Cannabis treatment in neurology

JERZY P. SZAFLARSKI, MD, PHD
PROFESSOR OF NEUROLOGY, NEUROBIOLOGY, AND NEUROSURGERY
DIRECTOR, UAB EPILEPSY CENTER
UAB HEERSINK SCHOOL OF MEDICINE

Disclosures

- Funding: NIH, NSF, DoD, State of Alabama, Shor Foundation for Epilepsy Research, UCB Pharma Inc., NeuroPace Inc., Greenwich Biosciences Inc., Biogen Inc., Xenon Pharmaceuticals, LivaNova Inc., Serina Therapeutics Inc., and Eisai, Inc.
- Consulting/Advisory Boards: Greenwich Biosciences Inc., NeuroPace, Inc., Serina Therapeutics Inc., AdCel Biopharma Inc, iFovea Inc, LivaNova Inc., UCB Pharma Inc., SK Lifesciences Inc., and medico-legal services.
- Paid Editorial Work: Epilepsy & Behavior Reports (Editor-in-Chief),
- Dr. Szaflarski has served as a member on the Alabama State Medical Cannabis Study Commission (nominated by Gov. Ivey).
- Dr. Szaflarski serves on the Alabama Medical Cannabis Commission (2021-2025; nominated by Dr. Scott Harris, State Health Officer).

UAB MEDICINE
Knowledge that will change your world

Objectives

1. Discuss the concept of "medical cannabis" and pros vs. cons of medical cannabis use in the treatment of neuropsychiatric symptoms
2. Discuss the evidence in support of medical cannabis use in various medical conditions
3. Briefly discuss the basic tenets of the AL Medical Cannabis Law (SB 46: Darren Wesley "Ato" Hall Compassion Act) – only if time permits

UAB MEDICINE
Knowledge that will change your world

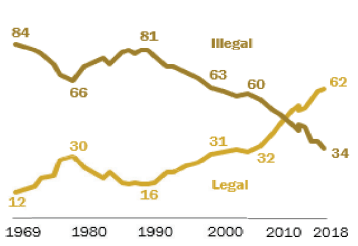
Objectives

Discuss the concept of "medical cannabis" and pros vs. cons of medical cannabis use in the treatment of neuropsychiatric symptoms

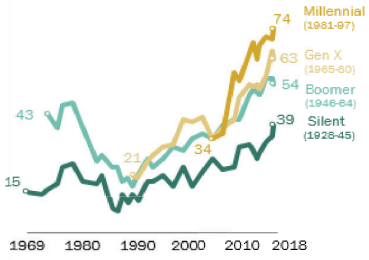
UAB MEDICINE
Knowledge that will change your world

U.S. public opinion on legalizing marijuana, 1969-2018

Do you think the use of marijuana should be made legal, or not? (%)

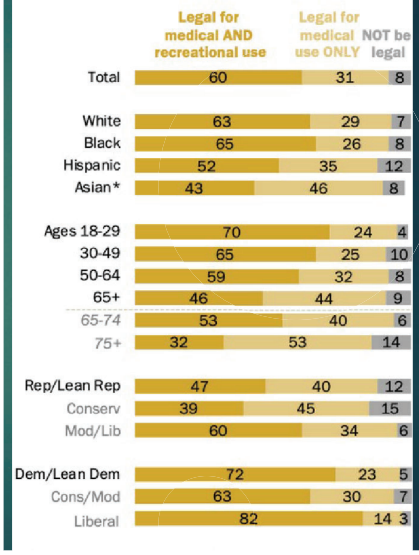


% who say marijuana should be made legal



Majorities across age groups – except 75 and older – say marijuana should be legal for medical and recreational uses

% who say marijuana should be ...



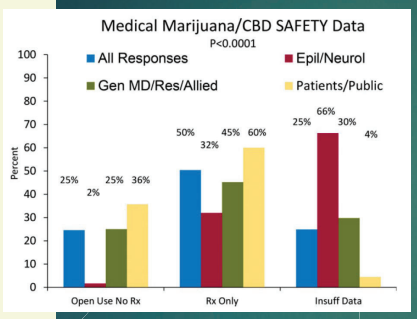
Medical Cannabis

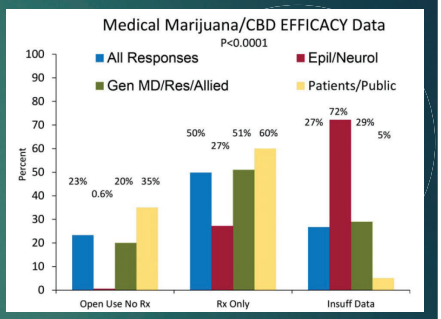
- *Medical cannabis (medical marijuana; MMJ)*
  - Whole, unprocessed cannabis plant or its basic extracts to treat symptoms of illness and other conditions
  - FDA has not recognized or approved the cannabis plant as medicine
- "…Because the [cannabis] plant contains chemicals that *may* help treat a range of illnesses and symptoms, many people argue that it *should* be legal for *medicinal* purposes…"
- *Cannabinoids*
  - Chemicals derived from the Cannabis plant (or manufactured/synthetic)
  - Dronabinol (pill and liquid) and Nabilone – synthetic FDA-approved Δ-9 THC/ Δ-9 THC-like products
  - SCRAs – K2, Spice, etc.

UAB MEDICINE
Knowledge that will change your world

Anthony et al., 2017 Curr Pharm Des; Mead 2017 EB
Colasanti et al., 1982 Pharmacol Biochem Behav;
Rossheim et al., 2023 J Study Alcohol Drugs

Opinion: Safety of Cannabis in Epilepsy





The safety question of "Natural Product"

UAB MEDICINE
Knowledge that will change your world

Mathern et al., 2015 Epilepsia

Current Affairs · News

US Nurses, Neurologists, and Pharmacists Showing Support for Cannabis-Based Therapies

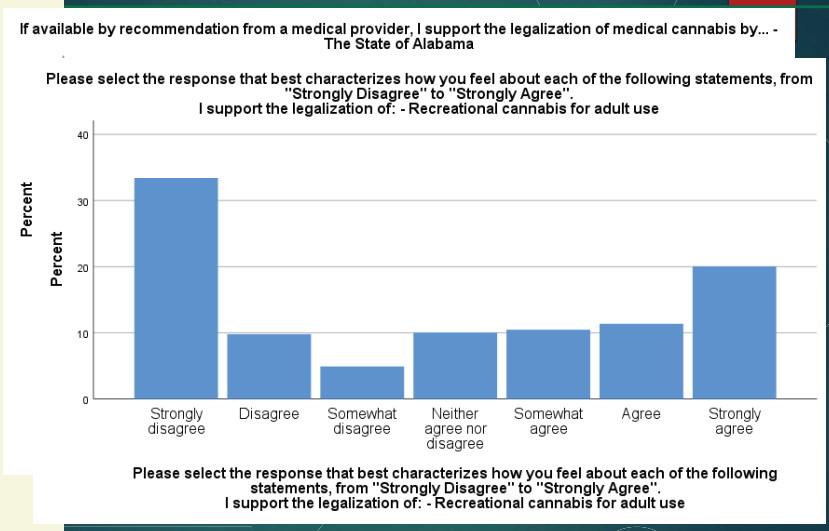
September 18, 2020 • Add Comment • by Caleb Summerill • 72 Views

- "Over 80% of those surveyed were in support of the use and legalization of medical cannabis.
- 43% support legal recreational cannabis use.
- 20-44% of participants felt they were not knowledgeable enough about medical cannabis use in their respective fields.
- Overall, there still seems to be a stigma surrounding medical cannabis recommendations with 88% of nurses, 92% of nurse practitioners, and 74% of neurologists stating as much."

Knowledge that will change your world

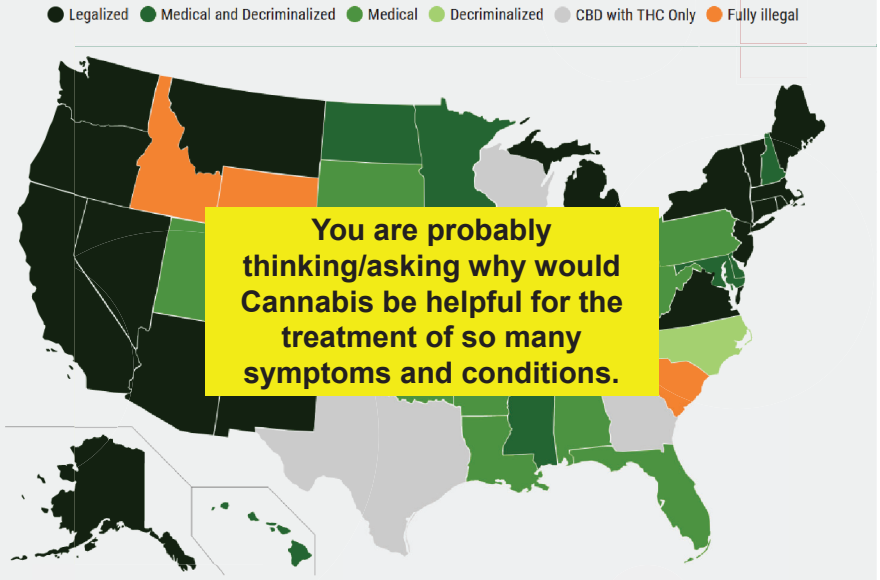
Szaflarski et al., 2020 Epilepsy and Behavior

AL Survey of Providers (N=449/50)



UAB MEDICINE
Knowledge that will change your world

https://www.uab.edu/news/research/item/12007-uab-researchers-survey-support-for-legalization-of-medical-cannabis-among-alabama-physicians



Disa.com – accessed 6/25/2023
Last updated 6/15/2023

Pacher and Kunos, FEBS Journal 2013

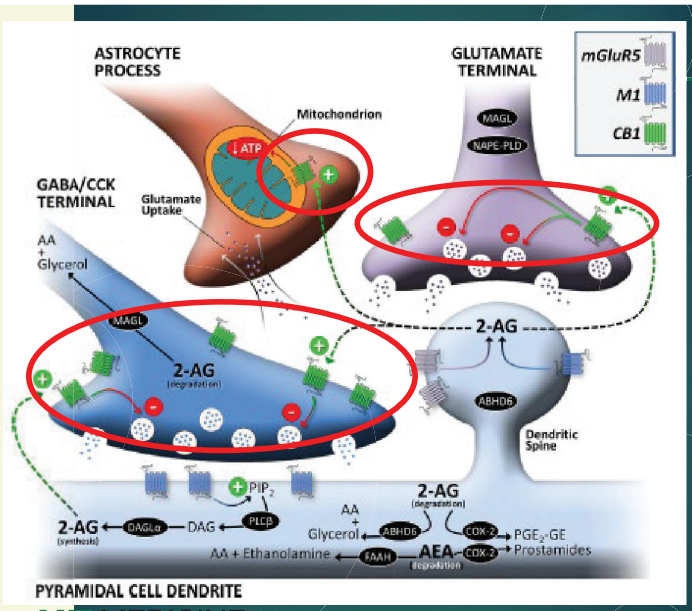
"…Modulating the endocannabinoid system (ECS) holds therapeutic potential in a broad range of diseases affecting humans…"

"… modulating endocannabinoid activity may have therapeutic potential in almost all disease affecting humans including obesity/metabolic syndrome, diabetes and diabetic complications, neurodegenerative, inflammatory, cardiovascular, liver, gastrointestinal, skin diseases, pain, psychiatric disorders, cachexia, cancer, chemotherapy-induced nausea and vomiting, among many others… (p. 1918)

Endocannabinoid System

- Group of receptors and lipid neurotransmitters involved in physiological processes:
  - Appetite, pain/sensation, mood, memory, immune function, female reproduction, sleep…
  - "Mediation of psychoactive effects of cannabis"
- Cannabinoid receptors: CB_1 and CB_2
  - CB_1 – "central" and CB_2 – "peripheral" (mainly located on blood cells and in immune tissue)
  - CB_1 – abundant in neurons but also present in glia
  - CB_2 – much less abundant but highly inducible via e.g., tissue injury or inflammation
  - G-protein-coupled (or other mechanisms)
- Endocannabinoids:
  - "Endocannabinoid tone"
  - Anandamide (AEA)
  - 2-arachidonoylglycerol (2-AG)
  - "On demand" synthesis potentially in response to elevated intracellular Ca^{++}
  - Once released inactivated by glia
    - AEA – FAAH or NAAA or COX-2
    - 2AG – MAGL or COX-2 (lesser degree ABHD6, ABHD12 and FAAH)

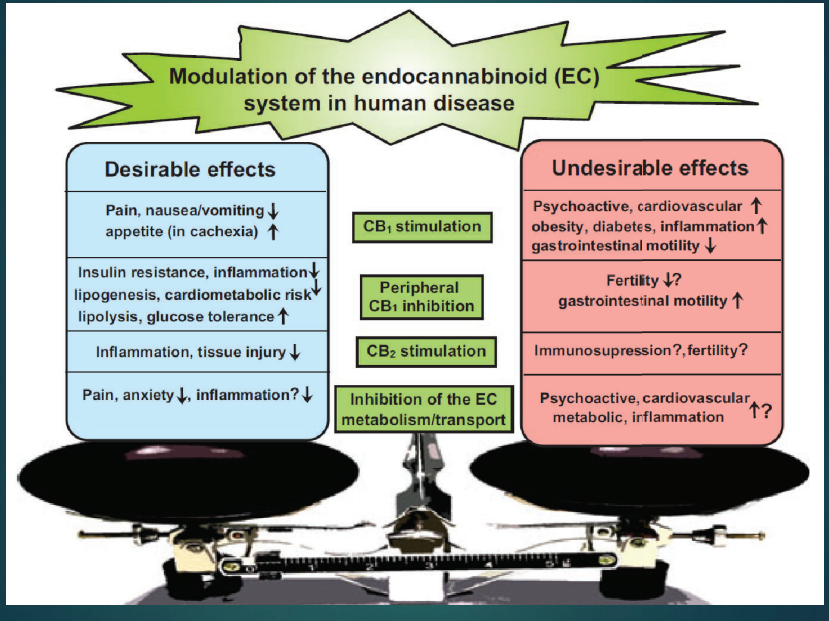
UAB MEDICINE
Knowledge that will change your world



- $mtCB_1$
- GABA/CCK terminals
- GLU terminals
- Degradation:
  - AEA – FAAH or NAAA or COX-2
  - 2AG – MAGL or COX-2 (lesser degree ABHD6, ABHD12 and FAAH)

UAB MEDICINE
Knowledge that will change your world

Lu and Mackie, 2016 Biol Psych; Benard et al., 2012 Nature Neurosc



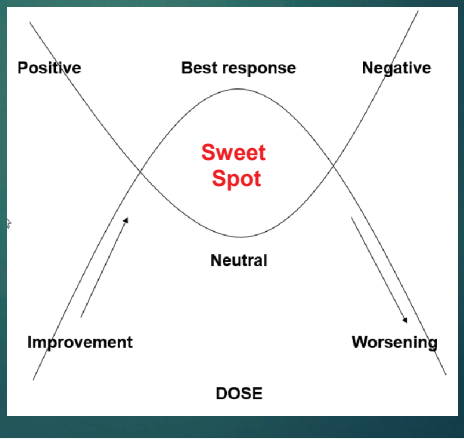
Modified after Ethan Russo, MD

Variability in Dosing and Response

- Psychological effects of cannabis are biphasic and bidirectional

E.g., Mood control

E.g., Seizure control



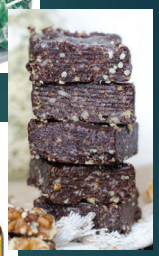
Cannabis Dosing and Response Variability

- **"Sweet spot"**
  - Cannabinoids upregulate ECS at acute and lower doses via increased EC production, CR expression, and/or affinity
  - Cannabinoids can downregulate ECS upon persistent agonism (long-term high doses) via membrane receptor endosome internalization
- Individual differences in objective and subjective effects of cannabis vary by variety/strain, dosage, route of administration, personality, and/or degree of tolerance
- Tolerance develops as a function of CB_1R downregulation
- With chronic use, any benefit derived from Δ^9-THC with regard to mental health could result in symptom exacerbation when not using Δ^9-THC

Pacher et a;l., 2006; Volkow et al., 2017, NEJM

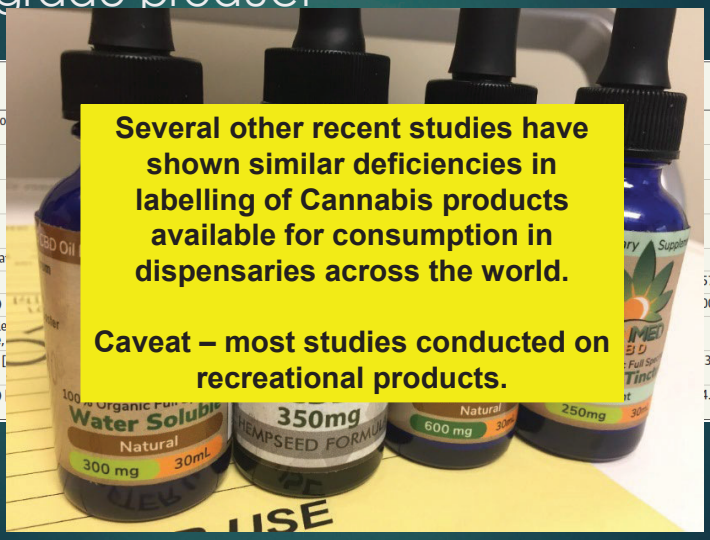
Artisanal vs. pharmaceutical-grade products?

- Dispensaries in San Francisco, Los Angeles, Seattle (randomly selected)
  - 75 edible products of different brands
- Results
  - Δ^9-THC content labeling (47 products)
    - 17% accurate
    - 23% under-labeled
    - 60% over-labeled
  - Non- Δ^9-THC content labeling
    - 44 products had detectable levels of CBD
    - 13 labeled
      - 0 accurate
      - 4 under-labeled
      - 9 over-labeled



Vandrey et al., 2015 JAMA

A case for a pharmaceutical grade product



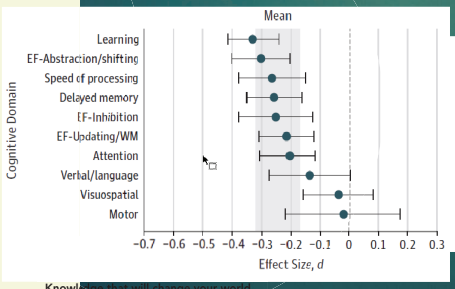
Several other recent studies have shown similar deficiencies in labelling of Cannabis products available for consumption in dispensaries across the world.

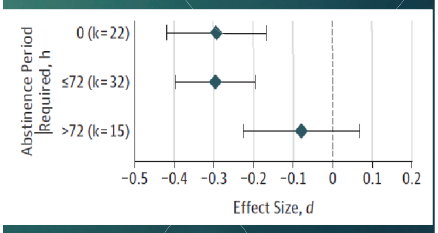
Caveat – most studies conducted on recreational products.

Vandrey et al., 2015 JAMA; Bon-Miller et al., 2017

Overall: Effects of Cannabis on Cognition

- Meta-analysis: 2152 cannabis users / 6575 comparison subjects
- Overall, the effect on cognition is small (*d* = -0.25; CI -0.32 to -0.17)
- If abstinent ≥72 hours the effect on is not significant (*d* = -0.08; CI -0.22 to 0.07)
- Abstinence for ≥ 72 hours diminishes the cognitive effects of cannabis use
- "Effects on cognition are relatively small and may be of questionable clinical importance"





Knowledge that will change your world

Scott et al., 2018 JAMA Psychiatry

Driving with Δ⁹-THC?

- Arkell et al, 2019
  - Randomized cross-over study of 125 mg of Δ⁹-THC dominant product vs. Δ⁹-THC/CBD equivalent vs. PCBO (11% of the vaping product) – N=14
  - Active products <u>negatively</u> affected driving performance – lane weaving (no difference between Δ⁹-THC vs. Δ⁹-THC/CBD) – at ~40 min and ~220 min
  - For other cognitive testing return to baseline occurred at ~220 min
  - Feeling "stoned" was not different between Δ⁹-THC vs. Δ⁹-THC/CBD
- Arkell et al, 2020
  - RCT vaping product - Δ⁹-THC, Δ⁹-THC/CBD, CBD, PCBO; N=26
  - Driving performance including on-road test was negatively affected at 40-100 minutes after Δ⁹-THC or Δ⁹-THC/CBD

UAB MEDICINE
Knowledge that will change your world

Arkell et al, 2020 JAMA; Arkell et al., 2019 Psychopharmacology

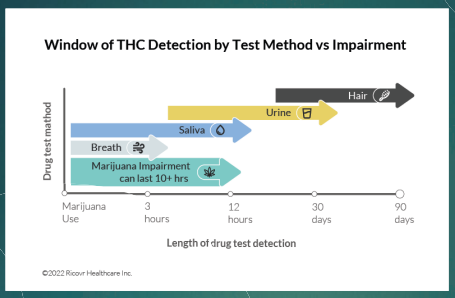
Cannabis use disorder (CUD)

- Definition: inability to stop cannabis even if it is causing physical or psychological harm
  - Chronic daily use results in ECS changes
  - Dependence vs. withdrawal
- In 2018, 4% of global adult population has used cannabis
- 10% of recreational cannabis users will develop CUD
- There are no data on the risk of developing CUD in people using cannabis for medicinal purposes
- Cannabis (Cannabinoid) Hyperemesis Syndrome
  - Recurrent nausea, vomiting, dehydration, abdominal pain resulting in frequent ER visits
  - Risk depends on frequency of use but even people who use Cannabis only 1/week can develop these symptoms

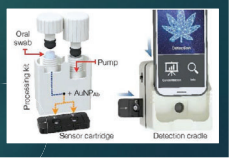
UAB MEDICINE
Knowledge that will change your world

Connor et al, 2021 Nat Rev; Chu @ Cascella, 2022 (NLofM)

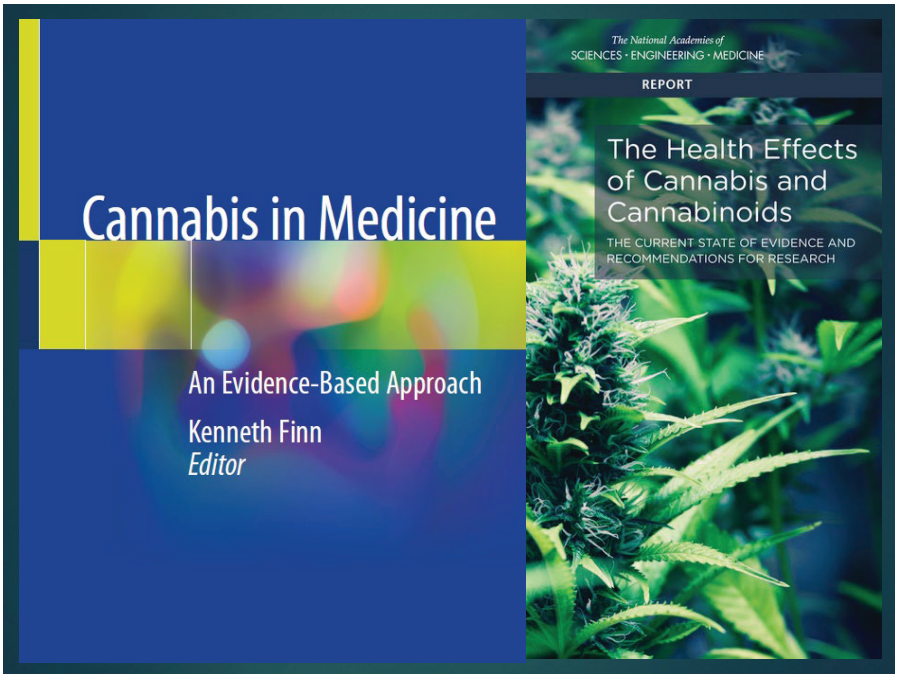
Testing - saliva



- If done properly, the swab may detect Cannabis for up to 72 hours after use
- NarcoCheck (cut-off 10 ng/mL, 4-6 hours after use)
- "The EPOCH system" H. Yu et al., Science Translational Medicine 2021 – (+) in 5 min



UAB MEDICINE
Knowledge that will change your world



Objectives

Discuss the evidence in support of medical cannabis use in various neuropsychiatric conditions

UAB MEDICINE
Knowledge that will change your world

Conditions Approved in SB 46

- Autism Spectrum Disorder
- Cancer-related cachexia, nausea or vomiting, weight loss, or chronic pain
- Crohn's disease
- Depression
- Epilepsy or condition causing seizures
- HIV / AIDS related nausea or weight loss
- Panic Disorder
- Parkinson's Disease
- Persistent nausea that is not significantly responsive to traditional treatment except for nausea related to pregnancy, cannabis-induced cyclical vomiting syndrome, or cannabinoid hyperemesis syndrome
- PTSD
- Sickle cell anemia
- Spasticity associated with a motor neuron disease, including ALS
- Spasticity associated with MS or SCI
- Terminal illness with life expectancy of <6 months (palliative care)
- Tourette syndrome
- A condition causing chronic pain or intractable pain in which conventional therapeutic intervention and opiate therapy are contraindicated or has proved ineffective

UAB MEDICINE
Knowledge that will change your world

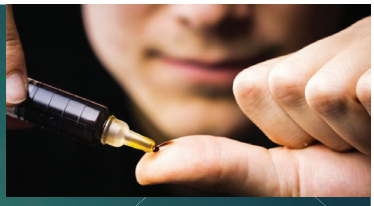
Products permitted in AL

- Capsules
- Inhaled products – liquids or oils
- Nebulizers
- Suppositories
- Tablets
- Tinctures
- Topical use products
  - gels, oils, and creams
- Transdermal patches

- "Many Americans wrongly believe exposure to marijuana smoke is safer than tobacco, study finds" (CNN accessed 2023/08/16)

UAB MEDICINE
Knowledge that will change your world

Whole Plant Extract (WPE)



- Whole plant extract
  - Extraction process preserves all minor and major cannabinoids and other phyto-compounds
  - Typically provided in a syringe to provide rice-grain size doses (0.025 grams of product)
  - Single supply = 1 gram (40 doses)
  - One dose of e.g., 55% Δ^9-THC = 550 mg x 0.025 = **13-14 mg Δ^9-THC**
  - WPE – basically 2:1 Δ^9-THC:CBD combination
- Micro-dosing – 1-5 mg of total cannabinoids
  - One drop under the tongue – held for 1-2 minutes = $T_{1/2}$ in 15-45 min

UAB MEDICINE
Knowledge that will change your world

www.docksidecannabis.com

Autism Spectrum Disorder (ASD)

UAB MEDICINE
Knowledge that will change your world

Autism Spectrum Disorder

- ASD is was not part of the NAS/E/M Report
- Animal studies suggest significant correlation between ECS function and the pathogenesis of ASD
- The story of "Ezra Fouquette"
  - www.cnn.com/2021/12/19/health/autism-medical-marijuana-cbd-weed-documentary/index.html
  - "I've seen CBD used for kids with epilepsy," she said. "I saw how much it helped other people, and I thought, 'it's all-natural. There may not be any real side effects with it. Why not try it?"

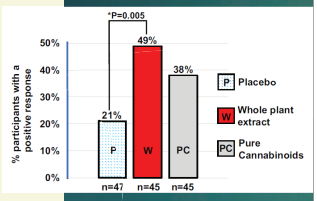
UAB MEDICINE
Knowledge that will change your world

Autism Spectrum Disorder

- Sulak et al., (Bonni Goldstein; 2017)
  - 17/27 patients aged 3-18 years treated with CBD-rich showed improved behavior, calmer, reduced self-mutilation, better focus etc.
  - Lower CBD:THC ratio (high CBD may be overstimulating)
- Schleider et al., (2019)
  - Prospective, observational study of 188 children (mean age 12.9 years) with ASD treated with whole plant extract
    - 30% CBD / 1.5% Δ⁹-THC (20:1 CBD:Δ⁹-THC)
  - 155/188 (82.4%) with 6-months data
    - 83.7% reported a significant or moderate improvement
    - 25.2% - at least one or more AEs

UAB MEDICINE
Knowledge that will change your world

- Several studies listed on clinicaltrials.gov
  - E.g., CBDV vs. PCBO – "recruiting"
- Aran et al., 2021 Molecular Autism (20:1 CBD/Δ⁹-THC – whole plant extract vs. purified product RCT)



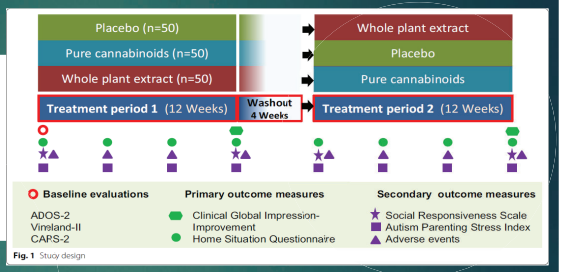


Fig. 1 Study design

  - Children and adolescents 5-21 years of age
  - Disruptive behavior on CGI-I improved in 49% of Cannabis group vs. 21% in placebo (p=0.005)
  - Social responsiveness scale improved by 14.9 points in Cannabis group vs. 3.6 points in placebo (p=0.009)
  - Pure cannabinoids had less AEs compared to whole plant extract

UAB MEDICINE
Knowledge that will change your world

Summary - ASD

- Aran et al., 2018 – (retrospective) - ~4mg/kg/d CBD + 0.3 mg/kg/d Δ⁹-THC
  - 61% improvement in behavior / 39% improvement in anxiety / 47% improvement in communication
- Barchel et al., 2018 (prospective 20:1 CBD : Δ⁹-THC)
  - 68% improvement in self harm / 68% improvement in hyperactivity / 71% improvement in sleep
- Pretzsch et al., 2019 (randomized CBD vs. placebo; neurotypical controls)
  - Spectroscopy – GABA response altered in ASD
- Pretzsch et al., 2019 (CBD in ASD compared to neurotypical)
  - FMRI – changes in connectivity in response to CBD compared to controls
- Schleider et al., 2019 (prospective cross-sectional; 20:1 CBD : Δ⁹-THC)
  - Improvements 78-91% in restlessness, anger, agitation and sleep
- Kurz and Blaas 2010 (dronabinol dissolved in sesame oil – 0.62 mg titrated up to 3.6 mg/d)
  - Improvements in hyperactivity, lethargy, and irritability
- Adams et al., 2019 (survey)
  - Improvements in irritability, agitation, sleep etc.
- Cannabis and cannabinoids may have promising effects in the treatment of symptoms related to ASD, and can be used as a therapeutic alternative in the relief of those symptoms (Silva Junior et al., 2022)

UAB MEDICINE
Knowledge that will change your world

Depression and Panic Disorder

UAB MEDICINE
Knowledge that will change your world

Anxiety

- **Conclusion 17**: There is limited evidence that cannabidiol is an effective treatment for the improvement of anxiety symptoms, as assessed by a public speaking test, in individuals with social anxiety disorders

- Cannabinoid signaling is important in control of stress, fear, and anxiety
- Both for anxiety and fear memory processing, ECS ensures appropriate reaction to stressful events and serves as a regulatory buffer system for emotional responses.
- CBD has been shown to have anxiolytic, antipsychotic, and neuroprotective properties
- Δ^9-THC can mitigate anxiety in lower doses and increase anxiety in higher doses
- Substantial animal evidence supports studying cannabinoids for the treatment of mental health but human data are missing / inconclusive
- Several trials are registered as starting or ongoing with clinicaltrials.gov

UAB MEDICINE
Knowledge that will change your world

Crippa et al., 2018, Frontiers of Immunology; Stoner 2017 UofWashington

CBD and Anxiety

- Conclusive preclinical evidence of CBD's efficacy in reducing anxiety behaviors relevant to PTSD, GAD, OCD, and SAD, with lack of anxiogenic effects
- CBD reverses anxiogenic effects of Δ^9-THC
- Human studies show single dose of 300-600 mg of oral CBD induced anxiety in individuals without anxiety disorders and reduced anxiety in patients with social anxiety disorder
  - No studies for chronic dosing
- CBD associated with greater improvement on anxiety factor compared with placebo during a simulated public speaking test ($p<0.01$)
  - Cannabis or Cannabinoids may be an effective treatment for anxiety symptoms

UAB MEDICINE
Knowledge that will change your world

Whiting et al., JAMA 2015; Blessing et al., Neurotherapeutics 2015; Sharpe et al., 2020 JTM

Δ^9-THC and Anxiety

- Four randomized controlled studies (combined 232 participants)
  - Dronabinol 10-20 mg
  - Nabilone max 2 mg daily
  - Nabiximols max 4-8 sprays/day.
- Outcomes typically assessed hours to weeks after randomization. Greater short term benefit with cannabinoids then placebo – no long-term data
- RCT of PCBO vs. Δ^9-THC single capsule of 7.5 mg or 12.5 mg
  - 7.5mg reduced the duration of negative emotional responses to the task and post-task appraisals of how threatening and challenging a stressor was
  - 12.5mg produced small but significant increases in anxiety, negative mood and subjective distress at baseline before and during the stress task
- Δ^9-THC may decrease anxiety at lower doses and increase at higher doses

UAB MEDICINE
Knowledge that will change your world

Whiting et al., JAMA 2015; Childs et al., 2017 Drug Alcohol Dependence

Registry: Anxiety and Depression

- 1,746 patients (9 medical cannabis clinics in CA)
  - Pain, insomnia, anxiety – most frequent reasons for cannabis use
  - **37.8% of patients reported using cannabis to relieve anxiety**
  - 16.9% to relieve panic attacks
  - 55.1% to improve relaxation
  - **Anxiety/depression** were identified as reasons for authorizing MM card for 13% of patients
- 1,429 cannabis users (social media) in WA from 2013-2016 about conditions treated, use patterns, perceptions of efficacy and physical and mental health
  - Pain (61.2%), **anxiety (58.1%)**, **depression (50.3%)**, headache/migraine (35.5%)....
  - 86% reduction in symptoms as a result of Cannabis use
  - 59.8% reported using cannabis as an alternative to pharmaceutical prescriptions.
  - **More than half (58%) reported they used cannabis for anxiety with symptom improvement**

UAB MEDICINE
Knowledge that will change your world

Reinarman et al, J Psychoactive Drugs , 2011
Sexton et al, Cannabis and Cannabinoid Research, 2016

Registry: Anxiety and Depression

- Word of caution (especially for pediatric recreational users):
- Patton et al., 2002 BMJ
  - 44 schools in State of Victoria, AU
  - 1601 students 14-15 followed for up to 7 years
  - 66%M/52%F reported cannabis use at some time (recreational)
  - 7% daily users (recreational)
  - 71M/188F reported depression and anxiety
  - Daily use in women – OR 5.6 for having depression or anxiety
  - Weekly use – OR 1.9 for later developing depression or anxiety
  - Existing depression or anxiety did not predict later use

UAB MEDICINE
Knowledge that will change your world

Depression

- There is a high co-occurrence of depression and cannabis use w/strong evidence that depression can lead to onset or increase of cannabis use
- 1,819 people / 5,876 cannabis self administration sessions -ReleafApp™ - self-report / no age / sex or other data
- 95.8% experienced symptom relief following consumption
- Average symptom intensity reduction of –3.76 points on a 0-10 visual analogue scale (SD = 2.64, d = 1.71, p <.001)
- Symptom relief independent of chemovars ("*C. indica*," "*C. sativa*," or "hybrid")
- Δ^9-THC levels were the strongest independent predictors of symptom relief
- CBD levels were unrelated to real time changes in symptom intensity level
- Cannabis use was associated with some negative side effects that correspond to increased depression (*e.g.* feeling unmotivated) in up to 20% of users, as well as positive side effects that correspond to decreased depression (*e.g.* feeling happy, optimistic, peaceful, or relaxed) in up to 64% of users.
- Results suggest acute / short-term benefits of cannabis use for the symptoms of depression

UAB MEDICINE
Knowledge that will change your world

Feingold & Weinstein 2021 Aadv Exp Med Biol; Li et al., 2020 Yale Journal of Biology and Medicine

What to use?

- Treatment of chronic vs. acute symptoms is different
- "Dr. Jim explains" – AU
  - Δ^9-THC can help depression but too much can cause worsening
  - CBD can be very beneficial
  - Terpenes (limonene, pinene, linalool, and mercene) reduce stress and anxiety
  - Dr. Jim says: no specific dose or formulation – all depends on the most prominent symptom and dosing needs to be individualized

UAB MEDICINE
Knowledge that will change your world

Epilepsy

UAB MEDICINE
Knowledge that will change your world

Epilepsy

- **Conclusion 6**: There is insufficient evidence to support or refute the conclusion that cannabinoids are an effective treatment for epilepsy

- https://en.wikipedia.org/wiki/Charlotte_Figi
  - Seizure onset at 3 months of age (~early 2007)
  - Mom started with cannabis plant extracts in 2012
  - "Hippie's Disappointment" – renamed "Charlotte's Web"
  - 2013 first documentary by Sanjay Gupta "Weed 1"
  - Died 4/2020 – accounts are divided – likely of complications of COVID
  - https://coloradosun.com/2020/04/08/charlotte-figi-cbd-coronavirus/
- https://www.montgomeryadvertiser.com/videos/news/politics/2014/04/04/7290393/

UAB MEDICINE
Knowledge that will change your world

Epilepsy

- Gaston et al., (2018):
  - **6 placebo-controlled RCTs were completed of highly-purified CBD**
  - At least 8 OL reports of highly-purified CBD
  - 14 open-label trials of various artisanal cannabis products were completed (all positive)
- Pamplona et al., (2018) – meta-analysis:
  - 64% of patients included in cannabis trials report improvement in seizure frequency
    - 71% reported improvement with "CBD-rich extracts"
    - 46% with "purified CBD"
  - Dose needed to achieve – 6 mg/kg/d with "CBD-rich extracts" vs. 25.3 mg/kg/d with "purified CBD"
  - "…the roots of this difference is likely due to synergistic effects of CBD with other phytocannabinoids (aka entourage effect)…"

UAB MEDICINE
Knowledge that will change your world

Parkinson's Disease

UAB MEDICINE
Knowledge that will change your world

- **Conclusion 11**: There is insufficient evidence that cannabinoids are an effective treatment for the motor symptoms associated with PD or the levodopa-induced dyskinesia
- Parkinson's Foundation: "The use of cannabinoids has been suggested to help with managing neurological and non-neurological conditions. Literature on medical marijuana is incredibly varied. Studies have not clearly supported the use of marijuana for PD. The clinical studies of cannabis as a PD treatment that have been conducted are generally small studies that are predisposed to biases. Most of studies have not followed the clinical trial gold standard of a double blind, placebo-controlled trial design. Some studies had as few as five subjects. While some results have been positive, the effects of medical marijuana are probably not completely understood. This is why more studies, especially those with more subjects, are needed." (accessed 4/30/2023)

UAB MEDICINE
Knowledge that will change your world

May 2021 - JPS

- "Parkinson's disease – while many anecdotal reports of improvement of symptoms of PD exist, there is also a whole host of studies that show no efficacy of cannabis for the treatment of symptoms associated with PD. National Academy of Sciences suggests there is insufficient evidence for the treatment of symptoms associated with PD – dyskinesia and motor symptoms."

UAB MEDICINE
Knowledge that will change your world

- Preclinical data support development of cannabis products for the treatment of symptoms of PD
- APA – convened a panel to develop and implement cannabis products for the treatment of PD and its symptoms
- Several states list PD as an "approved condition" however this is based on compassionate use rather than data
- There are some fair quality studies and some anecdotal evidence that symptoms of PD may be improved w/cannabis

UAB MEDICINE
Knowledge that will change your world

Numerous articles are available:

- Carroll et al (2004 Neurology) – "cannabis extract" vs. PCBO (RCT) in 19 patients with dyskinesia – no effect
- Lotan et al (2014 Clin Neuropharmacology) – smoked cannabis – improved motor and non-motor scores (sleep and pain)
- Chagas et al (2014 J Clin Pharmacy and Therapeutics) – CBD may control REM Behavior Disorder
- Zuardi et al (2008) J Psychopharmacology – CBD decreased psychotic symptoms in patients with psychosis associated with PD
- Chagas et al (2014) J Psychopharmacology – RCT PCBO vs. CBD (75 mg or 300 mg) – no effect on motor symptoms but PDQ scores much worse in the treatment groups before initiation.
- Finseth et al (2015) Hindawi – CAM use including cannabis helpful for non-motor symptoms of PD
- De Faria et al (2020) – J Psychopharmacology – RCT PCBO vs. CBD (300 mg capsules) – improvement in anxiety and tremor w/CBD

UAB MEDICINE
Knowledge that will change your world

- https://www.parkinson.org/living-with-parkinsons/treatment/medical-marijuana (re-accessed 2/8/2023)
- "Only 23% of physicians had any formal education on the subject of cannabis (such as a course or lecture), thus 93% of physicians want cannabis taught in medical school.
- Physicians reported that 80% of their people with PD have used cannabis.
- Only 10% of physicians have recommended the use of cannabis to people with PD.
- In terms of memory: 75% of physicians felt that cannabis would have negative effects on short-term memory and 55% felt that cannabis could have negative effects on long-term memory.
- Only 11% of physicians have recommended use of cannabis in the last year."
- Meta-analysis by Urbi et al., (12/2022; J Parkinson's Disease): "No compelling evidence was found to recommend the use of cannabis in PD patients. However, a potential benefit was identified with respect to alleviation of PD related tremor, anxiety, pain, improvement of sleep quality and quality of life."

UAB MEDICINE
Knowledge that will change your world

- Kogan: "start low and go slow"
  - Start with whole plant extract – micro-dosing 1-3 mg Δ^9-THC:CBD or Δ^9-THC:CBN (CBN may be more sedating than Δ^9-THC)
  - Kogan only comments on treating insomnia in PD
- Sulak:
  - Comment on REM behavior disorder – CBD 75 mg qhs + titrate up
  - Sleep disorder – recommends Δ^9-THC-based products as close to bedtime as possible

UAB MEDICINE
Knowledge that will change your world

PTSD

UAB MEDICINE
Knowledge that will change your world

Cannabis in PTSD

- MedPage today "Marijuana is not the solution for PTSD" – evidence shows it does not treat PTSD in the long-term and may worsen symptoms
  - "A growing number of states have identified post-traumatic stress disorder (PTSD) as an approved condition for medical marijuana. According to Colorado's Medical Marijuana Registry, there are 70,533 patients as of February 2023 with an active medical marijuana registration in the state, and 10,734 of them indicate PTSD as the reason they are using medical marijuana. This is despite the lack of any high-quality, randomized, controlled studies proving that marijuana helps PTSD in the long-term. Because of this lack of evidence, the American Psychiatric Association adopted a policy in 2019 opposed to using medical cannabis treatment for PTSD."

UAB MEDICINE
Knowledge that will change your world

https://www.medpagetoday.com/opinion/second-opinions/103944 (accessed 5/21/2023)

PTSD

- **Conclusion 20**: There is limited evidence that nabilone is effective for improving symptoms of PTSD
- Fraser at al., (2009)
  - 72% of patients receiving nabilone experienced cessation or improvement of nightmares
- Roitman et al., (2014)
  - 10 patients received Δ^9-THC 5 mg bid
  - Significant improvement in global symptom severity, sleep quality, frequency of nightmares, and PTSD hyperarousal symptoms
- Multidisciplinary Association of Psychodelic Studies (PTSD smoked cannabis trial) – completed 2/2019
  - https://www.phoenixnewtimes.com/news/sue-sisley-cannabis-researcher-loses-medical-society-position-over-new-times-quotes-6657862
  - Study approved by FDA, DEA, and NIDA; published in PLoS One: 3/2021

UAB MEDICINE
Knowledge that will change your world

PTSD – "Sue Sisley Trial"

- Three active concentrations of smoked cannabis RCT:
- F

VFW
VETERANS OF FOREIGN WARS.

Federal Study Finds Cannabis Beneficial for PTSD Treatment

Results of a study released in march revealed improvements among PTSD patients receiving cannabis doses with higher levels of THC

Sep 21, 2021

https://www.vfw.org/media-and-events/latest-releases/archives/2021/9/federal-study-finds-cannabis-beneficial-for-ptsd-treatment

UAB MEDICINE
Knowledge that will change your world

Bonn-Miller et al., 2021 PLoS One

PTSD

- Open label longitudinal study
  - Cannabis users vs. Cannabis non-users w/PTSD
  - Cannabis: significant decrease in PTSD symptom severity compared to controls (p=0.02).
  - Cannabis 2.57 times more likely to no longer meet DSM-5 criteria for PTSD at the end of the study (p=0.03)
- **American Psychiatric Association**
  - Position Statement
- "Because of the lack of any credible studies demonstrating clinical effectiveness, the APA cannot endorse the use of medical cannabis for the treatment of post-traumatic stress disorder (PTSD). The Council on Addiction Psychiatry, the Council on Research, and the Council on Quality Care reviewed available evidence regarding the use of cannabis in the treatment of PTSD and concluded that no published evidence of sufficient quality exists in the medical literature to support the practice. The APA does not endorse cannabis for treatment of PTSD at this time, as further study is needed."

UAB MEDICINE
Knowledge that will change your world

Bonn-Miller 2022 CCR

Spasticity

UAB MEDICINE
Knowledge that will change your world

Spasticity in MS or SCI or ALS

- **Conclusion 7A**: There is substantial evidence that oral cannabinoids are an effective treatment for improving patient-reported multiple sclerosis spasticity symptoms, but limited evidence for an effect on clinician-measured spasticity
- **Conclusion 7B**: There is insufficient evidence to support or refute the conclusion that cannabinoids are an effective treatment for spasticity in patients with paralysis due to spinal cord injury
- **Conclusion 9**: There is insufficient evidence that cannabinoids are an effective treatment for symptoms associated with ALS

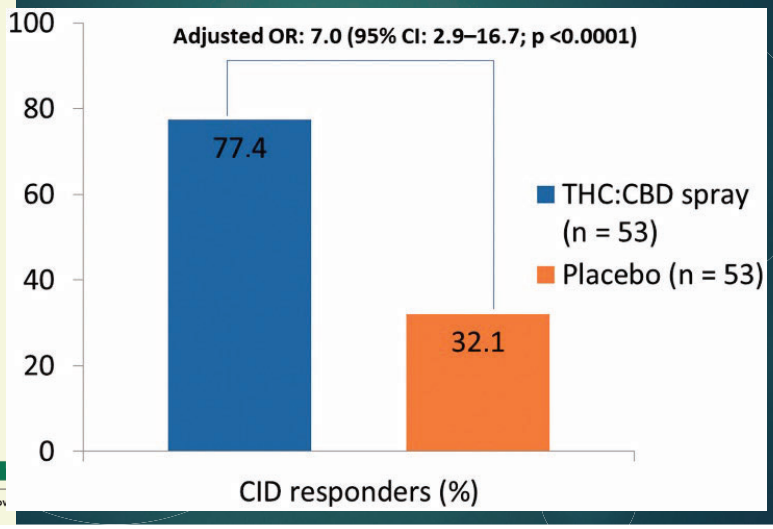
UAB MEDICINE
Knowledge that will change your world

Corey-Bloom et al, 2012 (CMAJ)

- Cross-over, placebo controlled trial of smoked cannabis for spasticity in MS
  - Investigators blinded to group assignment
- 37 started and 30 completed
- 3 days of treatment / 11 days of washout / 3 days of other treatment (treatment = 5-6% Δ^9-THC cigarettes)
- Primary outcome: Reduction in Ashworth spasticity scale by 2.74 points compared to placebo ($p<0.0001$)
- Reduction in pain scores by 5.28 points compared to placebo ($p=0.008$)
- Paced Serial Addition Test scores decreased with active treatment ($p=0.003$)

UAB MEDICINE
Knowledge that will change your world

Spasticity associated with MS (Markova et al., 2019)



Phase 3 RELEASE MSS1 trial

- Clinicaltrials.gov update 3/10/2023
- Multicenter, randomized, double-blind, placebo-controlled, two-treatment, two way crossover trial evaluating nabiximols on clinical measures of spasticity in people with MS
- The MSS1 trial did not meet the primary endpoint of change in lower limb muscle tone-6, between baseline and Day 21, as measured by the Modified Ashworth Scale.
- "No results posted"

UAB MEDICINE
Knowledge that will change your world

Press Release Jazz Pharmaceuticals accessed 6/28/2022

Hagenbach et al., 2007 (Spinal Cord)

- Dronabinol (synthetic Δ^9-THC) – oral or rectal suppository vs. placebo in SCI
- Mean spasticity for oral Δ^9-THC decreased significantly from 16.72 (±7.60) at baseline to 8.92 (±7.14) on day 43.
- Similar improvement was seen with rectal Δ^9-THC
- Significant improvement of spasticity with active drug (P=0.001) over placebo.
- Dose 10-20 mg required for treatment of SCI-related spasticity

- Overall, data regarding synthetic Δ^9-THC are insufficient to support or refute efficacy for the treatment of SCI and there are no good data on the use of artisanal products.

UAB MEDICINE
Knowledge that will change your world

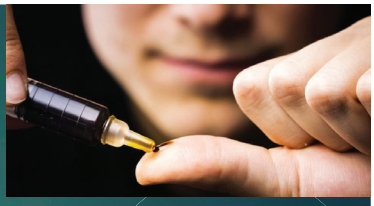
Amyotrophic Lateral Sclerosis

- **Conclusion 9**: There is insufficient evidence that cannabinoids are an effective treatment for symptoms associated with ALS

- Riva et al., (2019) – placebo-controlled RCT of nabiximols in motor neuron disease:
  - Nabiximols is a oro-mucosal spray containing 2.7 mg of Δ^9-THC and 2.5 mg CBD
  - Modified Ashworth Scale (measure of spasticity) scores improved by a mean of 0.11 (SD 0.48) in the nabiximols group and deteriorated by a mean of 0.16 (0.47) in the placebo group (adjusted effect estimate –0.32 [95% CI –0.57 to –0.069]; p=0.013)
  - Nabiximols was well tolerated, and no participants withdrew from the double-blind phase of the study
  - No serious adverse effects occurred.

UAB MEDICINE
Knowledge that will change your world

Whole Plant Extract (WPE)



- Whole plant extract
  - Extraction process preserves all minor and major cannabinoids and other phyto-compounds
  - Typically provided in a syringe to provide rice-grain size doses (0.025 grams of product)
  - Single supply = 1 gram (40 doses)
  - One dose of e.g., 55% Δ^9-THC = 550 mg x 0.025 = **13-14 mg Δ^9-THC**
  - WPE – basically 2:1 Δ^9-THC:CBD combination
- Micro-dosing – 1-5 mg of total cannabinoids
  - One drop under the tongue – held for 1-2 minutes = $T_{1/2}$ in 15-45 min

UAB MEDICINE
Knowledge that will change your world

www.docksidecannabis.com

Palliative Care

UAB MEDICINE
Knowledge that will change your world

Palliative care

- WHO: "…an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness…"
- Two evidence-based guidelines:
- First (College of Family Physicians of Canada; 2018): explicitly recommends against the use of medical cannabis as a first or second line option for palliative cancer pain. The guideline suggests that it could be considered in the case of refractory symptoms and with careful consideration of potential risks.
- Second (Therapeutic Goods Administration (AU); 2017): recommends that medical cannabis only be used in the palliative care setting when other treatments have failed, and after consideration of the potential for adverse events and drug interactions.

UAB MEDICINE
Knowledge that will change your world

MacDonald and Farrah, 2019

End-of-life / palliative care

- Luba et al (2018) J Psychoactive Drugs:
  - Palliative care providers (N = 426) completed a one-time online survey assessing these attitudes, beliefs, and practices.
  - Results demonstrated that palliative care providers endorse cannabis for a wide range of palliative care symptoms, end-of-life care generally, and as an adjuvant medication.
- Aggarwal (2016) Current Oncology:
  - "Cannabinoid Integrative Medicine" should be a part of end-of life palliative care
- Bar-Sela et al (2013)
  - 106/131 continued treatment with all cancer or anticancer treatment-related symptoms improvement ($P < 0.001$). No significant side effects except for decrease in memory ($P = 0.002$).
- "Although studies with a control group are missing, the improvement in symptoms should push the use of cannabis in palliative treatment of oncology patients."

UAB MEDICINE
Knowledge that will change your world

Palliative care

- 9 trials of cannabinoids in palliative care
- Moderate risk of bias / quality of evidence "low"
- Cancer - no significant differences between cannabinoids and placebo for improving caloric intake ($P = 0.65$), appetite ($P = 0.42$), nausea/vomiting ($P = 0.19$), >30% decrease in pain ($P = 0.07$), or sleep problems ($P = 0.72$)
  - In one study in cancer- associated anorexia, megestrol was superior to cannabinoids in improving appetite, producing >10% weight gain and tolerability
- HIV - cannabinoids superior to placebo for weight gain ($P = 0.001$) and appetite ($P = 0.02$) but not for N/V ($P = 0.26$)
  - In one study comparing megestrol to dronabinol in HIV patients, megestrol led to higher weight gain without any differences in tolerability and safety
- Side effects – no differences in cancer; in HIV – significant increase in mental health symptoms ($P = 0.05$)
- Tolerability/safety – same between cannabinoids and placebo
- Conclusion: No convincing, unbiased, high quality evidence suggesting that cannabinoids are of value for anorexia or cachexia in cancer or HIV patients.

UAB MEDICINE
Knowledge that will change your world

Mücke et al., 2017 (systematic literature review)

Tourette Syndrome

UAB MEDICINE
Knowledge that will change your world

Tourette Syndrome

- **Conclusion 8**: There is limited evidence that THC capsules are an effective treatment for improving symptoms of Tourette syndrome
- Tourette Association of America (TAA) sponsors several ongoing clinical trials + formed a consortium to study the issue
- Several trials are ongoing internationally but none reported data to date
  - "German trial" is singled out on the TAA web page and as "completed" on clinicaltrials.gov
  - Results not available / not published
- TAA web page lists several synthetic cannabinoids under development for the treatment of TS

UAB MEDICINE
Knowledge that will change your world

Tourette Syndrome

- Muller-Vahl et al., 1998
  - In standardized interviews 17/64 consecutive TS patients reported cannabis use with 82% experiencing a reduction or complete remission of tic symptoms
- Muller-Vahl et al., 2002
  - RCT cross-over trial of Δ^9-THC capsules vs. PCBO capsules
  - 12 adults / single dose trial
  - Improvements noted in complex motor tics (p=0.015) and trends towards other types of tics
- Muller-Vahl et al., 2003
  - RCT – 6 weeks trial
  - 24 adults (7 dropped out or were excluded)
  - Tourette Syndrome Symptom List (TSSL) and other scales
  - Mostly significant improvement (or trend towards improvement)
  - More AEs with Δ^9-THC
- https://tourette.org/research-medical/medical-marijuana/
  - "In the absence of conclusive medical research, they are especially concerned about medical marijuana in the treatment of children and adolescents. The Tourette Association of America shares that concern."

UAB MEDICINE
Knowledge that will change your world

Chronic Pain

UAB MEDICINE
Knowledge that will change your world

Chronic Pain

- **Conclusion 1**: There is substantial evidence that cannabis is an effective treatment for chronic pain

- Műcke et al., (Cochrane Database; 2018) – numerous RCTs were registered as completed with clinicaltrials.gov indicating advantage of cannabis over placebo for the treatment of chronic pain (at least 10 with plant-derived Δ^9-THC:CBD combinations and at least 2 that used synthetic Δ^9-THC)
- Stockings et al., (Pain, 2018) – Meta-analysis of available data:
  - Cannabis outperforms placebo but the effects may be limited (long-term data very limited)
  - AE: no impact on physical or emotional functioning; modest improvement in sleep and global impression of change

UAB MEDICINE
Knowledge that will change your world

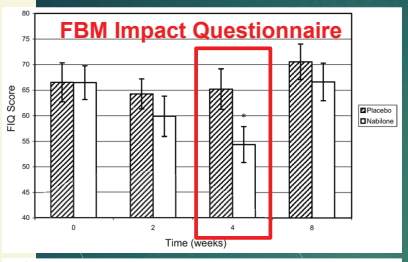
Cancer-related pain

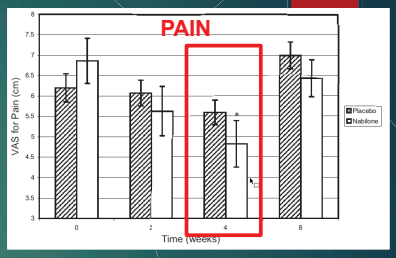
- 177 patients with cancer pain, who experienced inadequate analgesia despite chronic opioid dosing
- 2-week parallel group multi-center, double-blind RCT: Δ^9-THC:CBD extract (n = 60), Δ^9-THC extract (n = 58), or placebo (n = 59)
  - Δ^9-THC:CBD extract was 1:1; Δ^9-THC extract was same Δ^9-THC as in Δ^9-THC:CBD extract
  - Pain outcome: Numerical Rating Scale (NRS) baseline – end-of-study:
    - Δ^9-THC:CBD compared with placebo (improvement of 1.37 vs. 0.69); Δ^9-THC showed a non-significant change (1.01 vs. 0.69).
    - Twice as many patients taking Δ^9-THC:CBD showed a reduction of more than 30% from baseline pain NRS score when compared with placebo (23 [43%] vs. 12 [21%]). The associated odds ratio was statistically significant,
    - Δ^9-THC group responders were similar to placebo (12 [23%] vs. 12 [21%]) and did not reach statistical significance.

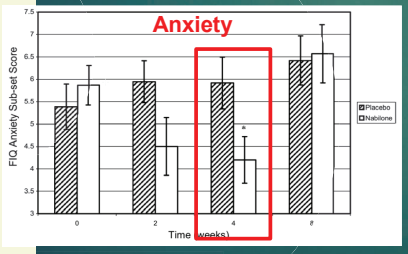
UAB MEDICINE
Knowledge that will change your world

Johnson et al., 2010

Fibromyalgia





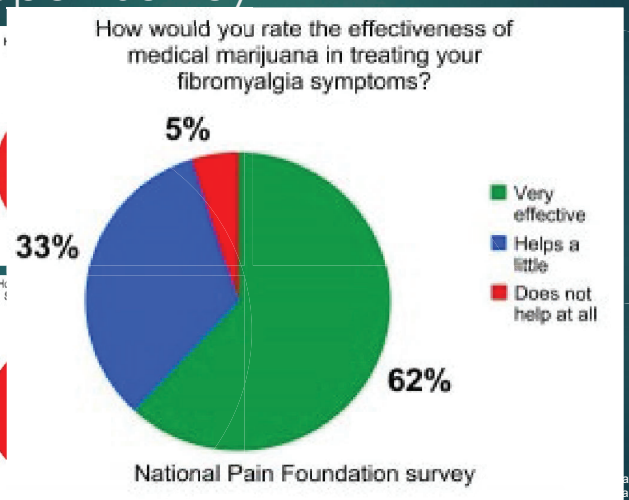


- 40 patients w/FBM
- **RCT** 1 mg bid Nabilone (Cesamet – synthetic THC) vs. PCBO
- 4-week Tx and 4-week washout

UAB MEDICINE
Knowledge that will change your world

Skrabek et al., 2008; J Pain

Fibromyalgia – National Pain Report Survey



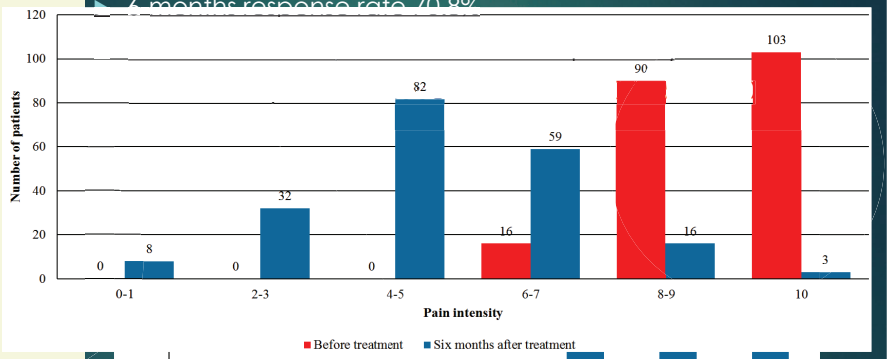
60%

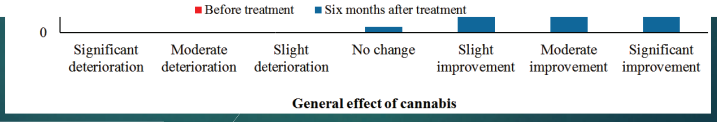
68%

ationalpainreport.com
ana-rated-most-
effective-for-treating-
fibromyalgia-8823638.html

Sagy et al., 2019

- 367 FBM patients / 82% women
- 6 months response rate 70.8%





Objectives

Briefly discuss the AL Medical Cannabis Law (SB 46: Darren Wesley "Ato" Hall Compassion Act)

Medical Cannabis in AL

- "Carly's Law" and "Leni's Law"
- SB46: "Darren Wesley 'Ato' Hall Compassion Act"
- https://amcc.alabama.gov/
- First meeting on 8/12/2021
- Rules and regulations
- Anticipated medical cannabis availability is summer 2023
- What conditions are approved under the law?
- Who will be eligible to recommend medical cannabis?
- How will this be done?
- Multidisciplinary Medical Cannabis Clinic at UAB
  - Possibly located offsite

UAB MEDICINE
Knowledge that will change your world

Current Progress

- AL BME rules approved and implemented
  - CMEs and exams should be available in 3/2023
- AMCC rules implemented and approved 8/11/2022
  - Request for application period closed on 10/17/2022:
    - Integrated Facility: 133 (up to 5 licenses w/up to 5 dispensaries)
    - Cultivator: 124 (up to 12 licenses)
    - Processor: 35 (up to 4 licenses)
    - Dispensary: 239 (up to 4 licenses for up to 3 dispensaries)
    - Secure Transporter: 69 (no limit)
    - State Testing Laboratory: 7 (no limit)
- Deadline to file applications: 12/30/2022
  - Review or all compete applications will be managed by USA
- Deadline for approving applications (by vote): 6/12/2023

UAB MEDICINE
Knowledge that will change your world

Conditions Approved in SB 46

- Autism Spectrum Disorder
- Cancer-related cachexia, nausea or vomiting, weight loss, or chronic pain
- Crohn's disease
- Depression
- Epilepsy or condition causing seizures
- HIV / AIDS related nausea or weight loss
- Panic Disorder
- Parkinson's Disease
- Persistent nausea that is not significantly responsive to traditional treatment except for nausea related to pregnancy, cannabis-induced cyclical vomiting syndrome, or cannabinoid hyperemesis syndrome
- PTSD
- Sickle cell anemia
- Spasticity associated with a motor neuron disease, including ALS
- Spasticity associated with MS or SCI
- Terminal illness with life expectancy of <6 months (palliative care)
- Tourette syndrome
- A condition causing chronic pain or intractable pain in which conventional therapeutic intervention and opiate therapy are contraindicated or has proved ineffective

Mostly treated by:
Internal Medicine
Neurology
Psychiatry

UAB MEDICINE
Knowledge that will change your world

AL BME Requirements for Practitioners

- Complete application on a form prescribed by the AL BME
- Complete 4 CMEs related to medical cannabis and a passing grade
- Active unrestricted medical license in AL
- Active unrestricted AL Controlled Substances Certificate
- Active unrestricted AL-specific DEA
- Provide proof of PDMP registration
- Provide proof of a current registration with the AL Medical Cannabis Patient Registry System established by AMCC
  - Metrc (https://www.metrc.com/)
- Practice location where medical cannabis medicine will be practiced
- Pay fees
- Initial certification to practice cannabis medicine needs to be renewed annually

UAB MEDICINE
Knowledge that will change your world

CME Requirements

- Prior to initial license issuance:
  - 4 CMEs related to medical cannabis offered by AL BME within 2 years of application
  - Receive passing grade on the test
- In order to maintain license to practice cannabis medicine:
  - Certifying physician needs to complete 2 CMEs every 2 years – CMEs need to be approved by the Board
- Limitations on Registered Certifying Providers:
  - No interactions with cannabis industry except for research
  - No solicitation of patients or referral to specific dispensaries
  - Certifying provider cannot hold interest in any medical cannabis related businesses
  - Certifying provider cannot advertise their services and cannot be located in the same office space as dispensary
  - Both, patient and provider need to be physically located in the same space in AL – in person visits are required
  - Certifying provider can only certify qualifying conditions which are treated in his/her usual practice
  - No recommendation to pregnant, breastfeeding, or trying to conceive patients

UAB MEDICINE
Knowledge that will change your world

More rules

- To recommend medical cannabis the clinician needs to have a relationship with the patient and diagnose the patient with at least one certifying condition – personally or through primary source verification
- Bona fide relationship – in-person visit (no telehealth)
  - Provider will need to continue to be the sole provider – if change in providers – the entire process starts from the beginning
- Specific consent
- Create medical record for medical cannabis management and develop a medical cannabis treatment plan
  - Review PDMP for the particular patient x 24 months
- Annual report of observations reflecting on the effectiveness of medical cannabis

UAB MEDICINE
Knowledge that will change your world

Dosing Rules

- Starting dose not to exceed 50 mg of Δ9-THC / day
- Maximum 2-months supply may be obtained at once
- Maximum 70-days supply may be in the possession of the certified patient
- Δ9-THC dose may be increased to 75 mg/day after 90 days of continued care
- Δ9-THC dose may be increased to >75 mg/day in cases of terminal illness (patient to be notified their DL will be suspended)
- Minors – maximum concentration 3% Δ9-THC
- Alabama Medical Cannabis Patient Registry System w/ access to law enforcement, HCPs, RCPs, Dispensaries, State Board of Medical Examiners, Licensed Pharmacists

UAB MEDICINE
Knowledge that will change your world

Clinic and Location

- Medical Cannabis and Medical Cannabis Medicine practice are not covered by healthcare insurance
- To avoid potential problems there should be a clear separation between standard medical practice and medical cannabis practice
- Best approach:
  - Separate medical practice from medical cannabis practice by space (location) and financial arrangements – e.g., locate UAB medical cannabis practice in a dedicated space that is not shared with any other medical practices
  - All patients sign consent that includes research clause (similar to Carly's law)
  - Not by prescription but by recommendation
  - "Consortium for Medical Cannabis Research"

UAB MEDICINE
Knowledge that will change your world

Multidisciplinary Clinic

- Beacon Parkway Facility
  - Addiction Psychiatry offices location
- The role of the physician in the clinic is to determine eligibility for receiving medical cannabis.
- All activities will be consent and IRB-driven
- UAB medical cannabis privileges approved (special form)

UAB MEDICINE
Knowledge that will change your world

Knowledge that will change your world

Cannabis can be a medicine if used correctly and thoughtfully

There are many conditions and symptoms that can be helped or alleviated by cannabis and cannabinoids

SB46 is being implemented and my hope is that patients will be able to access medical cannabis in AL soon.