

EMERGENCE OF CANNABIDIOL IN MEDICINE

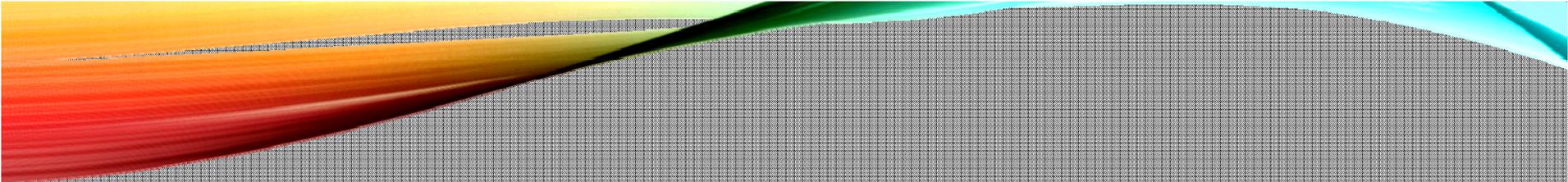
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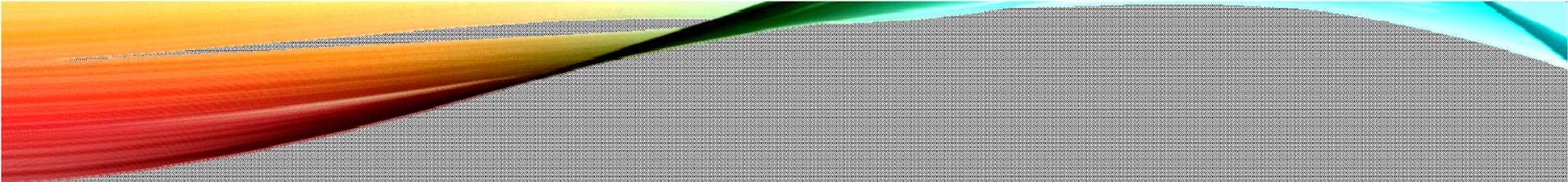
Southwest Cancer Center

Orlando, Florida



BACKGROUND

- Cannabis-There are 483 chemical constituents, 140 different cannabinoids
- Nomenclature can be confusing
- Easiest way to think of the genus Cannabis is based on plant strains rather than species
- Various names: C. Sativa, C. Indica, and hemp etc

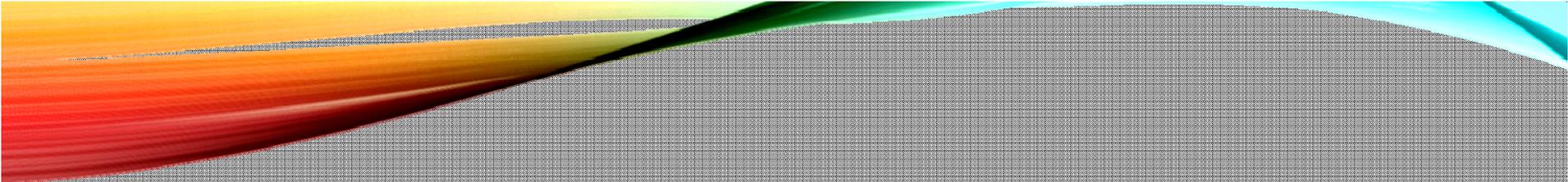


BACKGROUND

- High THC (psychoactive)
- High CBD (fibrous hemp industrial)
- Intermediate (THC and CBD)
- High CBG (Cannabigerol)
- Low THC/CBD

BACKGROUND

- The second highest cannabinoid in *Cannabis sativa L* is cannabidiol or CBD
- This is derived from the hemp strain
- No psycho-activity
- The presence or absence of THC defines Cannabis as marijuana or industrial hemp



FARM ACT OF 2018

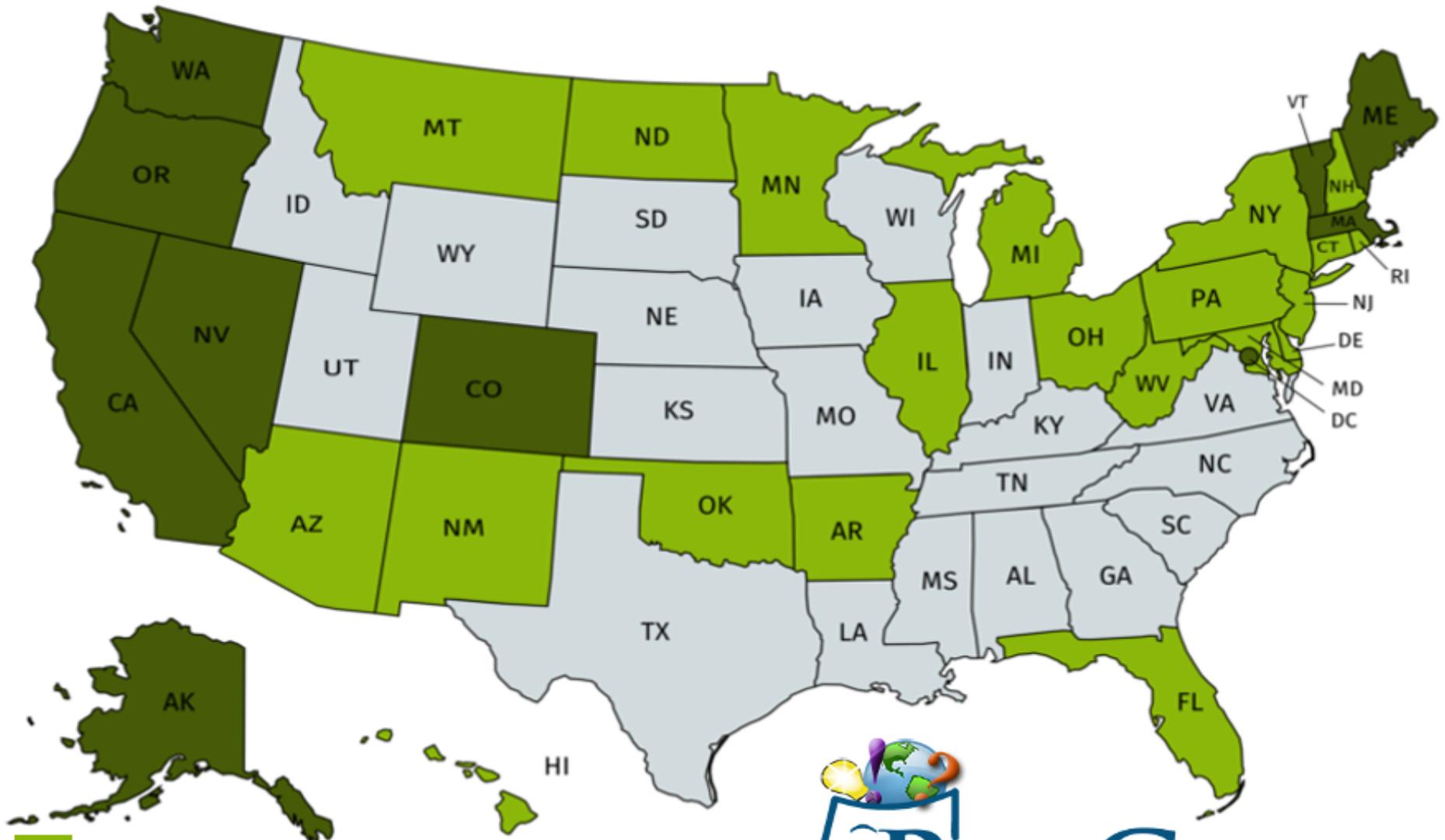
- Hemp Farming Act of 2018. The Hemp Farming Act of 2018 is a law to remove hemp (defined as cannabis with less than 0.3% THC) from Schedule I controlled substances and making it an ordinary agricultural commodity.

Research Timeline

- 1940. Cannabidiol (CBD) isolated from plant
- 1964. THC isolated from plant
- 1981. CBD anticonvulsant effect demonstrated
- 1985. Synthetic THC approved by FDA
- 1988. CB1 receptor identified
- 1992. Endogenous anandamide (AEA)
- 1993. CB2 receptor identified
- 1995. Endogenous 2-arachidonoyl glycerol

30 Legal Medical Marijuana States & DC

9 Legal Recreational Marijuana States & DC

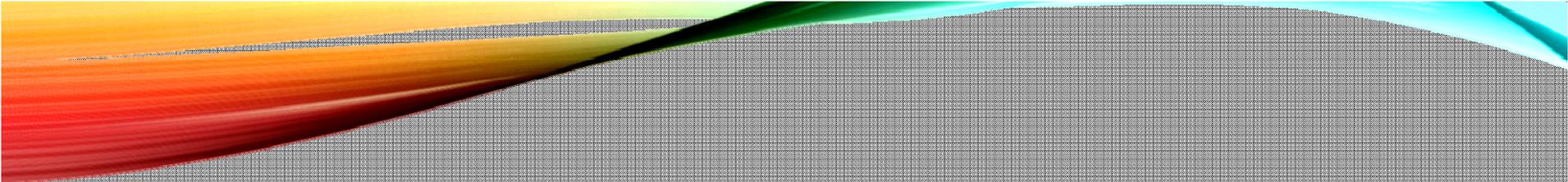


- States with Legal Medical Marijuana
- States with Legal Medical & Recreational Marijuana



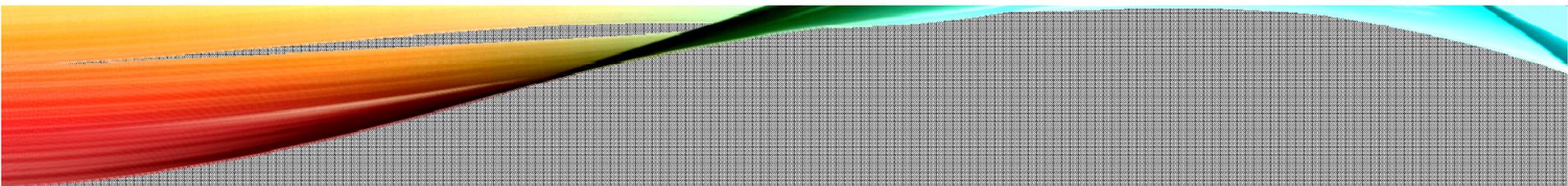


**CBD OIL LEGAL IN
50 STATES**



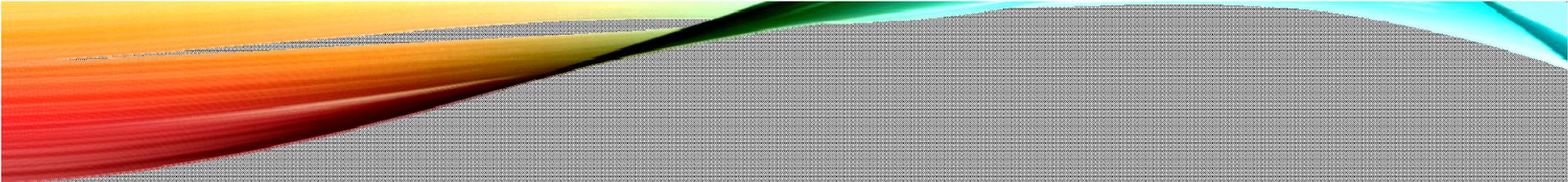
BACKGROUND

- oils, supplements, gums, tinctures
- Trade Names: Epidiolex® (approved) Arvisol® (in development)
- In clinical trials and research studies, CBD is generally administered orally as either a capsule, or dissolved in an oil solution (e.g. olive or sesame oil).
- It can also be administered through sublingual or intranasal routes. A wide range of oral doses have been reported in the literature, with most from 100-800mg/day



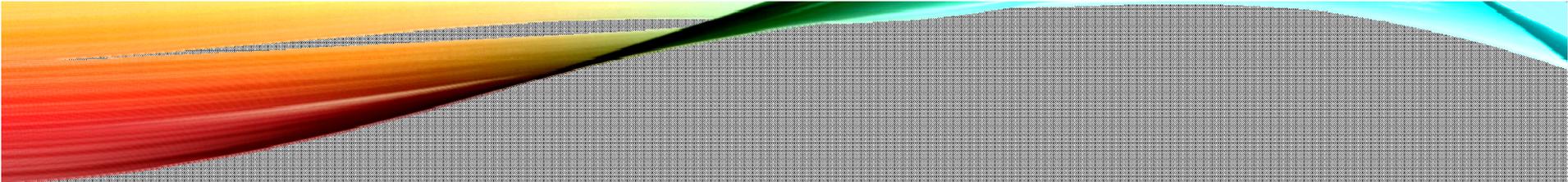
FORMULATIONS

- JAMA-Marcel et al, Labeling Accuracy of Cannabidiol Extracts Sold Online;318 (17) 1708-09, 2017
- Researchers tested 84 CBD products purchased from 31 different retailers
- Results showed that 70% items had different levels of CBD than what was written on the label
- Over half had more CBD than was stated
- ¼ had less
- 18 were THC positive



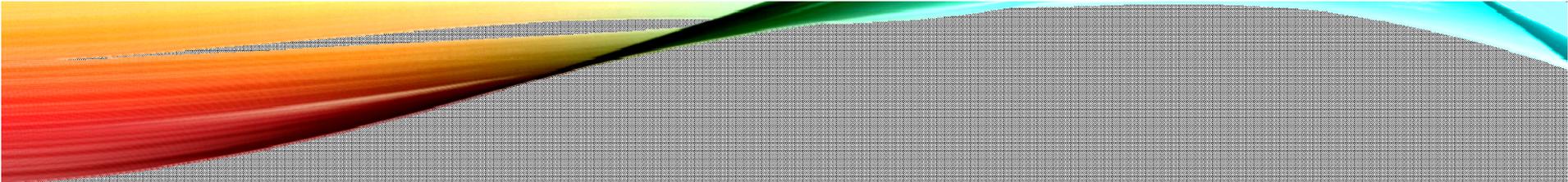
PHARMOKINETICS

- Distribution
- Metabolism
- Elimination



ADVERSE EFFECTS

- Dry mouth.
- Low blood pressure.
- Lightheadedness.
- Somnolence

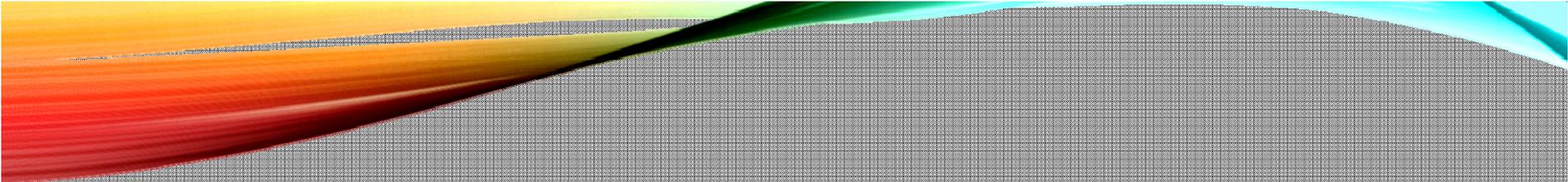


CYP3A4 INTERACTIONS

- Macrolides
- Calcium channel blockers
- Benzodiazepines
- Cyclosporine
- Sildenafil (and other PDE5 inhibitors)
- Antihistamines
- Haloperidol
- Antiretrovirals
- Some statins (seen with atorvastatin and simvastatin, but not pravastatin or rosuvastatin)

CYP2D6 INTERACTIONS

- Selective Serotonin Reuptake Inhibitors (SSRIS)
- Tricyclic Antidepressants (TCA)
- Antipsychotics
- Beta Blockers
- Opioids (Codeine and Oxycodone)

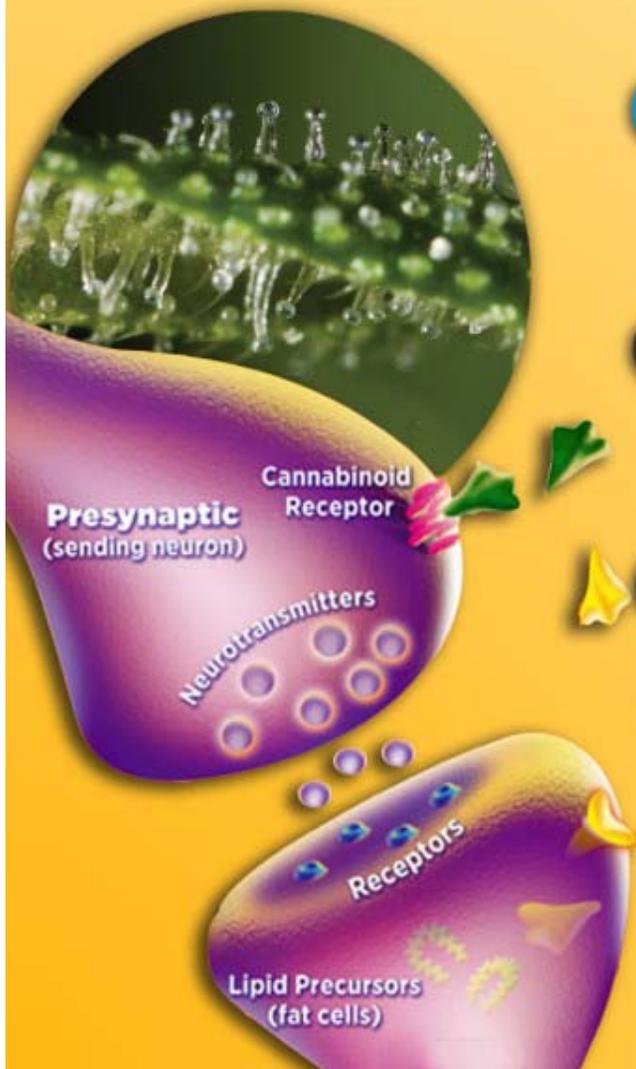


USE IN PREGNANCY AND LACTATION

- No studies have addressed this, but avoid with pregnancy and lactation

The Human Endocannabinoid System

THC and CBN are known to "fit" like lock and key into network of existing receptors. The Endocannabinoid System exists to receive cannabinoids produced inside the body called "Anandamide" and "2-Arachidonyl-glycerol". Stimulating the ECS with plant-based cannabinoids restores balance and helps maintain symptoms.



Tetrahydrocannabinol



Cannabidiol

CBD does not directly "fit" CB1 or CB2 receptors but has powerful indirect effects still being studied.

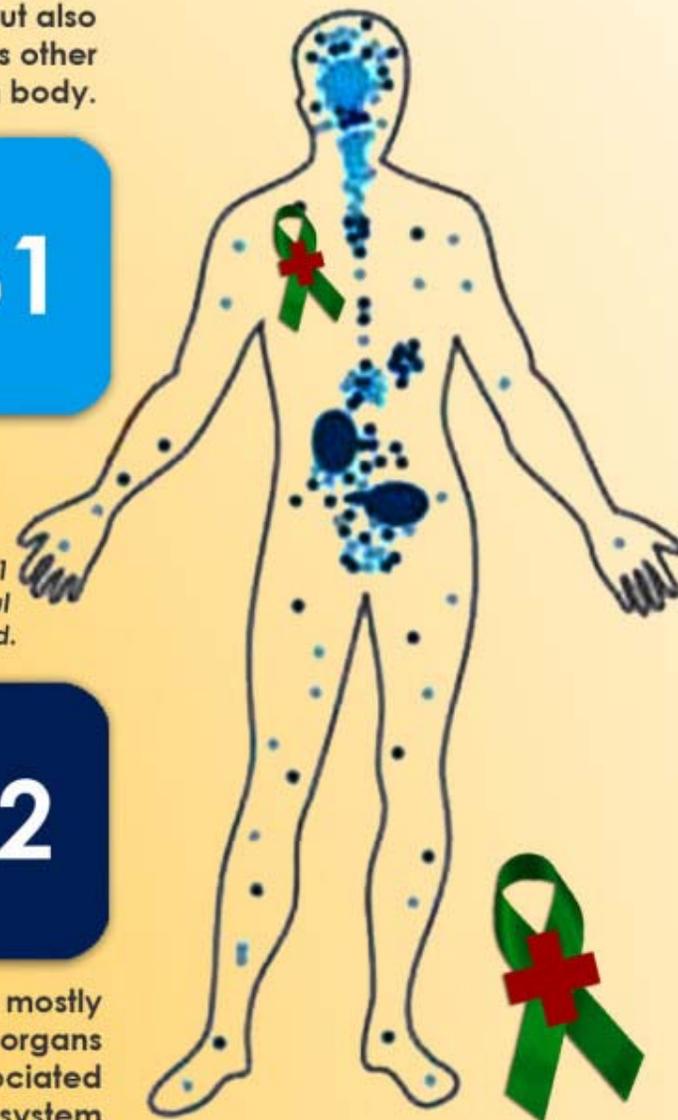


Cannabinol



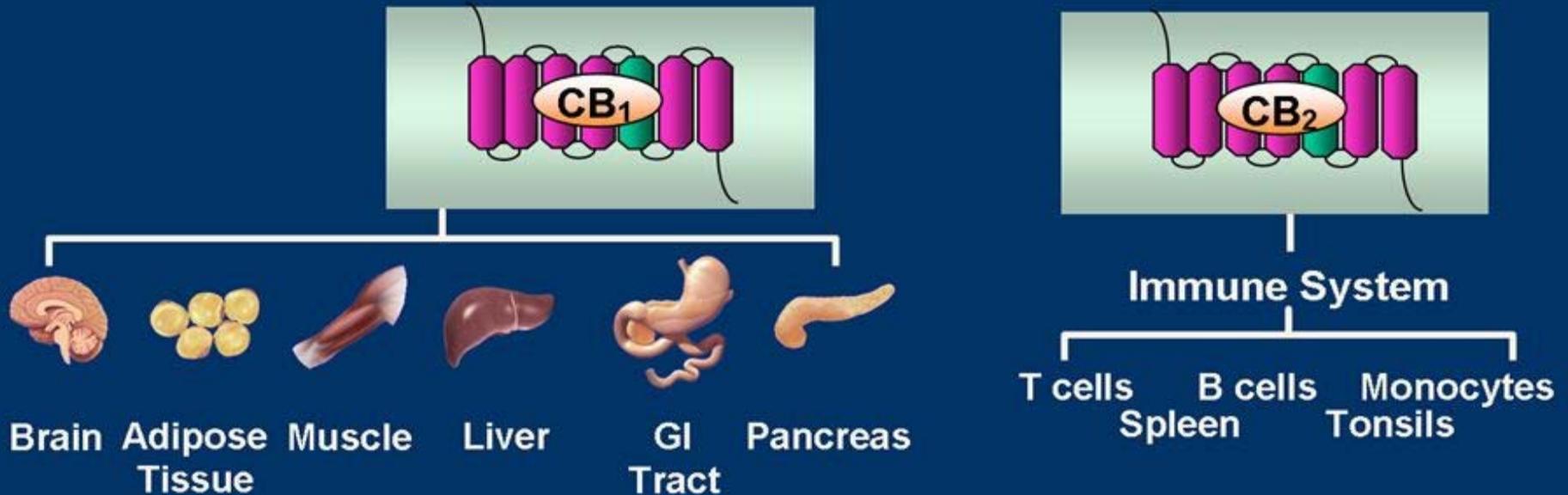
CB2 receptors are mostly in the peripheral organs especially cells associated with the immune system.

Receptors are found on cell surfaces



www.the-human-solution.org

Cannabinoid Receptors



- G-protein-coupled receptors
- CB₁ receptors highly expressed in the brain
 - CB₁ receptors also found in adipose tissue, liver, muscle, the gastrointestinal tract, pancreas, as well as reproductive and cardiovascular tissues
- CB₂ receptors are expressed primarily in immune cells
 - CB₂ receptor expression in neurons is being studied

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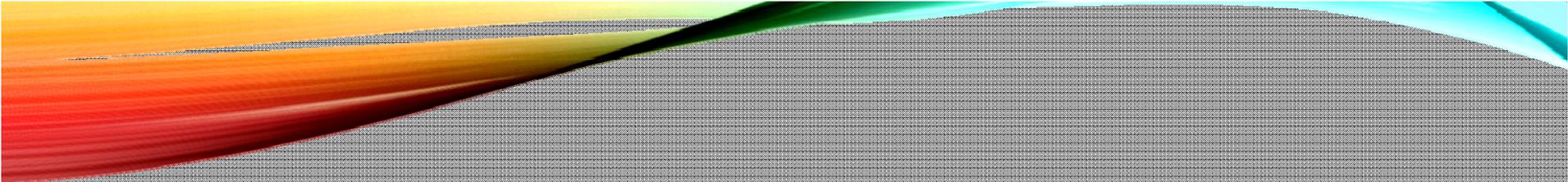
CBD RECEPTORS

CBD 1

- Adipose tissue
- Connective tissue
- Endocrine glands
- GI tract
- Exocrine glands
- Heart
- Leukocytes
- Liver
- Skin
- Spleen
- Testes, uterus

CBD 2

- Immune system
- Vascular
- Hemotopoeic



CBD AND NEUROLOGY

- Seizures
- Parkinsons disease
- ALS
- MS
- TBI
- CVA
- Movement disorders
- Tourettes syndome

Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome

Orrin Devinsky, M.D., J. Helen Cross, Ph.D., F.R.C.P.C.H., Linda Laux, M.D., Eric Marsh, M.D., Ian Miller, M.D., Rima Nabbout, M.D., Ingrid E. Scheffer, M.B., B.S., Ph.D., Elizabeth A. Thiele, M.D., Ph.D., and Stephen Wright, M.D., for the Cannabidiol in Dravet Syndrome Study Group*

ABSTRACT

BACKGROUND

The Dravet syndrome is a complex childhood epilepsy disorder that is associated with drug-resistant seizures and a high mortality rate. We studied cannabidiol for the treatment of drug-resistant seizures in the Dravet syndrome.

METHODS

In this double-blind, placebo-controlled trial, we randomly assigned 120 children and young adults with the Dravet syndrome and drug-resistant seizures to receive either cannabidiol oral solution at a dose of 20 mg per kilogram of body weight per day or placebo, in addition to standard antiepileptic treatment. The primary end point was the change in convulsive-seizure frequency over a 14-week treatment period, as compared with a 4-week baseline period.

RESULTS

The median frequency of convulsive seizures per month decreased from 12.4 to 5.9 with cannabidiol, as compared with a decrease from 14.9 to 14.1 with placebo (adjusted median difference between the cannabidiol group and the placebo group in change in seizure frequency, -22.8 percentage points; 95% confidence interval [CI], -41.1 to -5.4 ; $P=0.01$). The percentage of patients who had at least a 50% reduction in convulsive-seizure frequency was 43% with cannabidiol and 27% with placebo (odds ratio, 2.00; 95% CI, 0.93 to 4.30; $P=0.08$). The patient's overall condition improved by at least one category on the seven-category Caregiver Global Impression of Change scale in 62% of the cannabidiol group as compared with 34% of the placebo group ($P=0.02$). The frequency of total seizures of all types was significantly reduced with cannabidiol ($P=0.03$), but there was no significant reduction in nonconvulsive seizures. The percentage of patients who became seizure-free was 5% with cannabidiol and 0% with placebo ($P=0.08$). Adverse events that occurred more frequently in the cannabidiol group than in the placebo group included diarrhea, vomiting, fatigue, pyrexia, somnolence, and abnormal results on liver-function tests. There were more withdrawals from the trial in the cannabidiol group.

CONCLUSIONS

Among patients with the Dravet syndrome, cannabidiol resulted in a greater reduction in convulsive-seizure frequency than placebo and was associated with higher rates of adverse events. (Funded by GW Pharmaceuticals; ClinicalTrials.gov number, NCT02091375.)

From the New York University Langone Comprehensive Epilepsy Center, New York (O.D.); the University College London Great Ormond Street Institute of Child Health (J.H.C.) and GW Pharmaceuticals (S.W.) — both in London; Lurie Children's Epilepsy Center, Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago (L.L.); the Children's Hospital of Philadelphia, Philadelphia (E.M.); Miami Children's Hospital, Miami (I.M.); Hôpital Necker-Enfants Malades, Paris (R.N.); Florey Institute, Austin Health and Royal Children's Hospital, University of Melbourne, Melbourne, VIC, Australia (I.E.S.); and Massachusetts General Hospital, Boston (E.A.T.). Address reprint requests to Dr. Devinsky at the Department of Neurology, NYU Langone School of Medicine, 223 E. 34th St., New York, NY 10016, or at od4@nyu.edu.

*A complete list of investigators in the Cannabidiol in Dravet Syndrome Study Group is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Devinsky and Cross contributed equally to this article.

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DRAVET SYNDROME

- The Dravet syndrome is a complex childhood epilepsy disorder that is associated with drug-resistant seizures and a high mortality rate.

Table 2. Primary Efficacy End Point of Percentage Change in Convulsive-Seizure Frequency in Each Trial Group.*

Variable	Cannabidiol	Placebo	Adjusted Median Difference (95% CI) <i>percentage points</i>	P Value†
No. of convulsive seizures per mo — median (range)				
Baseline	12.4 (3.9 to 1717)	14.9 (3.7 to 718)		
Treatment period	5.9 (0.0 to 2159)	14.1 (0.9 to 709)		
Percentage change in seizure frequency — median (range)	-38.9 (-100 to 337)	-13.3 (-91.5 to 230)	-22.8 (-41.1 to -5.4)	0.01

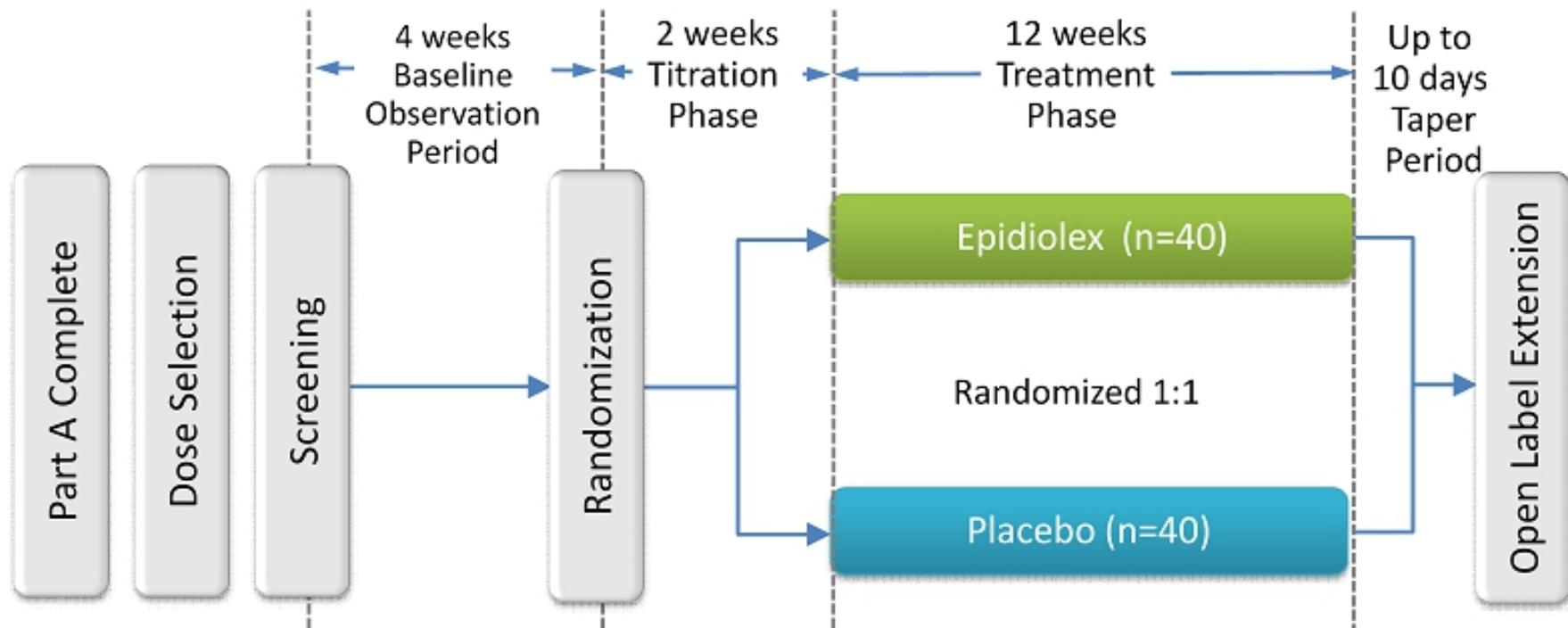
* CI denotes confidence interval.

† The P value was calculated with the use of a Wilcoxon rank-sum test with the Hodges–Lehmann approach.

Epidiolex in Dravet Syndrome

Part B Trial Design

Objective: Provide pivotal evidence of safety and efficacy



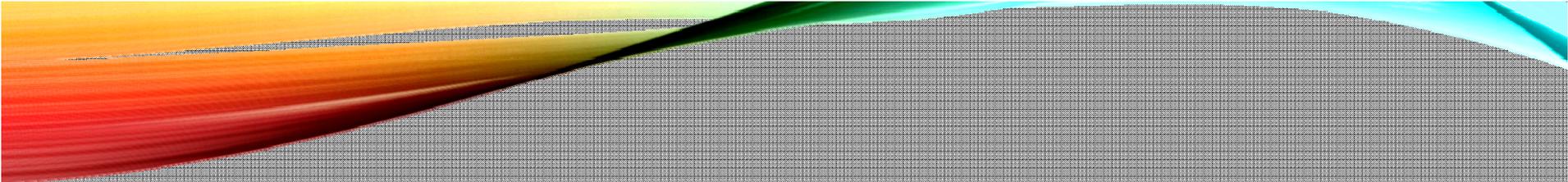
Primary Endpoint: Average % change from baseline in convulsive seizure frequency

Secondary Endpoints:

- % change non-convulsive seizures
- Change in seizure subtypes
- % seizure freedom
- Responder rate
- Cognition
- Daytime sleepiness scale
- Night time sleep disruption
- Caregiver Global Impression of Change
- Palatability of the drug product
- Quality of Life

CONCLUSIONS

- Among patients with the Dravet syndrome, cannabidiol resulted in a greater reduction in convulsive-seizure frequency than placebo and was associated with higher rates of adverse events.
- Adverse events that occurred more frequently in the cannabidiol group than in the placebo group included diarrhea, vomiting, fatigue, pyrexia, somnolence, and abnormal results on liver-function tests.
- There were more withdrawals from the trial in the cannabidiol group.



CBD AND PSYCHIATRY

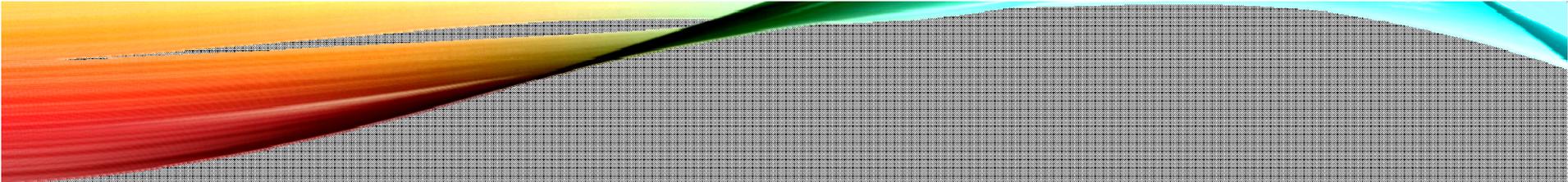
- Anxiety
- ADHD
- Schizophrenia
- Insomnia

CBD AND HIV

- Kaposi Sarcoma
- HIV wasting syndrome
- A study of response to smoked cannabis, dronabinol, or placebo in patients with AIDS demonstrated that the patients using smoked cannabis experienced the greatest weight gain (3.51 kg vs. 3.18 kg vs. 1.5 kg respectively)

PAIN AND CBD

- CBD has a low reinforcing profile with limited abuse potential and it appears to inhibit drug seeking behavior.
- Furthermore, CBD decreases stress vulnerability and reduces anxiety.



CBD AND CHRONIC PAIN

-Two publications confirmed the benefit of cannabinoid use, with twenty-nine randomized studies having been examined and included in separate systematic analyses

-Cannabinoids were found to be safe, modestly effective, and a reasonable option for treating chronic neuropathic pain.

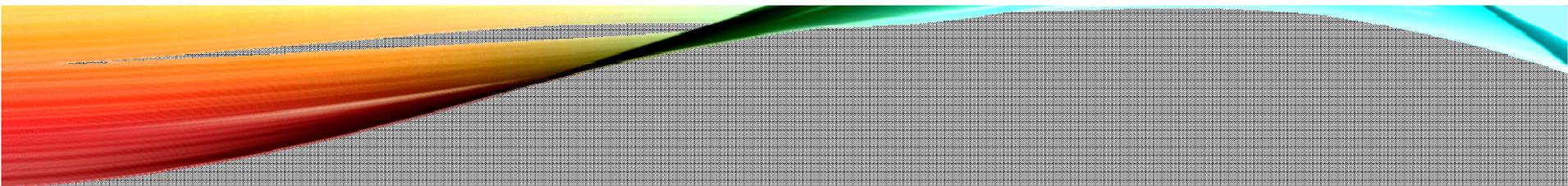
-Those data have contributed to the revision, by the Canadian Pain Society, of their consensus statement on the treatment of chronic neuropathic pain to include cannabinoids as third-level therapy

DOSAGE

- not well established
- preliminary clinical trials suggest that high-dose oral CBD (150–600 mg/d) may exert a therapeutic effect for social anxiety disorder, insomnia and epilepsy, but also that it may cause mental sedation
- Lower doses such as 10-100 mg are used to treat pain and inflammation

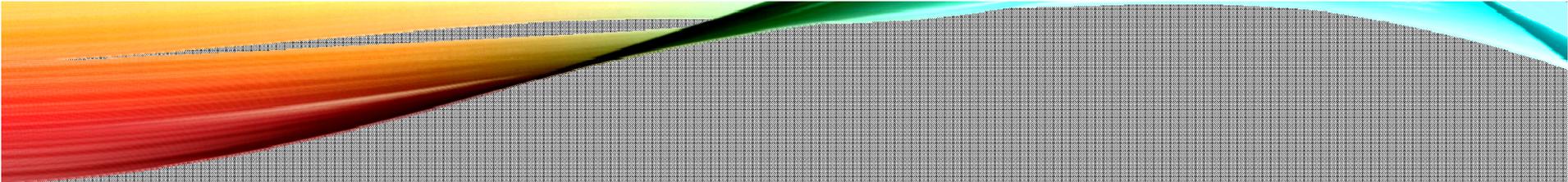
QUITTING SMOKING AND DRUG WITHDRAWALS

- A study published in *Addictive Behaviors* found that smokers who used inhalers containing CBD smoked fewer cigarettes than usual
- Furthermore, smoked fewer cigarettes than usual and had no further cravings for nicotine



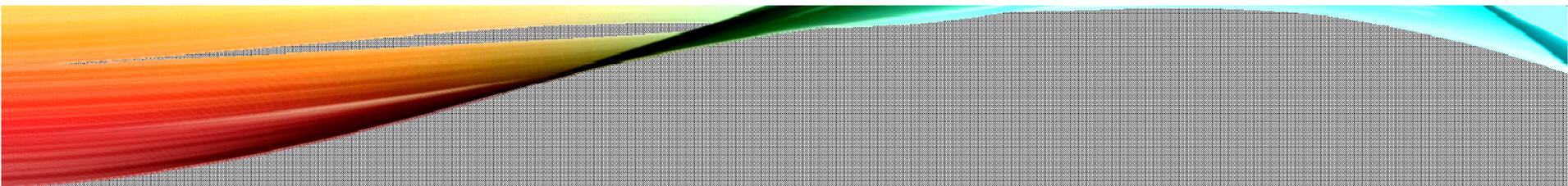
QUITTING SMOKING AND DRUG WITHDRAWALS

- A similar review in *Neurotherapeutics* found that CBD may be a promising treatment for people with opioid addiction disorders
- More research is necessary, but these findings suggest that CBD may help to prevent or reduce withdrawal symptoms



CBD AND ONCOLOGY

- The most studied and established roles for cannabinoid therapies include pain, chemotherapy-induced nausea and vomiting, and anorexia.
- use of cannabinoid therapies could be effective in improving quality of life
- Cannabinoid treatments for cancer pain have been studied in a few randomized trials, but the evidence has been less than convincing.
- Earlier studies (published before 2001, as reviewed by Campbell *et al*) demonstrated mild benefits, with adverse effects limiting the dose used



CBD AND ONCOLOGY- ANTIEMETIC

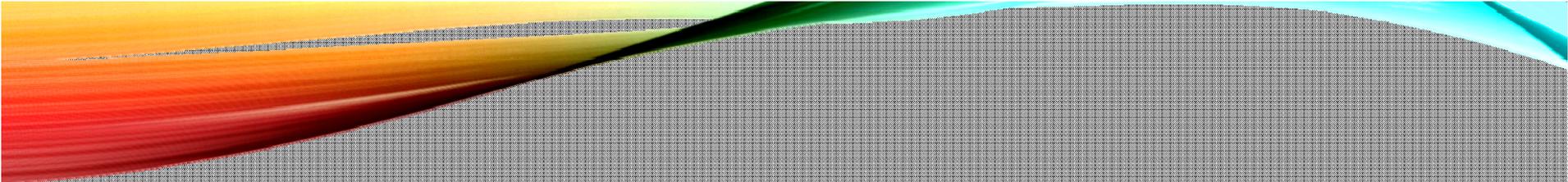
- In 1975, Sallan *et al.* showed that use of THC could control the nausea associated with chemotherapy and almost eliminate emesis.
- Since then, several larger-scale studies, mostly placebo-controlled randomized studies, have been completed.

CBD AND ONCOLOGY- APPETITE STIMULATOR

- When used in cancer patients with cachexia, cannabinoids appear to be only modestly effective.
- A study from the North Central Cancer Trial Group compared the use of an oral cannabinoid (dronabinol) with oral megestrol acetate and with the two drugs together.
- Final results did not show any statistical improvement in weight with dronabinol, either alone or in combination

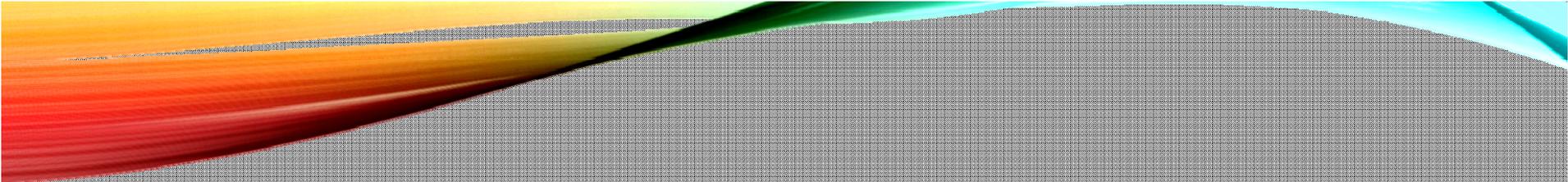
PAST TRIALS IN CBD

- The first documented experiments on the effects of CBD were performed in the 1970s
- First documented trials have been reported in glioma cells and lung cancer
- 1975-Munson et al reported anti-proliferative actions of CBD *in vitro* and *in vivo* on Lewis lung adenocarcinoma
- Effects on glioma cells were selective, meaning it did not cause apoptosis in normal glioma cells
- In the last few years , there has been renewed interest in CBD as an anti cancer drug



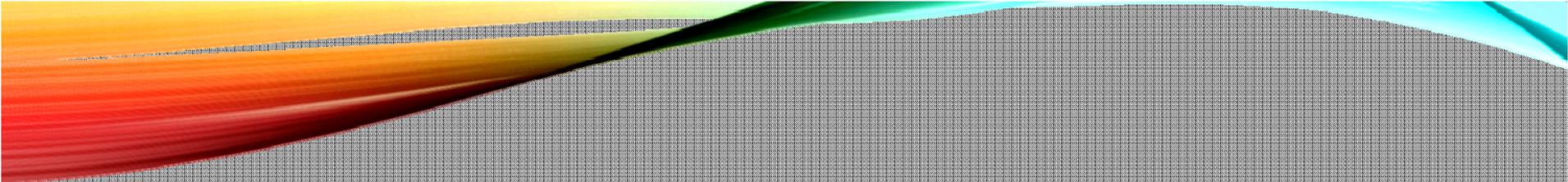
MECHANISM OF ACTION IN CANCER

- The ATP depended drug efflux transporter (PgP) confers multidrug resistance (MDR) by effluxing a diverse array of anti neoplastic agents
- PgP is overexpressed in malignant cells
- Preliminary evidence shows that cannabinoids do not exacerbate Pgp mediated MDR



INDUCTION OF CANCER CELL DEATH

- Apoptosis
- Inhibit angiogenesis
- Regulation of antitumor activity



MECHANISM OF ACTION IN ONCOLOGY

- Cannabinoids have been shown to enhance the uptake of chemotherapy into malignant cells without affecting normal cells
- CBD exhibits anti-proliferative and pro apoptotic effects, inhibits cancer cell migration, adhesion, and invasion

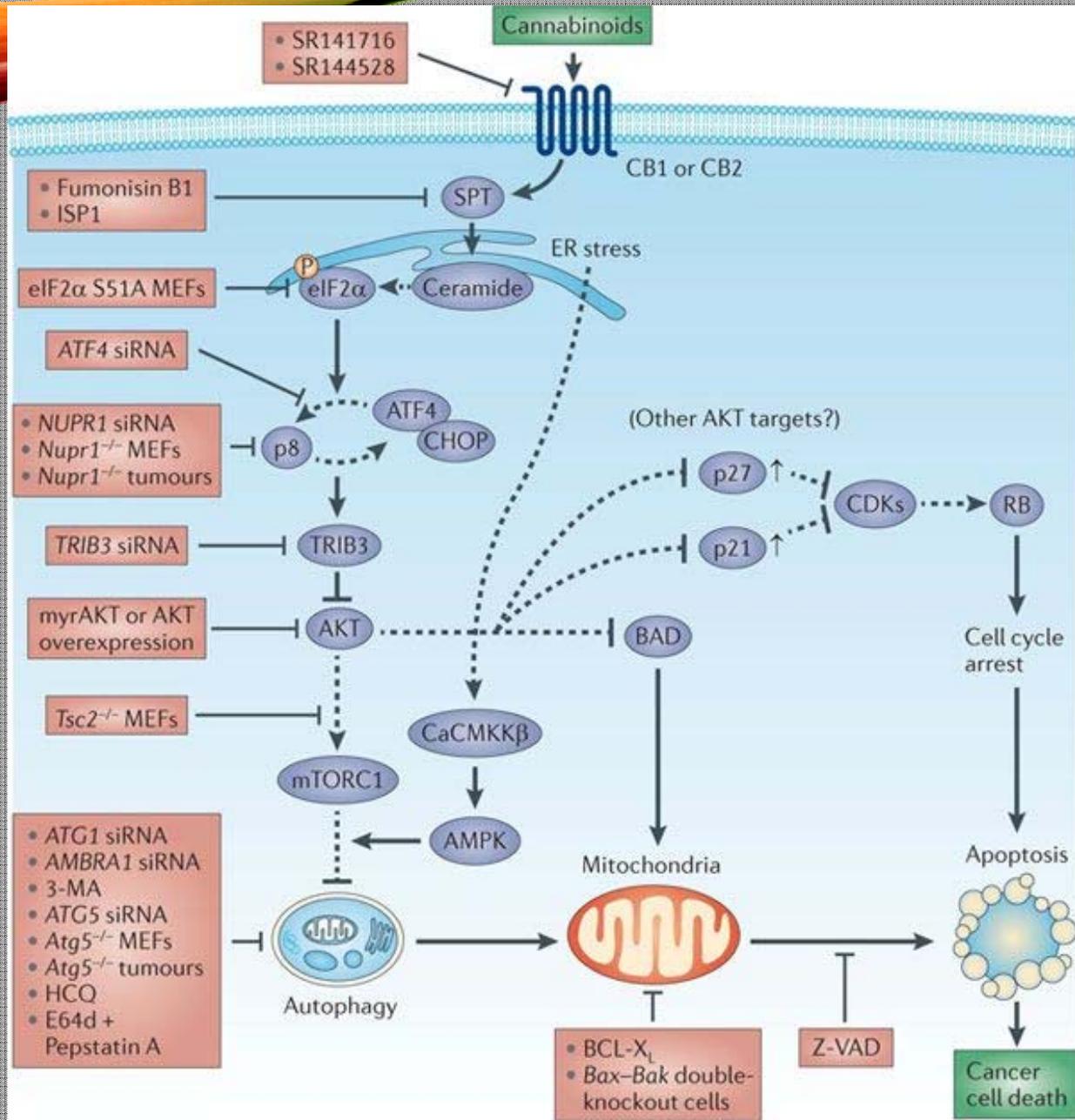
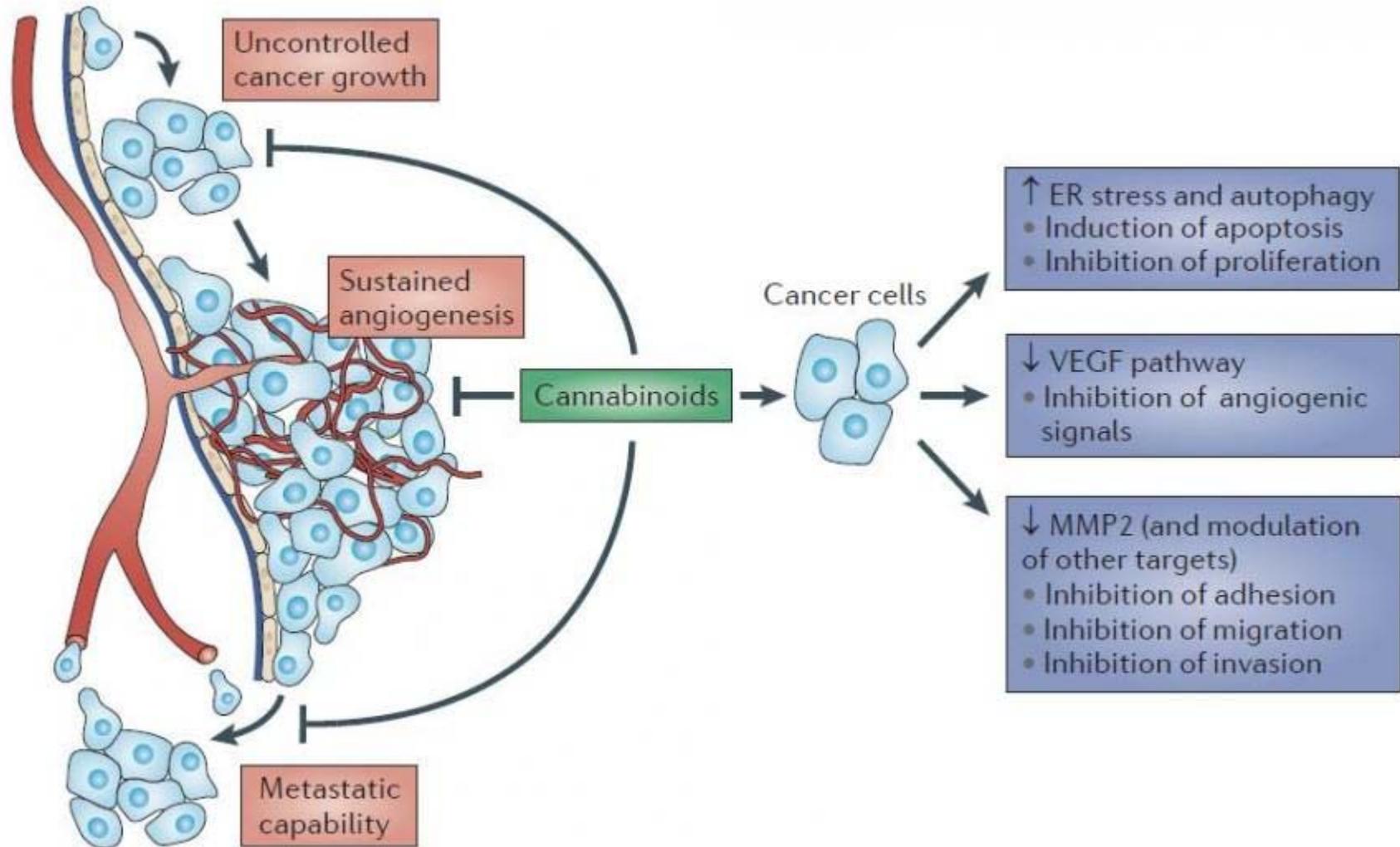


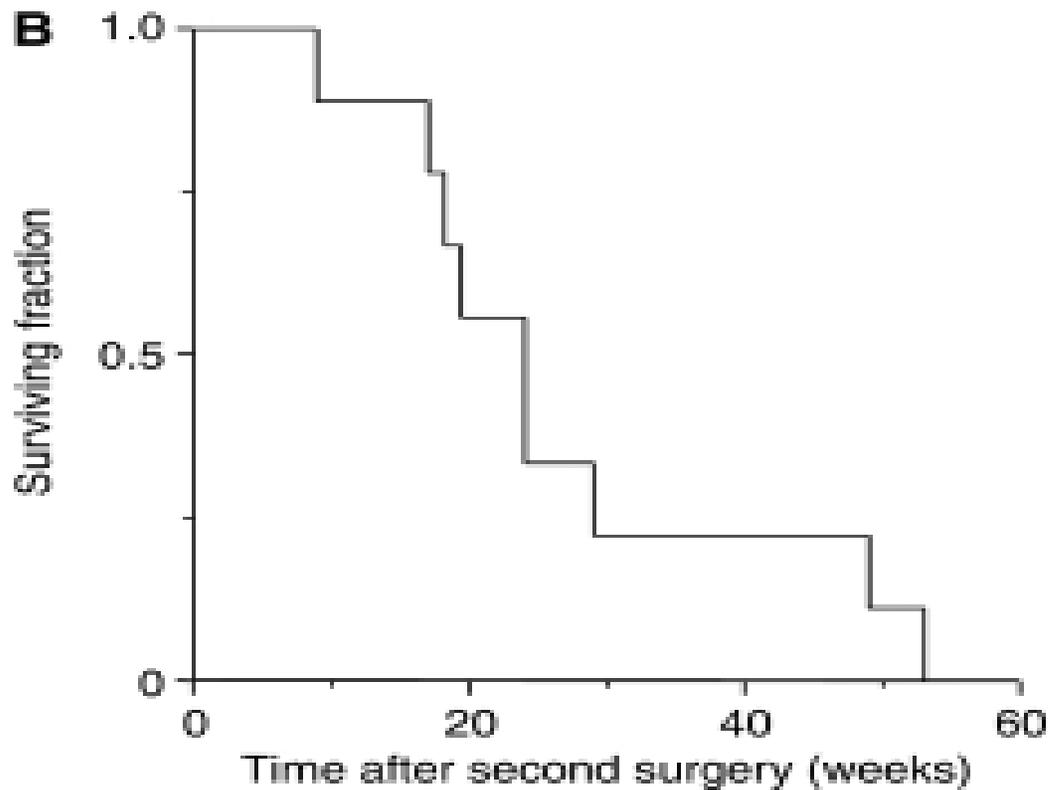
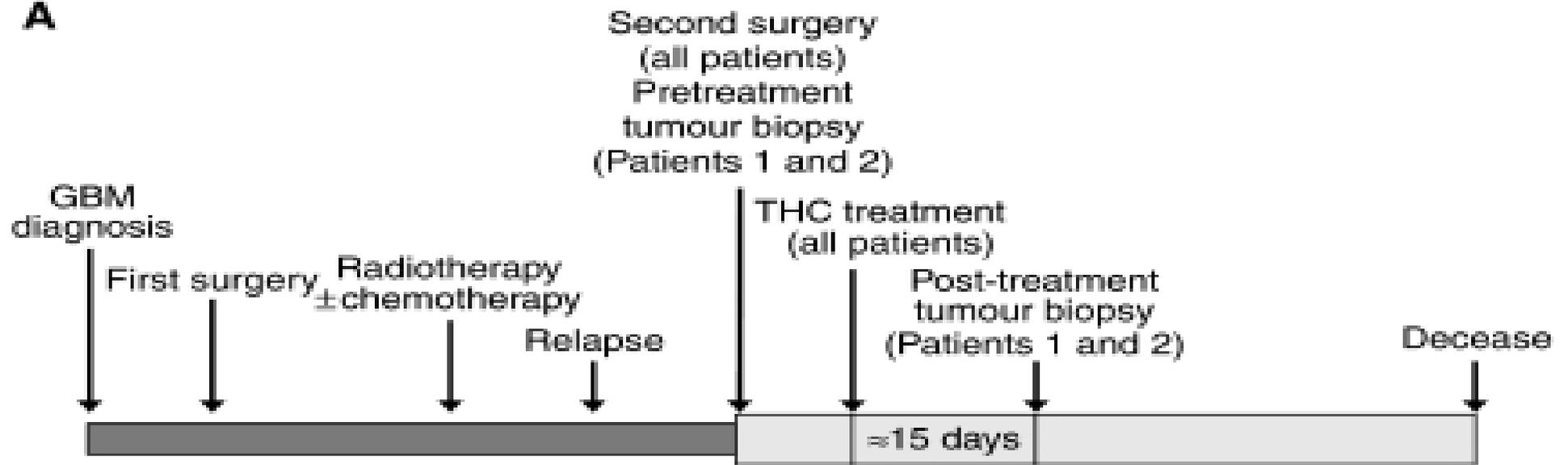
Table 1 | Cannabinoids activate a similar pro-apoptotic mechanism in different types of cancer cells*

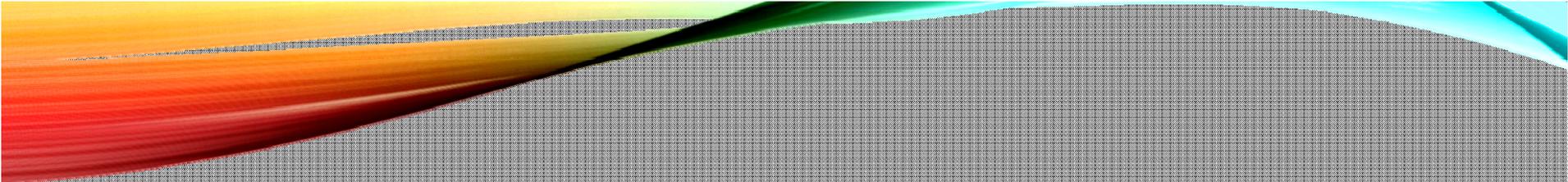
Cancer cell	CB receptor involved	Ceramide synthesis	ER stress	p8-TRIB3 induction	AKT inhibition	Autophagy	Apoptosis
Glioma	CB1 and CB2	✓	✓	✓	✓	✓	✓
Pancreatic cancer	CB2	✓	✓	✓	✓	✓	✓
Hepatocellular carcinoma	CB2	✓	✓	✓	✓	✓	✓
Breast cancer	CB2	ND	ND	✓	✓	✓ (UO) [‡]	✓
Rhabdomyosarcoma	CB1	ND	✓	✓	✓	ND	✓
Mantle cell lymphoma	CB1 and CB2	✓	✓	ND	ND	✓ (WIN 55,212-2) [§]	✓ (WIN 55,212-2) [§]
Leukaemia	CB2	✓	ND	ND	✓	ND	✓
Prostate cancer	CB2	✓	ND	ND	✓	ND	✓
Melanoma	CB2	ND	ND	✓	✓	✓ (UO) [‡]	✓
Lung carcinoma	ND	ND	ND	ND	✓	ND	✓



PAST TRIALS IN GLIOBLASTOMA

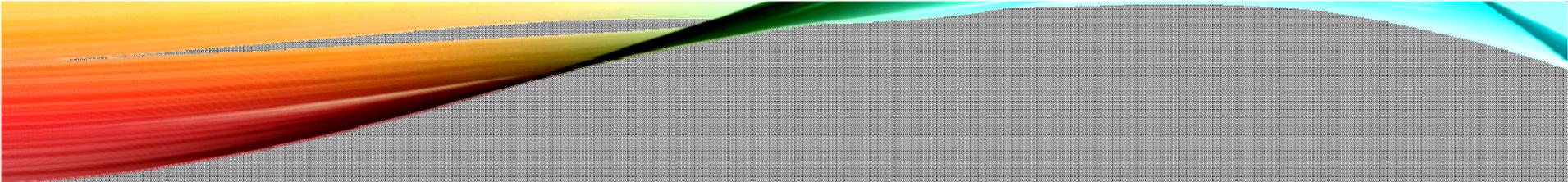
- BJM Cancer 2006 95 197-200 *A pilot study of Delta 9 Tetrahydrocannabinidiol in patients with recurrent Glioblastoma Multiforme*
- Current standard of care involves resection follow by radiation therapy and Temazolamide (Temador)
- Median survival of the cohort from the beginning of cannabinoid administration was 24 weeks (95% confidence interval)
-

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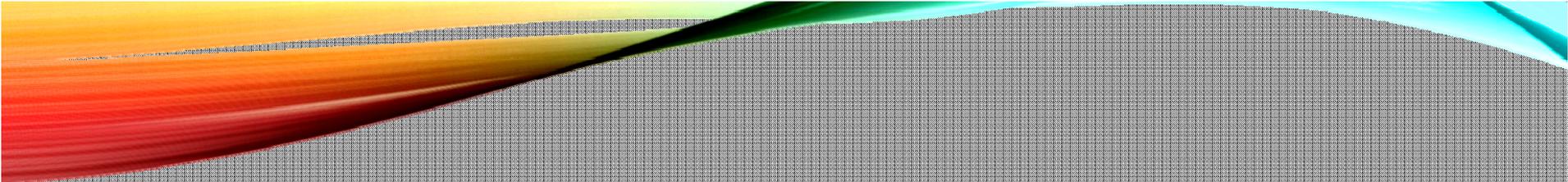
BREAST CANCER

- CBD has been reported to inhibit the proliferation of both estrogen receptor (ER) positive and ER negative human breast cancer cell lines
- Causes autophagy induced death in breast cancer cells by induction of endoplasmic reticulum stress
- Inhibits mTOR signaling (AKT mammalian target of rapamycin)



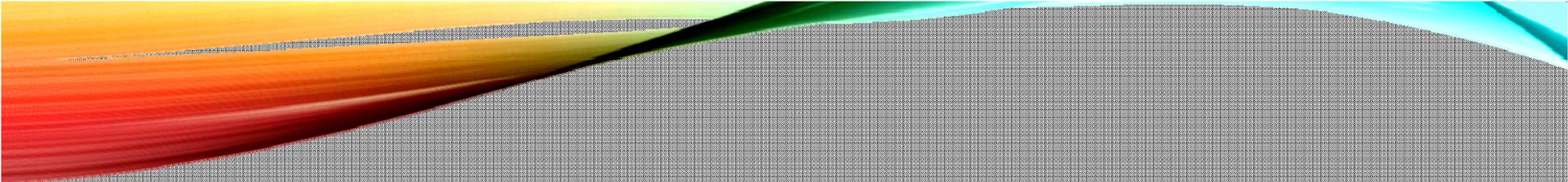
LUNG CANCER

- CBD decreased cancer cell invasiveness inducing both the expression of ICAM-1 and the levels of tissue inhibitor metalloproteinases in several lung cancer cell lines



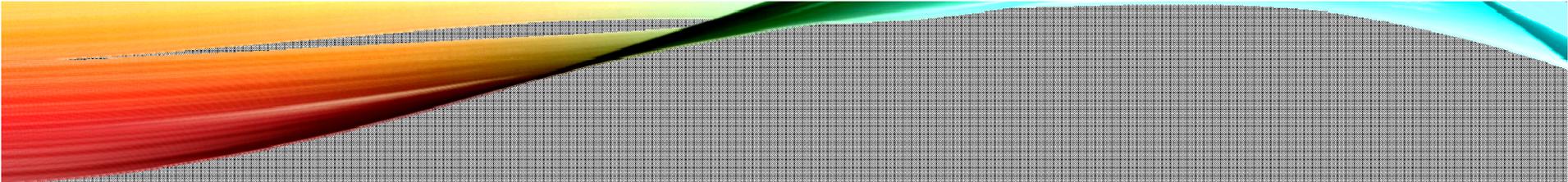
COLON CANCER

- High cause of mortality in the Western hemisphere
- CBD is able to reduce intestinal inflammation, exerts anti oxidant effects
- Chemopreventative effects have been shown



CNS MALIGNANCIES

- CBD has been shown to reduce proliferation and invasiveness of glioblastoma cells
- Causes a decrease of proteins involved in growth, invasion and angiogenesis



SAFETY DATA

- **Methods:** 14 patients with various malignancies in Orlando voluntarily utilized 200mg cannabidiol dose per day (100mg morning/100mg evening before meals) in combination with standard of care chemotherapy. Safety data, using heart rate, blood pressure, body temperature, hematologic parameters, chemistries, kidney and liver function tests were assessed at each patient visit.
- **Findings:** Cannabidiol did not affect heart rate, blood pressure and body temperature, hemoglobin, hematocrit, platelet, renal or liver functions. Patient Reported Outcome included feeling more stable and were more able to adhere to their chemotherapy schedules, were less nauseated, had better sleep and had less pain compared to before using the formula.

	No Adverse Effects	Mild	Medium	Moderate	Severe
BEFORE CANNABIDIOL	61.04%	5.84%	12.34%	7.79%	12.99%
AFTER CANNABIDIOL	68.63%	18.95%	7.19%	3.27%	1.96%

*Adverse Effects recorded:

Nausea

Visual Issues

Anxiety

Headaches

Vomiting

Weakness

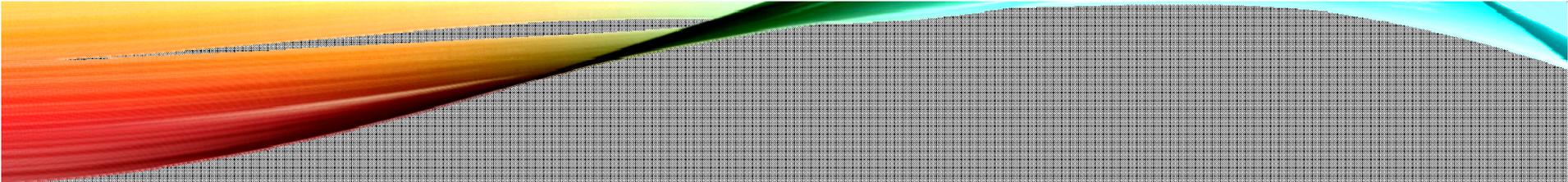
Loss of Appetite

Stomach Pain

Overall Pain

Diarrhea

Sleep Issues



OUR RESEARCH

- Current trials in GBM, GI malignancies, and Multiple myeloma
- Future trials in Breast Cancer, leukemia, and other solid tumors

CONCLUSION

- CBD has an role in several aspects of medicine, including neurology, psychiatry, and oncology
- Has been shown to be safe in several patient populations
- CBD is an adjunct to standard of care in oncology
- Further studies will be needed to determine its place as part of standard of care