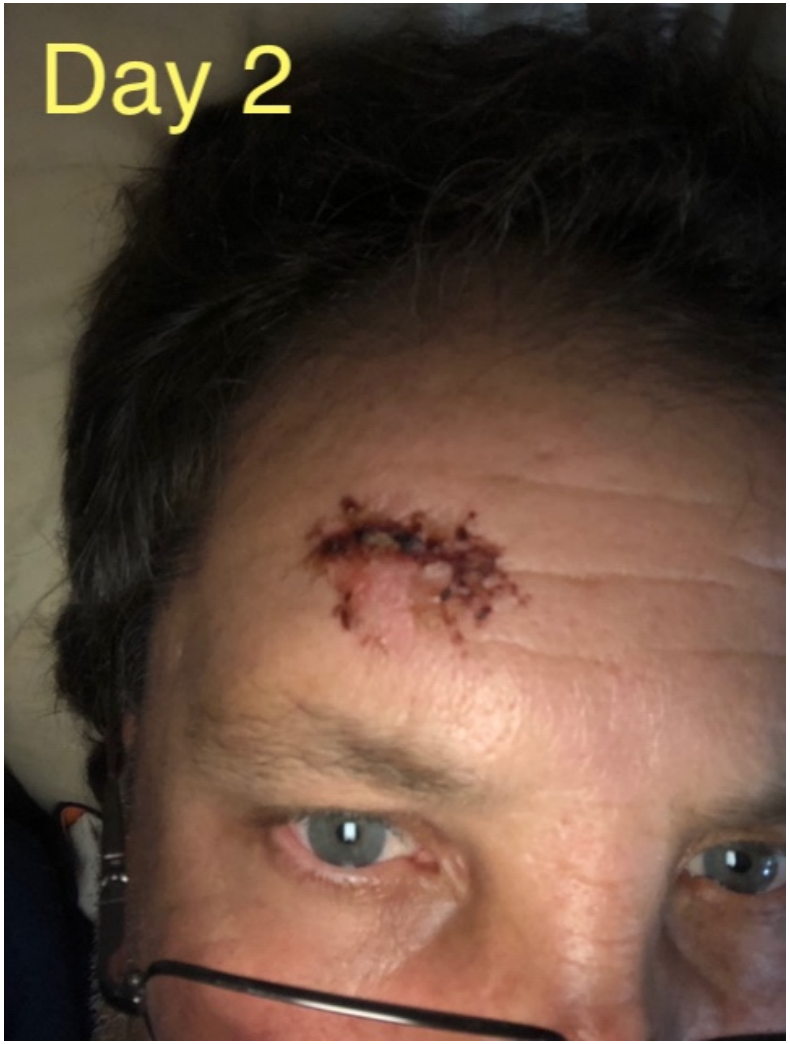
Cannabis Wound Care Solution

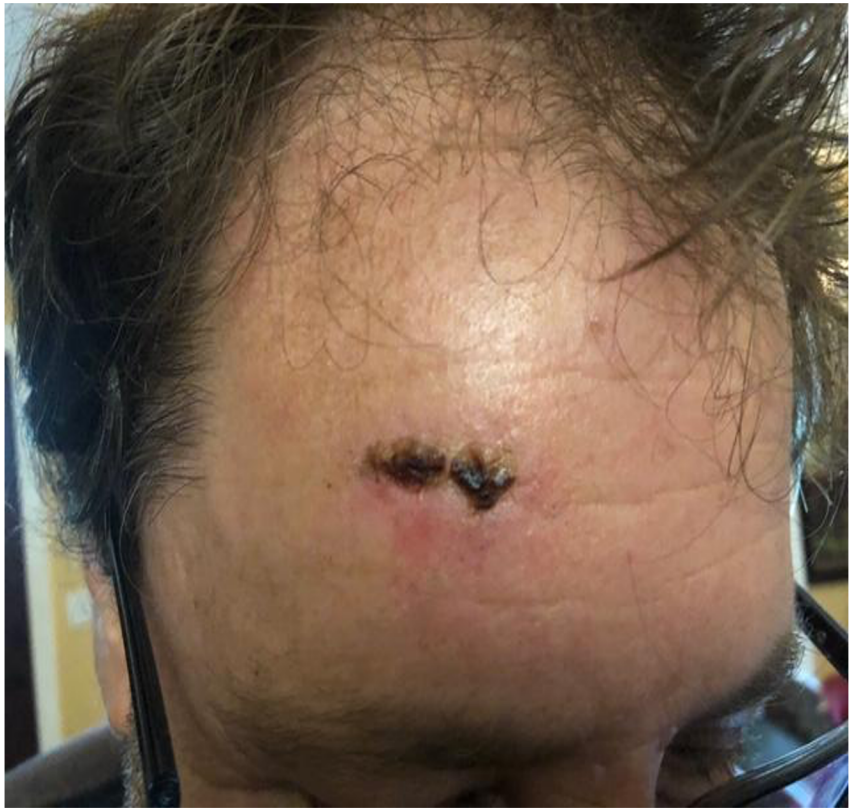
- JG, 52-year-old WM, Cannabis expert & activist
- Tripped and planted face on a concrete stair
- Decided to treat himself, no MD, no stiches
- Used his 1% CBD/THC, API's -> ETOH extraction
- and his 1% CBD spray, API -> Isolate
- **Other ingredients:** Coconut Oil, Grapeseed Oil, Camellia Oil, Pomegranate Oil, Colloidal Silver, CBD Isolate (or 1:1 - 2%), Witch Hazel, Proprietary Blend Of Essential Oils.
- Applied each solution QID, cleaning with H2O2 BID

Day 1

Tripped during work at his nursery and did a face plant into concrete stairs

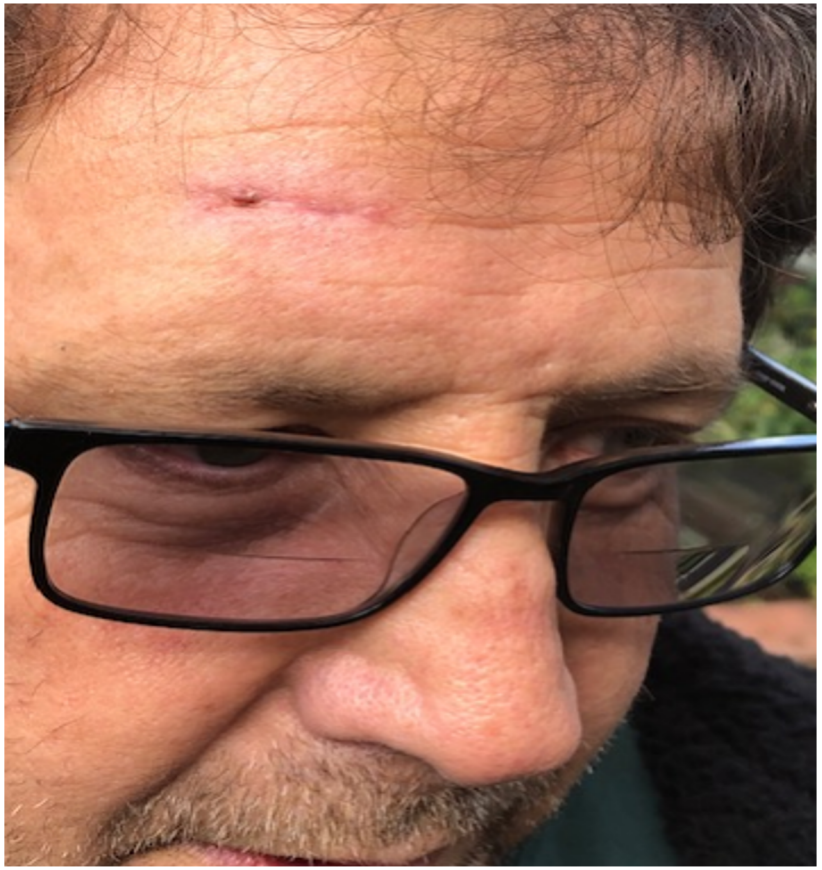
Tx: Cleaned with H2O2 BID, and used a 1% CBD:THC and 1% CBD topical spray QID and did a very poor tape job


Day 2



Day 7

Day 9



PAIN in Older Adults

- Up to 50% of community-dwelling and 80% of nursing-home residents
- Pain affects 80% of patients ≥ 85 Years old
- Common causes of pain in older adults: diabetes, degenerative bone diseases, spinal stenosis, nocturnal leg pain, postherpetic neuralgia, and pain from various chronic diseases
- Pain leads to decreased functional status, increased falls, depression, interrupted sleep, anxiety, agitation, poor QOL

Reuben DB, et al. Geriatrics At Your Fingertips. 19th Ed. NY: American Geriatrics Society: 2017:240

AE's of Pain Treatment in Elderly

- Falls and fractures
- Delirium, sedation and confusion
- Constipation
- Urinary incontinence or retention
- Drug-Drug interactions and polypharmacy
- Addiction or tolerance
- Dizziness and hypotension
- Decreased quality of life (QOL)
- Concerns about opioid-related deaths:
  - >67,367 fatalities in 2018 in USA

    https://www.cdc.gov/drugoverdose/data/statedeaths.html

Medical Cannabis in the Elderly

•Abuhasira R, et al 2018: Prospective study 2736 patients ≥65yo using cannabis (2015-2017)

- Most common indications:
  - Pain (66.6%)
  - Cancer (60.8%)
- Results after 6 months of inhaled cannabis use (n=1186):
  - 93.7% reported improvement in their condition
  - Pain level drop from median of 8 (0-10 NAS) to a median of 4.
  - Number of reported falls was significantly reduced
- Most common adverse events reported:
  - Dizziness (9.7%)
  - Dry mouth (7.1%)
- After six months of cannabis use:
  - 18.1% decreased or stopped opiate use

PCC Case Study - RC

RC is a 76yo WF, a retired pharmacist

- **PMHx**: FMS & OA (1985), Hypothyroid (2003), Achalasia (2016), Lyme (2017), facet degeneration (2017)
- **Chief Complaints**: Insomnia (9.5/10), chronic pain (7/10) S/P fall (back, neck, shoulders)
- **Meds Tried**: NSAIDS (renal, GI AE's), benzos, opiates, gabapentin, pregabalin, LDN, TCA's, SSRI's, TP injections, herbs, nutraceuticals
- **Current Rx/Tx**:
  - LDN 3mg QHS
  - Herbs (controlling Lyme) & nutraceuticals
  - Physical Therapy 2 x week
  - Cannabis

PCC Case Study - RC

- **Cannabis Tx:**
  - Start: CBD buccal troche 12.5mg TID (pain 7/10 to 4/10)
  - Added CBD 25mg Cap (broad spectrum) BID
  - Added THCA-A:THC 6:4 ratio 10mg Cap QHS (sleep 9.5/10 to 3/10)
- Continued to adjust cannabis Tx to current regimen
  - CBD 50mg cap BID (broad spectrum) (3/10)
  - THCA-A/THC 6:4 ratio 30mg QHS (sleep 0-1/10)

PCC Case Study - BJ

BJ is a 73 yo WM, overweight retired Judge

- **PMHx:** Jock in high school, during college worked the loading docs x 7 yrs and wore his joints down, OA (Dx 1991) in toes, ankles, hips. 6', now 225lbs, BMI=30.5 (past up to 255lbs). 6.5 yrs ago, twisted Lt knee (8-9/10). No other medical problems.
- **Chief Complaints:** Pain in joints (7-8/10) and could not get below a (6/10) on meds tried, insomnia (6-7/10)
- **Meds Tried:**
  - NSAIDS max dosing (ibuprofen, naproxen) until renal function declined, then changed to
  - APAP 4gm/day until abnormal LFT's presented
  - Opiates (Norco, Vicodin, etc.) did not like feeling and DC'ed

PCC Case Study - BJ

- **Current Rx/Tx:**
  - Therapeutic dose of fish oil (mol distilled, EPA 3900mg& 1950 DHA/10ml) 5ml BID with a meal (3/10)
  - Cannabis
- **Cannabis Tx** (once won over his trust):
  - Start: CBD 10mg troche buccally TID-QID (2/10) but did not like the ROA/taste
  - CBD 25mg cap QAM moving to 50mg QAM
  - CBD SL Oil (50mg/ml) 100-150mg/day (BID to TID)
  - CBD:THC 18:2 ratio 20mg caps QHS
    - Pain now 0-1/10 and sleeps like a baby again

Chronic Neuropathic Pain

Neuropathic Pain meta-analysis (Mücke M, et al 2018)

- Review of 16 studies with 1750 participants
- Nabiximols (10 studies), Nabilone (2 studies), inhaled cannabis (2 studies), dronabinol (2 studies), placebo (15 studies), analgesic opiate (dihydrocodeine) (1 study)

- Concluded that **cannabis based medicine may increase the number of people achieving 50% or greater pain relief** compared to placebo
- Concluded that **cannabis based medicine has probably increased the number of people achieving pain relief of 30% or greater** compared to placebo

PEA for Facial Postherpetic Neuralgia

- Human Open Label Trial on Facial PHN (n-8)
- PEA (N-palmitoylethanolamide)
  - Cannabinoid receptor agonist
  - Topical application of a PEA cream
- Goal to suppress facial burning pain
- Results
  - Reduction of overall pain and reduced rate of PHN
  - 5/8 patients reported an 87.8% mean reduction in pain
  - No adverse events reported

Phan NG, et al. J Dtsch Derm Ges 2010;8:88-91

Fibromyalgia Syndrome (FMS)

- Observational, retrospective, survey study (n=56) 28 cannabis users vs 28 nonusers (>90%F) with moderate to severe Sx of FMS that were resistant to pharmacological Tx. Mean age: 50, matched
- **Methods**:
  - 11% smoked, 41% orally, rest used both routes of administration
  - Visual Analogue Scales (VAS) used for perceived benefits
  - Fibromyalgia Impact Questionnaire (FIQ), Pittsburgh Sleep Quality Index (PSQI), Short Form 36 Health Survey (SF-36)
- **Results**: Significant improvement of Sx's of FMS in patients using cannabis in this study although there was variability of patterns
- **Conclusion**:
  - Endocannabinoid and Stress Response System is involved in FMS
  - Cannabinoid Tx demonstrates a benefit on FMS symptomatology
  - Further studies regarding efficacy of cannabinoids in FMS is warranted

Fiz, J et al. 2011. doi:10.1371/journal.pone.0018440

Fibromyalgia Syndrome (FMS), Fiz et al. (2011)

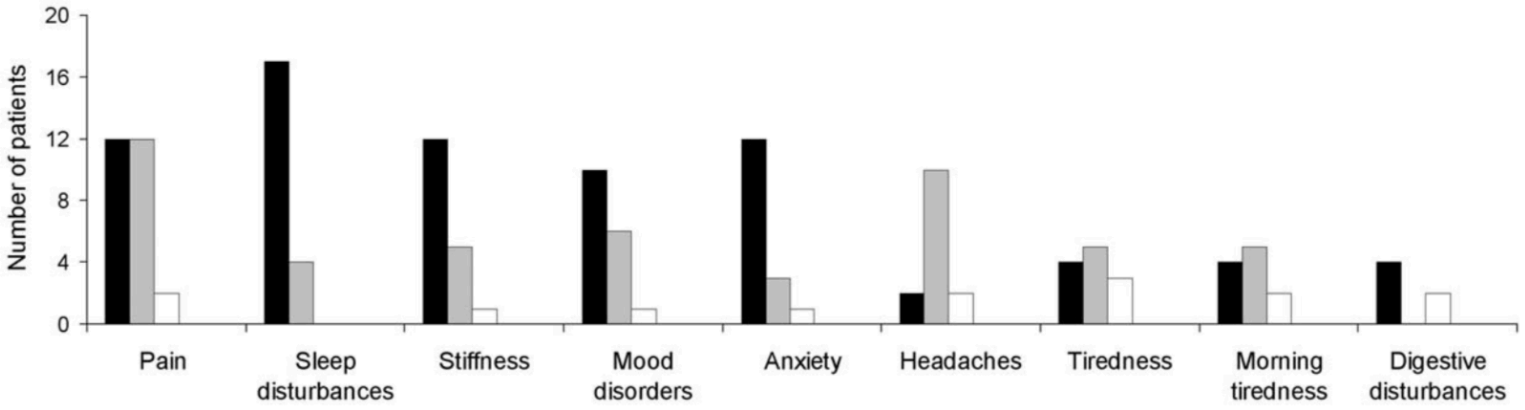


Figure 1. Symptoms and perceived relief reported by FM patients using cannabis. Note: Perceived relief was recorded using 5-point Likert scale (strong relief, mild relief, not change, slight worsening, great worsening). Black bars: strong relief; grey bars: mild relief; white bars: not change.

doi:10.1371/journal.pone.0018440.g001

Fibromyalgia Syndrome (FMS), Fiz et al. (2011)

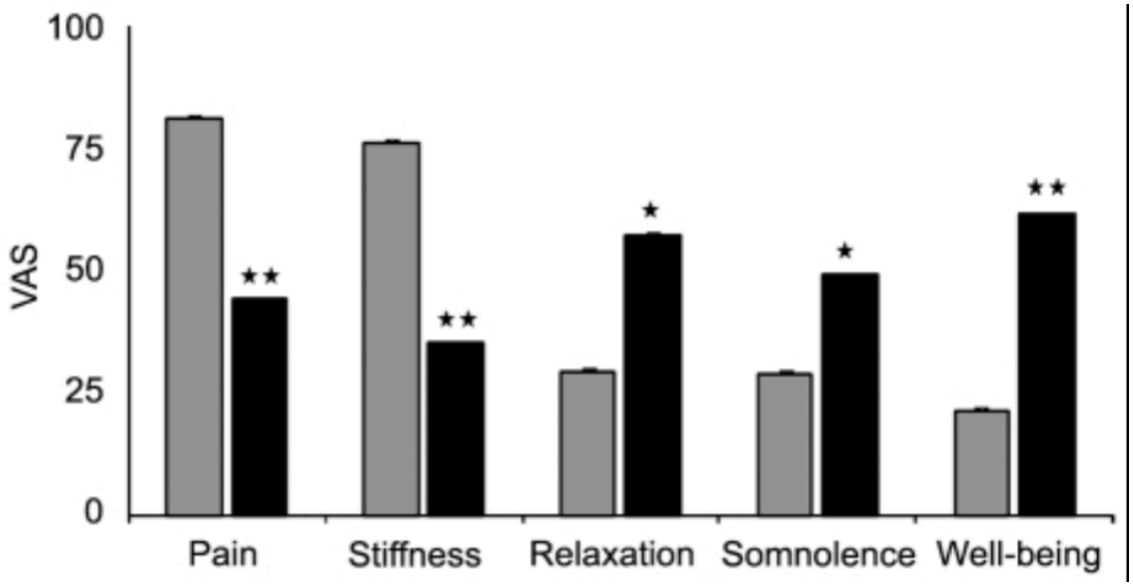


Figure 2. Perceived effects of cannabis self administration.

Note: Perceived benefits of cannabis recorded by patients on a range of symptoms using 100-mm VAS scales before and at 2 hours of cannabis consumptions. Grey bars: pre-cannabis; black bars: post-cannabis. * * = $p<0.001$; * = $p<0.05$.

doi:10.1371/journal.pone.0018440.g002

Fibromyalgia Syndrome (FMS)

Randomized, double-blind, placebo-controlled trial of nabilone in FMS

- **Methods**:
  - Nabilone vs Placebo, cohorts matched, n=40
  - Nabilone 0.5 up to 1mg BID titrated up over 4 weeks
- **Results:**
  - Nabilone group had statistically significant decreases in:
  - **Pain** in the VAS (-2.04, P < .02), **FIQ** (-12.07, P < .02) and **anxiety** (-1.67, P < .02)
  - No significant improvement in the placebo group
- **Conclusion:** Nabilone appears to be beneficial, well-tolerated, with significant benefits in pain relief and functional improvement for FMS

Skrabek et al, J Pain. 2008 Feb;9(2):164-73.

Fibromyalgia Syndrome (FMS)

- Characteristics of medical cannabis usage in FMS
- Follow-up from previous study, n=121
- Mean age=45, 73% Female
- Mean cannabis consumption = 28.6gm/month
- Most popular species for daytime was "Alaska" and "Erez" for night-time supplied by Tikun Olam
- Mean improvement in sleep and pain was slightly more than 77%
- 47% of all the participants stopped any other treatment for fibromyalgia and 51% reduced the dose or the number of other medications for fibromyalgia

Habib, et al. Harefuah 2020 May;159(5):343-348

Objective

Determine benefit of a THC-rich full spectrum oil on Sx & QOL in 17 Female FMS

Methods

8 wk, FIQ/visit (5), THC/CBD 24.44mg/0.51mg/ml Olive
Starting Dose: 1gtt QD, titrate by 1gtt/day q 10 days

Results

Mean dose = 3.6gtts/day
FIQ baseline similar/cohort
P vs Cannabis (P=0.005)
Cannabis pre/post P=<0.001)

Conclusions

Low cost, well-tolerated Tx
Better QOL, reduced Sx

Pain Medicine, 21(10), 2020, 2212–2218
doi: 10.1093/pm/pnaa303
Original Research Article

OXFORD

PAIN & SUBSTANCE USE DISORDERS

Ingestion of a THC-Rich Cannabis Oil in People with Fibromyalgia: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial

Carolina Chaves, MD,* Paulo Cesar T. Bittencourt, MD, MSc,† and Andreia Pelegrini, PhD‡

*Public Health School, Municipal Health Secretary, Florianopolis, Brazil; †Department of Internal Medicine, Federal University of Santa Catarina, Florianopolis, Brazil; ‡Department of Physical Education, Santa Catarina State University, Florianopolis, Brazil

Correspondence to: Paulo Cesar T. Bittencourt, MD, MSc, Department of Internal Medicine of Universitary Hospital, Federal University of Santa Catarina, Prof. Maria Flora Pausewang St, Trindade 88036-800, Florianopolis. Tel +55-48-32719106; Fax: +55 (48) 3721-9100; E-mail: paulo.bittencourt@ufsc.br.

Funding sources: There was no funding source for this study.

Conflicts of interest: The authors declare no competing interests.

Abstract

Objective. To determine the benefit of a tetrahydrocannabinol (THC)-rich cannabis oil on symptoms and quality of life of fibromyalgia patients. **Methods.** A double-blind, randomized, placebo-controlled clinical trial was conducted for eight weeks to determine the benefit of a THC-rich cannabis oil (24.44 mg/mL of THC and 0.51 mg/mL of cannabidiol [CBD]) on symptoms and quality of life of 17 women with fibromyalgia, residents of a neighborhood with a low socioeconomic profile and a high incidence of violence in the city of Florianopolis, Brazil. The initial dose was one drop (~1.22 mg of THC and 0.02 mg of CBD) a day with subsequent increases according to symptoms. The Fibromyalgia Impact Questionnaire (FIQ) was applied at pre- and postintervention moments and in five visits over eight weeks. **Results.** There were no significant differences on baseline FIQ score between groups. However, after the intervention, the cannabis group presented a significant decrease in FIQ score in comparison with the placebo group ($P = 0.005$) and in comparison with cannabis group baseline score. ($P < 0.001$). Analyzing isolated items on the FIQ, the cannabis group presented significant improvement on the "feel good," "pain," "do work," and "fatigue" scores. The placebo group presented significant improvement on the "depression" score after intervention. There were no intolerable adverse effects. **Conclusions.** Phytocannabinoids can be a low-cost and well-tolerated therapy to reduce symptoms and increase the quality of life of patients with fibromyalgia. Future studies are still needed to assess long-term benefits, and studies with different varieties of cannabinoids associated with a washout period must be done to enhance our knowledge of cannabis action in this health condition.

Case Study Migraines/Headaches

Brief History and Target Symptomatology:

AG, 28 YO WF with daily migraines, worse around menstrual cycle. Duration for chronic migraines 3 years; daily the last 7 months.

Previous and Current Conventional Therapies:

Prior doctors prescribed pain medication and preventatives that caused bad side-effects with minimal relief. May 1, 2016 began taking 12.5mg CBD buccal troche three times per day and adding a THCA-A/THC 6:4 ratio 10mg capsule at bedtime to help with sleep.

Clinical Responses to treatment:

By day 2, AG experienced reduced migraine NAS from 7-8/10 down to 4/10. By end of month was having days with no migraines and now takes as needed when she has a breakthrough migraine.

Chronic Noncancer Pain

Crowley, et al. Frontiers in Neuro 2018 Aug
(doi: 10.3389/fnins.2018.00564)

- Observational, longitudinal study over 12 weeks (n=49)
- Primary diagnosis: Chronic noncancer pain
- Buccal route of administration of a standardized delivery method of cannabis extracts
- Onset of analgesia: 5 to 40 min
- Average reduction in PI-NRS score: 4.9 $\pm$ 2.0 ($p<0.0001$)
- 31 subjects were using opiates, 26 (84%) reduced or discontinued use with no reported symptoms of withdrawal
- 100% reported feeling an improvement in a global rating scale

Other Chronic Pain Conditions

- Blake et al, Rheumatology (Oxford) 2006 Jan;45(1):50-2.
- Rheumatoid Arthritis (n=58)
  - Randomized, double-blind, placebo controlled 5 wk study
  - 31 Sativex vs 27 placebo
  - Sativex patients had statistically **significant improvements in pain on movement, pain at rest, and sleep** using SF-MPQ and DAS28 (measure of disease activity)
  - No effect on morning stiffness but baseline scores were low
  - AE mild or moderate
  - No patients withdrew

Cannabis, Back Pain, Chronic Opioid Users

- Takakuwa et al. Canna Canna Res 2020 Sep 2;5(3):263-270.
- Retrospective cohort study, Dx LBP (M54.5), on opioids, n=61
- **Methods**
  - Single practice, CR 10/2018, 50.1 mean age, 62% male
  - Median yrs on opioids=3, MME=21mg/day (range=1.1-500), chronic users (n=30), intermittent users (n=31)
  - Median cannabis 1.45gm/day (range=0.01-18.7g) 72% smoked, also used multiple ROA & forms (i.e. edibles, etc.)
- **Results**
  - 50.8%(n=30) stopped opioids, mTime=6.4yrs (range=0.4-15.7)
  - N=29, 9 reduced dose, 3 same dose, 17 increased dose
  - No variables collected predicted who stopped opiates, but higher cannabis usage had greater success at stopping opiates

Chronic Pain and Opioid Use (in press)

- Meng H, et al. Can J Anaesth. 2021 Jan 20.[in press]
- **Patient-reported outcomes in those consuming medical cannabis: a prospective longitudinal observational study in chronic pain patients**
- In an observational study with 757 pain patients about one third of patients remained on cannabis for 6 months and reported reduced pain intensity.
- data from community-based cannabis clinics in Ontario. At six and 12 months, 230 and 104 of participants were followed up, respectively.
- The proportion of cannabis users who reported using opioids decreased by half, from 40.8% at baseline to 23.9% at 12 months. Pain intensity and pain-related interference scores were reduced, quality of life and general health symptoms scores were improved compared with baseline.

Source: **IACM-Bulletin of 31 January 2021**

Other Chronic Pain Conditions

- Ware et al, J Pain. 2015 Dec;16(12):1233-1242
- 215 cannabis users vs. 216 controls, followed for 1 year (101 lost to follow-up) with Chronic pain from 7 clinics across Canada
- 12.5% herbal cannabis was smoked, vaped or taken orally (average: 2.5gm/day)
- POM: No increase risk of serious adverse events with cannabis
- 2ndSOM: lung, neurocognitive & endocrine function, hematology, biochemistry
- Both groups experienced improved neurocognitive function
- Significant improvements in the cannabis users (2ndEOM):
  - Pain intensity
  - Measures of sensory components of pain
  - Symptom distress
  - QOL
  - Mood disturbance

Chronic Cancer & Noncancer Pain

- Schmerz. 2019 Oct;33(5):399-406. doi: 10.1007/s00482-019-0383-1
- Pain physicians survey on prescribed cannabis Tx's (n=13/20)
- Dx: Chronic cancer and noncancer pain
- 136 patients received prescriptions for dronabinol (1.9% total patient population)
- Most frequent reason:
  - Failure of established treatments (73%)
  - Desire of patient (63%)
- Types of pain:
  - Nociceptive (35%), neuropathic (34%), nociceptive & neuropathic (29%), nociplastic (13%)
- Results:
  - 71% were responders (clinically relevant reduction of pain or other symptoms)
  - 29% discontinued treatment (lack of efficacy or adverse events)

Cancer Pain

Schleider et al 2018: doi.org/10.1016/j.ejim.2018.01.023

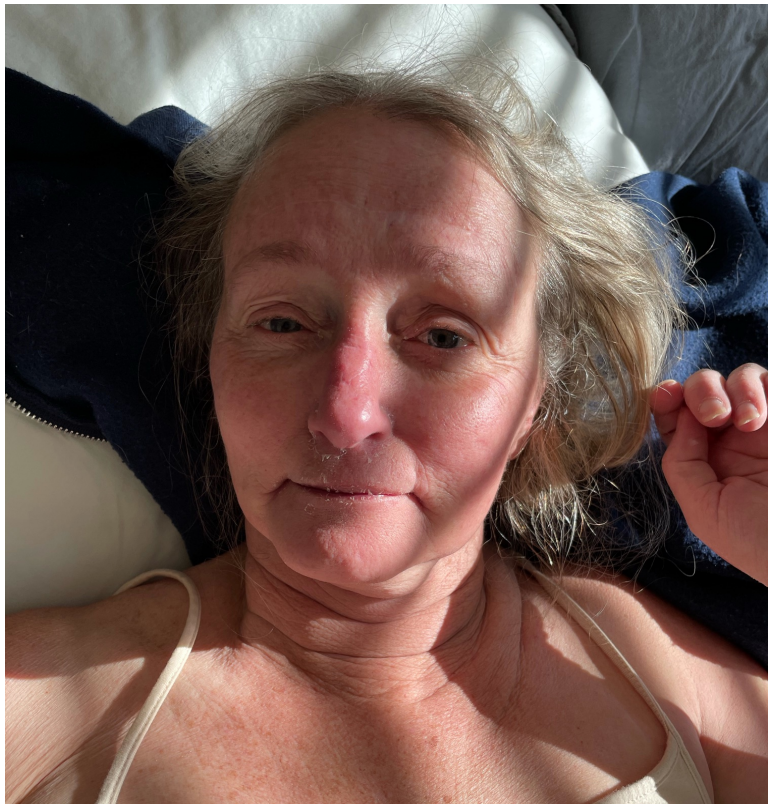
- 2970 cancer patients were treated in Israel 2015-2017
- 1144 patients surveyed about pain
  - Prior to cannabis treatment 53% had a pain score of 8/10 pain
  - At 6 months 4.6% of patients had an 8/10 pain score
- 1165 patients surveyed about QOL
  - Prior to cannabis treatment 19% reported a Good QOL
  - At 6 months 69.5% reported a Good QOL
- 33.9% on opioids prior to cannabis Treatment
  - At 6 months of cannabis treatment
  - 36% discontinued, 10% decreased, 51% same dose, 1% increased
  - 1% not on opioids (n=32)

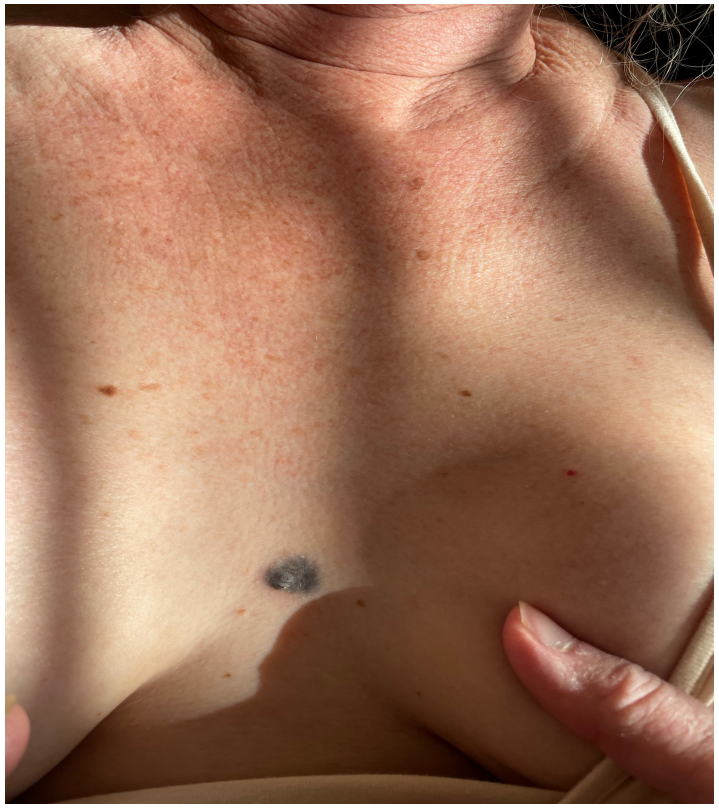
PCC Case Study - MEV

MEV is a 60 yo WF that works for the Nevada Farm Bureau and avid horseback rider. Spent lots of years sunbathing as well.

- **PMHx:** 2010 HTN, 2016 S/P removal of BRAF+ cutaneous melanoma with clear margins, 8/2020 pancreatitis, 12/2020 return of BRAF+ metastatic cutaneous melanoma (V600E)
- **FHx:** Younger bother died from melanoma (no details)
- **Chief Complaints:** chemotherapy induced N/V (9/10), loss of appetite (10/10), pain (7/10), limited mobility (8-9/10) and exhaustion (8-9/10)

MEV 01/30/21 Case Study





PCC Case Study - MEV

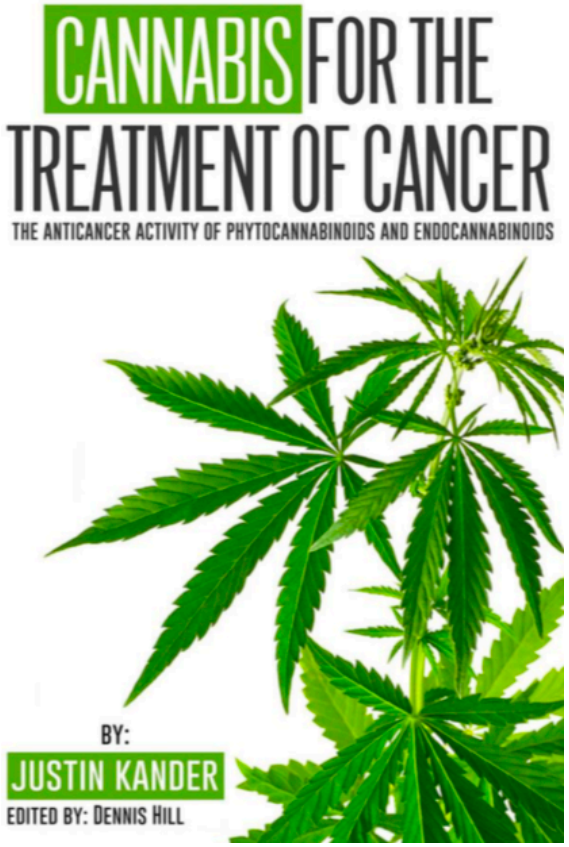
- **Meds Rx/meds tried:**
  - Braftovi/Mektovi protocol (BMP)
  - Amlodipine 10mg QD, Hydralazine 25mg Q6H
  - Oxycodone 5mg QAM, 10mg QPM (6/10)
  - Anti-emetics (5/10)
- Current Rx/Tx:
  - Braftovi/Mektovi protocol (BMP)
  - Amlodipine 10mg QD
  - Oxycodone 10mg QAM, 10mg QPM
  - Cannabis
- Cannabis Tx (1/13/21):
  - Started CBD:THC SL oil 1:5 ratio 1mg/5mg/ml; ½ -1 DF QHS
  - Family states within 12 hrs a noticeable difference. Able to eat, and move better
  - 1/16/21: Opiate DC'ed, on cannabis & chemo and can walk to car

Cancer Symptoms

Bar-Sela et al, Evid Based Complement Alternat Med. 2013; 2013: 510392

- 106 patients, all cancer or anti-cancer treatment-related symptoms evaluated in patients with continuous cannabis use, two interviews 6 to 8 weeks apart
- Patients used whole plant cannabis from Israeli dispensaries (up to 30gms/month)
- **Nausea, vomiting, mood disorders, fatigue, weight loss, anorexia, constipation, sexual function, sleep disorder, itching, and pain had significant improvement ($p < 0.001$)**
- 70% using pain medication at start → 43% reduction in dosing (n=31)
- 51% had severe pain at first interview → 25% at second interview
- 33% reduced dosing of antidepressants and/or anxiolytics (n=21)
- Only significant side effect was memory lessening

Cannabinoids as Anticancer Agents



Great Reference – Free

Science and case studies

Fifth Edition, July 2018

https://www.dropbox.com/s/rk0vbpcjz3pbehe/Cannabis%20and%20Cancer.pdf

Breast Cancer and Cannabis: Cautions and Considerations when Recommending Medicinal Cannabis for Patients with Breast Cancer

Potential benefits and risks of managing Breast Cancer Symptoms and Treatment Side Effects with Medicinal Cannabis

Presented by: Kristin Wohlschlagel, RN and Elizabeth Sherwood, RN, ANP, MS ~~ Specializing in Oncology, Hospice and Palliative Care
September, 2019: Pasadena, California ~~ CannMed Conference

This information is based on:

- Observations and interviews with more than 1,200 patients with Breast Cancer who use(d) medicinal cannabis
- The majority of patients had breast cancer but we also interacted with hundreds of patients with other cancers as well.
- Pre-clinical and clinical research articles
- Personal communication with top Researchers and Practitioners from around the world and more than 2 years of intense focus
- Ongoing formal survey efforts to determine Patterns of Use & Results; Challenges/Benefits; Information Sources used, and more.

Clinical Observations:

- Tens of thousands of cancer patients are using medicinal cannabis, often without any guidance from healthcare practitioners
- Most clinicians, even those recommending cannabis, and patients reported believing there were no real risks of adverse drug interactions.
- With lower oral dosing of no more than 75 to 100 mg of CBD, and/or 25 mg of THC/THCa per day, or *moderate inhaled doses*, interactions appear minimal, if at all. Most appeared to have *no* adverse effects, only benefits.
- **Medicinal Cannabis, used with some *reasonable* caution, provided profound benefits to most patients, including often *extremely* effective symptom control of:**

  Pain, (especially nerve and bone); Insomnia; Nausea; Anxiety; body aches and joint inflammation. It appears to also help patients to better tolerate their conventional side effects, thereby assisting completion of their conventional treatment protocol or treatment plan.

Patterns of clinical cancer regression or suppression responses are emerging among many cancer subtypes. Patterns appear to closely match what subtypes pre-clinical researchers indicated *may* be possible.

- ***Not all breast cancer subtypes appear equally vulnerable to anticancer mechanisms of cannabinoids, especially to THC and/or THCa.***
- ***Most cancers are appearing somewhat vulnerable to significant dosing of at least CBD but the THC/THCa dosing needs careful consideration and monitoring.***
- **Approximately 30-50% of Patients dosing with large amounts of THC, above about 50-100 mg per day, *reported faster tumor growth within 6 to 8 weeks, which slowed within 1 month of reducing THC and/or THCa dosing to 25 mg or less per day.***
  - *Perhaps they suppressed their Helper T-cell proliferation enough to allow for faster tumor growth *and* their particular cancer subtype was not vulnerable to THC and/or THCa[1]?*
- **Patterns of response provide clinical information and foundations for clinical research.**

Breast Cancer and Cannabis: Drug interaction Potential:

- **Cannabidiol (CBD & CBDa) may potentially act as a moderate inhibitor of at least: CYP2C19, CYP2D6 and CYP3A4 as well as p-Glycoprotein transport.**
  - **Most notably, interactions with CYP3A4 appear to begin happening at about 75 mg of oral CBD per day, with stronger effects seen at 100+ mg per day.**
- **THC & THCa may potentially act as a moderate inhibitor of at least CYP2C9, CYP2C19, CYP3A4 as well as p-Glycoprotein transport.**
  - Interactions with CYP450 appear to begin happening at about 50 to 100 mg of oral THC per day, but seems much less certain.

Apparent drug interactions observed, using large oral doses with,

- Blood thinners such as **Warfarin, Coumadin, Lovenox (increased bleeding times observed)**
- **Tamoxifen** concern: This is a prodrug and requires CYP450 metabolism to its more effective metabolites. Therefore use with large, especially oral, doses of cannabis medicines could interfere with metabolism.
- **Oral breast cancer treatments such as: palbociclib (Ibrance), ribociclib (Kisqali) as we repeatedly observed:**
  - **Decreased neutrophils; Increased fatigue and/or Elevated liver enzymes, likely due to CYP3A4 inhibition of clearance of these drugs, which are toxic to the liver; Patients were using over about 75 to 100 mg CBD orally per day, when this pattern appeared.**

Considering the use of Cannabis with Immunotherapies:

Because most commonly used immunotherapies depend on robust Helper T-cell proliferation for anticancer effects, avoid or minimize concurrent use with immunotherapies, such as PDL1 inhibitors, due to potential suppression of Helper T-Cells with high doses of THC/THCa, *especially if their pathology testing showed very high chance of immunotherapy potential benefit.*

Common immunotherapy drug names are: **Pembrolizumab (Keytruda); Nivolumab (Opdivo) and Atezolizumab (Tecentriq).**

The immunosuppressive effects of high-doses of cannabis must be outpaced by the anticancer effects of cannabis dosing[1]:

- **This appears under-appreciated by most patients and even their recommending cannabis healthcare practitioners.**
- Researchers studying anticancer effects of cannabinoids clearly explain this immunosuppression risk[1]
- Medicinal cannabis is often extremely effective in managing autoimmune diseases, which involve abnormal and harmful Helper T-cell proliferation. Some are getting profound benefits when higher doses of THC/THCa are used to suppress Helper T-cell proliferation.
- **But for *some* cancer patients, this same effect appears to allow for faster tumor growth. Observed with THC & THCa.**
- **Reassessment of tumor regression or progression must be done within 6 to 8 weeks of starting any high dose cannabis protocol, as with *any* therapy. Continued monitoring is crucial, as adjustments may be needed.**

Best results with Breast Cancer treatment appear most often when both optimized conventional and cannabis therapies are carefully used together, rather than exclusively as an "either/or" option. *Unfortunately, many using medicinal cannabis in the hope of treating their cancer do not realize this.*

- In some cases, patients reporting significant cancer/tumor regression after using large doses of cannabis *appear to be only suppressing at least some remaining cancer cells and the cancer progresses again after cannabis dosing is stopped.*
- If cannabis dosing is working and is well tolerated by the patient, it may need to be continued at some significant level to continue to suppress their cancer. There appear to be no valid "easy" ways to determine best "maintenance" dosing.
- We urgently need to begin considering "what's next" for these patients, as there appears to be very strong potential benefit in combination therapies.

Breast Cancer Subtypes and patterns of Cannabinoid Therapy Response (CTR):

HER2-Positive Ductal Breast Cancer (regardless of Hormonal status):

- **Appears most likely to benefit from doses of THC above 25 to 50 mg per day. Observed likelihood of benefit: 80%**
- **Appears compatible and to enhance effectiveness of Trastuzumab (Herceptin); Trastuzumab plus DM1 (Kadcyla);**
- **Because most anti-HER2 drugs do not cross the Blood Brain Barrier (BBB) yet HER2+ Breast Cancer often does, the potential benefits of cannabinoids for these patients seems most urgently deserving of Clinical Trials[2].**

Triple Negative Ductal Breast Cancer (TNBC):

- **Appears somewhat likely to benefit from doses of THC above 25 to 50 mg per day. Observed likelihood of benefit: 40-50%**
- **This very aggressive subtype of Breast Cancer has fewer good treatment options.**
- **Many patients with TNBC are using Cannabis in the hope for benefit and to allow them to reduce their need for repeated chemotherapy protocols, as TNBC recurs often. Preclinical researchers confirm there may be CB2 overexpression in some[3].**

Estrogen Receptor (ER)-Positive but Progesterone Receptor (PR)-negative (or low percentage) that is also HER2-Negative Ductal Breast Cancer:

- **Appears somewhat likely to benefit from doses of THC above 25 to 50 mg per day. Observed likelihood of benefit: 40-50%**

ER-Positive and PR-Positive (high percentages for both) that is also HER2-Negative, Ductal Breast Cancer:

- **Appears LEAST likely to benefit from doses of THC above 25 to 50 mg per day. Observed likelihood of benefit: 10%**
- **At least 30 women, observed over a span of 3 years, reported clearly that their tumor activity INCREASED dramatically after about 6 weeks of THC doses above 50-100+ total mg. per day, regardless of CBD dosing or any "ratio" of THC and CBD.**
- **Pre-clinical researchers published some limited data showing this subtype of breast cancer may overexpress Cannabinoid Receptor 2 (CB2) much less often than other subtypes[3].**
- **Most common subtype of Breast Cancer therefore this information is important to consider.**

Inflammatory Breast Cancer and Lobular Breast Cancer:

- **Rare subtypes without enough observations to provide any patterns of response to cannabis yet.**

Conclusion and Steps Forward:

- Cannabis appears to have a very promising role in Breast Cancer care but there is primarily pre-clinical research at this time.
- Pathology report details that seem associated with more THC vulnerability are Grade 3 as well as HER2-Positive status.
- As we strive to serve our patients, collaboration among researchers and clinicians will ideally lead to better outcomes as guidelines for care become more established.
- Acknowledging that all medicines, including plant-based medicines, may interact is a foundation of good medicine.
- Collaboration, Education and Advocacy are required to move the benefits of cannabis into conventional oncology treatment.
- Combination therapies may provide the best outcomes.

We are exploring various assessment methods, for:

- HER2 Activity -- with serum HER2 Elisa or other testing in addition to common cancer antigens, to assess initial and ongoing therapeutic responses to any therapy used, cannabis or conventional. This is in addition to standard imaging techniques, such as CT-PET scans. Valid assessment methods assist with monitoring cancer's response to cannabis, just like any other therapy.
- Pathology report details from biopsies and Genomic tumor analysis for eventual better understanding of which may indicate potential cannabinoid efficacy.

Disclaimer: Please do not consider any information presented herein to be medical advice or to encourage reckless self-treatment with large doses of medicinal cannabis preparations. The goal of this presentation is educational and is intended for Healthcare Practitioners and Researchers. Any reference to THC, THCa or CBD actually means THC-rich or CBD-rich cannabis medicines as I did not observe anyone knowingly using only isolated cannabinoids.

I am deeply grateful for the brave:

- **Patients and Support Groups, Researchers, Physicians and Nurses**
- **Dedicated Medicinal Cannabis Advocates & Medicine Makers around the world who have generously shared their knowledge & experiences with me.**

Without their determined efforts, often at great personal risk, none of this would be possible.

References:

1. Anticancer mechanisms of Cannabinoids. Velasco G, Sánchez C, Guzmán M. *Current Oncology*. 2016;23(Suppl 2):S23-S32. doi:10.3747/co.23.3080. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4791144/
2. Therapeutic targeting of HER2–CB2R heteromers in HER2-positive breast cancer. Sandra Blasco-Benito, Estefanía Moreno, Marta Seijo-Vila, Isabel Tundidor, Clara Andradas, María M. Caffarel, Miriam Caro-Villalobos, Leyre Urigüen, Rebeca Diez-Alarcia, Gema Moreno-Bueno, Lucía Hernández, Luis Manso, Patricia Homar-Ruano, Peter J. McCormick, Lucka Bibic, Cristina Bernadó-Morales, Joaquín Arribas, Meritxell Canals, Vicent Casadó, Enric I. Canela, Manuel Guzmán, Eduardo Pérez-Gómez, Cristina Sánchez. Proceedings of the National Academy of Sciences Feb 2019, 116 (9) 3863-3872; DOI: 10.1073/pnas.1815034116 https://www.pnas.org/content/116/9/3863/tab-article-info
3. Δ9-Tetrahydrocannabinol Inhibits Cell Cycle Progression in Human Breast Cancer Cells through Cdc2 Regulation. María M. Caffarel, David Sarrió, José Palacios, Manuel Guzmán and Cristina Sánchez. **DOI:** 10.1158/0008-5472.CAN-05-4566 Published July 2006. https://cancerres.aacrjournals.org/content/66/13/6615

Kristin Wohlschlagel

Kristin Wohlschlagel, RN and Elizabeth Sherwood, RN, ANP, MS, are members of the Oncology Nurses Society and the American Cannabis Nurses Association.
They are Oncology & Hospice Nurse Navigators, supporting many with metastatic and treatment-resistant disease, especially those with rare subtypes of cancer with no effective conventional therapies available to them. We work with patients, families and their Oncology and other Healthcare Teams.

Contact information: Email: kristin@nursekristin.com or Phone: 808-747-3507 and liz@nursekristin.com or Phone: 919-260-6058

Liz Sherwood

PCC Case Study Prostate Cancer

Brief History and Target Symptomatology:

MP, a 68yo WM diagnosed 2 years prior with prostate cancer, Grade 1, G3 (cT2a,PSA 9.0) and anxiety 8/10 requesting trial of CBD for anxiety.

Previous and Current Conventional Therapies:

Refused radiation, tried freezing cancer resulting in Tx failure and created more issues. Since then, no treatments or diet changes occurred. He has a family history of cancer.

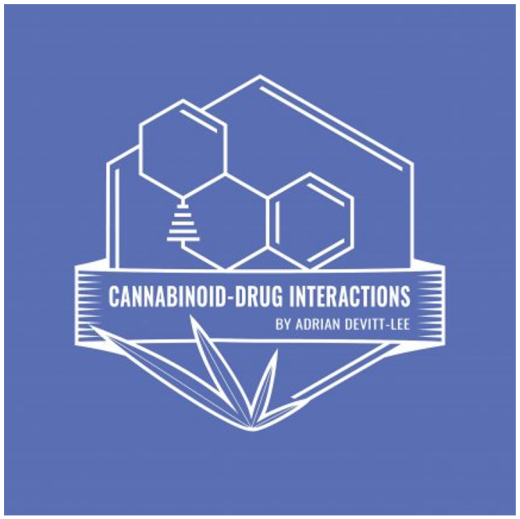
Clinical Responses to treatment:

Began taking 12.5mg CBD troche three times per day. After 7 days with minimal relief from anxiety, increased dose to 12.5mg in the morning, 25mg at noon and 12.5mg in the evening. Blood work at day 24 showed PSA number dropped by half. Continued 50mg per day and each month PSA numbers kept falling until the third month PSA = 0.9. A biopsy, blood work and cat scan confirmed complete remission with no detectable CA

420tv.com

- https://420tv.com/show/medical-marijuana-miracles/season-1

- PCC patient interview/story of a survivor of stage 4 metastatic ovarian cancer using cannabis after told to go home and die.



ProjectCBD.org

Free downloadable "Primer on Cannabinoid-Drug interactions"

Information Sources/organizations

- Society of Cannabis Clinicians
  - https://www.cannabisclinicians.org
    - Monthly Journal club, Quarterly meetings
- International Association for Cannabinoid Medicines (IACM)
  - https://www.cannabis-med.org/index.php?lng=en
    - Outstanding Bulletin
- International Cannabinoid Research Society (ICRS)
  - https://icrs.co/index.html
- International Society of Cannabis Pharmacists (ISCPh)
  - https://cannabispharmacist.org
- www.ProjectCBD.org
- www.leafly.com

THANK YOU!

drkent@trokie.com