MEDICAL USES OF CBD OIL

Seventh Annual Northern Ontario Pediatrics Conference

Sudbury, Ontario

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Maria Zak, MN, NP-Paediatrics

SickKids

DISCLOSURE

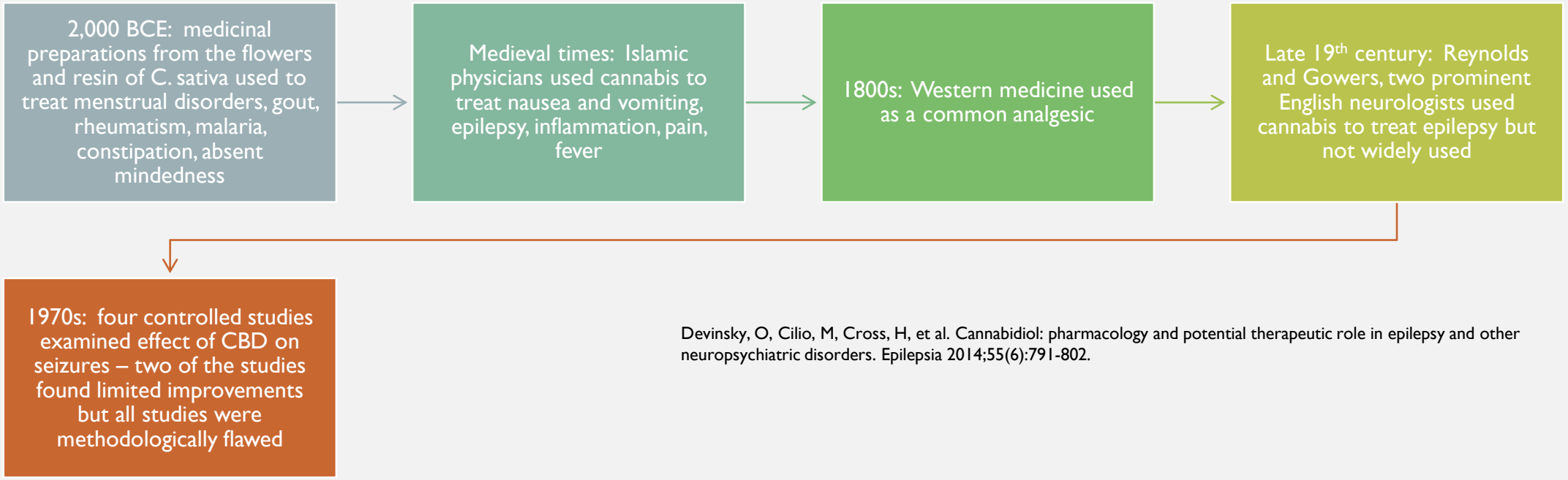
Co-investigator on a prospective open-label study of a CBD/THC cannabis oil in Dravet Syndrome

CBD/THC cannabis oil supplied in kind by Tilray™

LEARNING OBJECTIVES

Identify	Identify three medical uses of CBD oil.
Describe	Describe which medical uses of CBD oil have research evidence to support its use in disease management.
Apply	Apply the knowledge gained about the uses of medical cannabis and the conditions for which they are used to counsel patients about the known information and current research evidence in order to guide treatment.

BRIEF HISTORY OF CANNABIS USE IN MEDICINE



Devinsky, O, Cilio, M, Cross, H, et al. Cannabidiol: pharmacology and potential therapeutic role in epilepsy and other neuropsychiatric disorders. Epilepsia 2014;55(6):791-802.

BRIEF HISTORY OF CANNABIS USE IN MEDICINE (CONT'D)

One epidemiologic study of illicit drug use and new onset seizures found cannabis to be a protective factor against first seizures in men with no effect observed in women

The study concluded cannabis was protective against provoked and unprovoked seizures in men

Brust JC, Ng SK, Hauser A, et all. Marijuana use and the risk of new onset seizures. Trans Am Clin Climatol Assoc 1992;103:176-181.

CANNABIS AND ITS COMPONENTS

Cannabis sativa (e.g. cannabis, marihuana, marijuana) – hemp plant grows in temperate and tropical climates

Flowering tops and leaves the of the cannabis plant contain:

- > 500 distinct compounds that are part of 18 different chemical classes
- Consist of > 100 different phytocannabinoids with the primary phytocannabinoids being:
  - Delta-9-tetrahydrocannabinol (Δ^9-THC, THC), CBN, and cannabidiol (CBD)
  - Other phytocannabinoids: cannabigerol (CBG), cannabichromene (CBC), tetrahydrocannabivarin (THCV) among many others

Devinsky, O, Cilio, M, Cross, H, et al. Cannabidiol:pharmacology and potential therapeutic role in epilepsy and other neuropsychiatricisorders. Epilepsia 2014;55(6):791-802.

CANNABIS AND ITS COMPONENTS (CONT'D)

- Chemical classes of compounds found in cannabis:
  - Phytocannabinoids
  - Nitrogenous compounds
  - Amino acids
  - Proteins
  - Enzymes
  - Glycoproteins
  - Hydrocarbons
  - Simple alcohols
  - Aldehydes
  - Ketones and acids
  - Fatty acids
  - Simple esters and lactones
  - Steroids
  - Terpenes
  - Non-cannabinoid phenols
  - Flavonoids
  - Vitamins
  - Pigments

Elsohly MA, Slade D. Chemical constituents of marijuana: The complex mixture of natural cannabinoids . Life Sci 2005 12/22;78(0024-3205; 0024-3205; 5):539-48.

CANNABIS AND ITS COMPONENTS (CONT'D)

Little known about the pharmacological actions of the various compounds found in cannabis

Terpenes (In Vitro and In Vivo Studies Only)

- Broad spectrum of action
- Anti-oxidant, anti-anxiety, anti-inflammatory, anti-bacterial, anti-neoplastic, anti-malarial
- Vary widely among cannabis strains – thought to be responsible for the differences in fragrance
- May contribute to the different smoking qualities and possibly the character of the "high" experienced when smoking Cannabis

Russo E, McPartland J. Cannabis is more than simply delta(9)-tetrahydrocannabinol. Psychopharacology (Berl) 2003 02;165:431-2.

CANNABINOIDS

Δ^9-THC – best studied among the cannabinoids

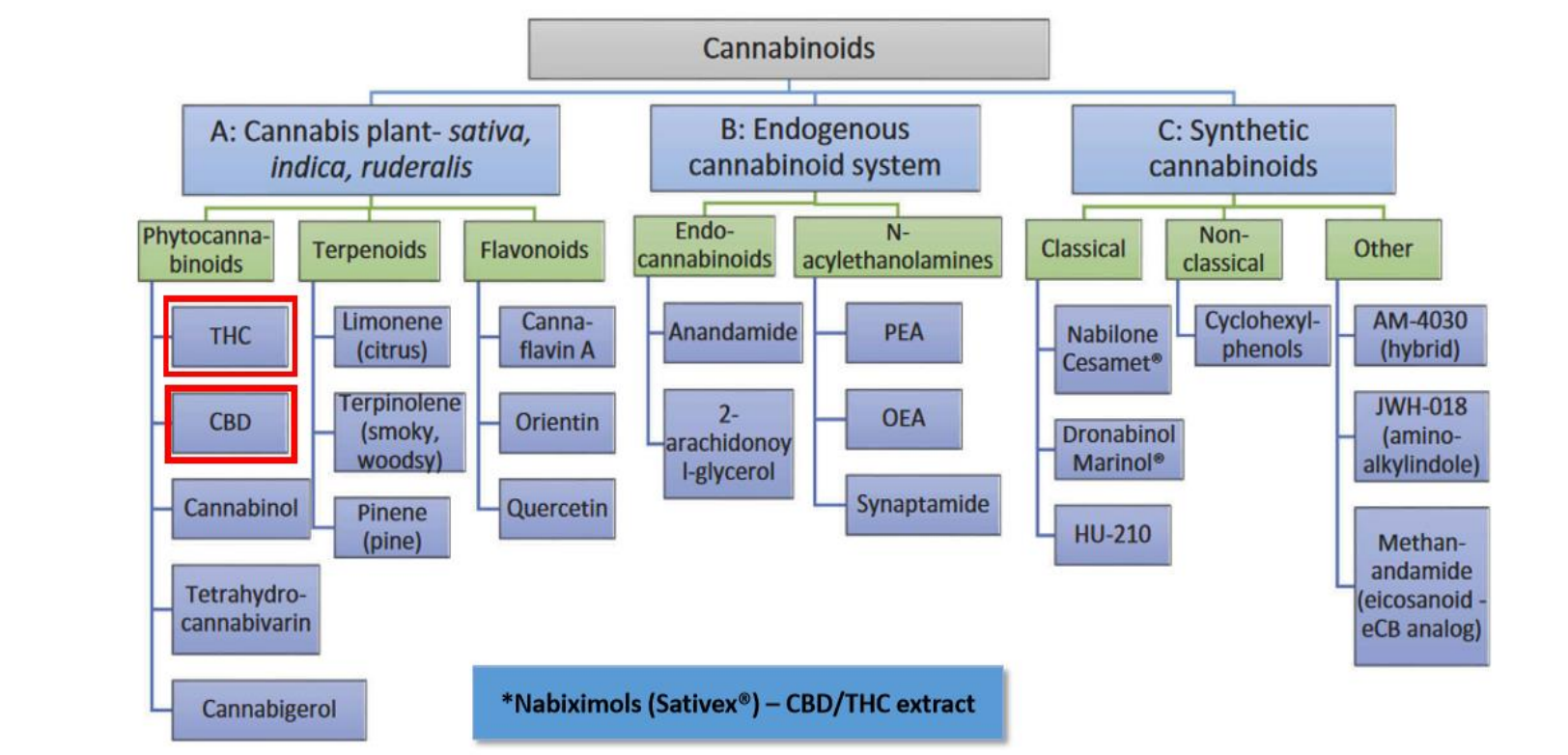
- Responsible for many or most of the physical and psychotrophic effects of cannabis `

Phytocannabinoids (CBD, CBC, CBG)

- Present in lesser amounts in the plant
- Little if any psychotrophic properties

Ashton CH. Pharmacology and effects of cannabis: A brief review. Br J Psychiatry 2001 02;178(0007-1250):101-6.

CANNABINOIDS



Expert Opinion on Investigational Drugs, 28:3,285-296.

CANNABINOID PRODUCTS

TABLE 1 Cannabis Products

Products Generic (Brand)	Cannabinoid Content	Administration Formulation and Dosage	FDA Approval	Indications	Approved Countries
Dronabinol (Marinol and Syndros)	Synthetic δ-9-THC	Oral capsule or solution 5–15 mg/m^2 per dose, up to 6 doses daily	Approved in 1985, Schedule III controlled substance	CINV (pediatric and adult), anorexia associated with weight loss in AIDS (adult)	United States, Australia, Germany, New Zealand, and South Africa
Nabilone (Cesamet)	Synthetic δ-9-THC	Oral capsule 1 or 2 mg twice a day, up to 6 mg daily (adult)	Approved in 1985, Schedule II controlled substance	CINV	United States, Canada, Ireland, Mexico, and United Kingdom
Nabiximols (Sativex)	Ratio of 2.7 δ-9-THC to 2.5 CBD, plant derived	Oromucosal spray 1 spray daily, up to 12 sprays daily with at least 15 min between sprays (adult)	Phase III trials	Neuropathic pain, cancer pain, multiple sclerosis spasticity	Canada, Czech Republic, United Kingdom, Denmark, Germany, Poland, Spain, and Sweden
CBD (Epidiolex)	CBD, plant derived	Oral solution 2 up to 50 mg/kg per d (research trials)	Phase III trials, fast-track designation	Epilepsy	None
Cannabis plant products (eg, marijuana and oral cannabis extracts)	Varying concentration of plant-derived THC to CBD	Includes smoking (marijuana) and oral (cannabis extracts)	None, Schedule I controlled substance	None approved	Medically and recreationally legal in certain states via physician certification

Wong SS and Wilens TE. Medical Cannabinoids in Children and Adolescents: A Systematic Review. Pediatrics. 2017;140(5):e20171818

THE ENDOCANNABINOID SYSTEM (ECS)

Lipid signaling system found in all vertebrates

Appears to have important regulatory functions throughout the human body

Physiological and Pathophysiological Systems Affected by ECS

- Nervous system development
- Immune function
- Inflammation
- Appetite
- Metabolism and energy
- Homeostasis
- Cardiovascular function
- Digestion
- Bone development and bone density
- Synaptic plasticity and learning
- Pain
- Reproduction
- Psychiatric disease
- Psychomotor behavior
- Memory
- Wake/sleep cycles
- Regulation of stress and emotional state/mood

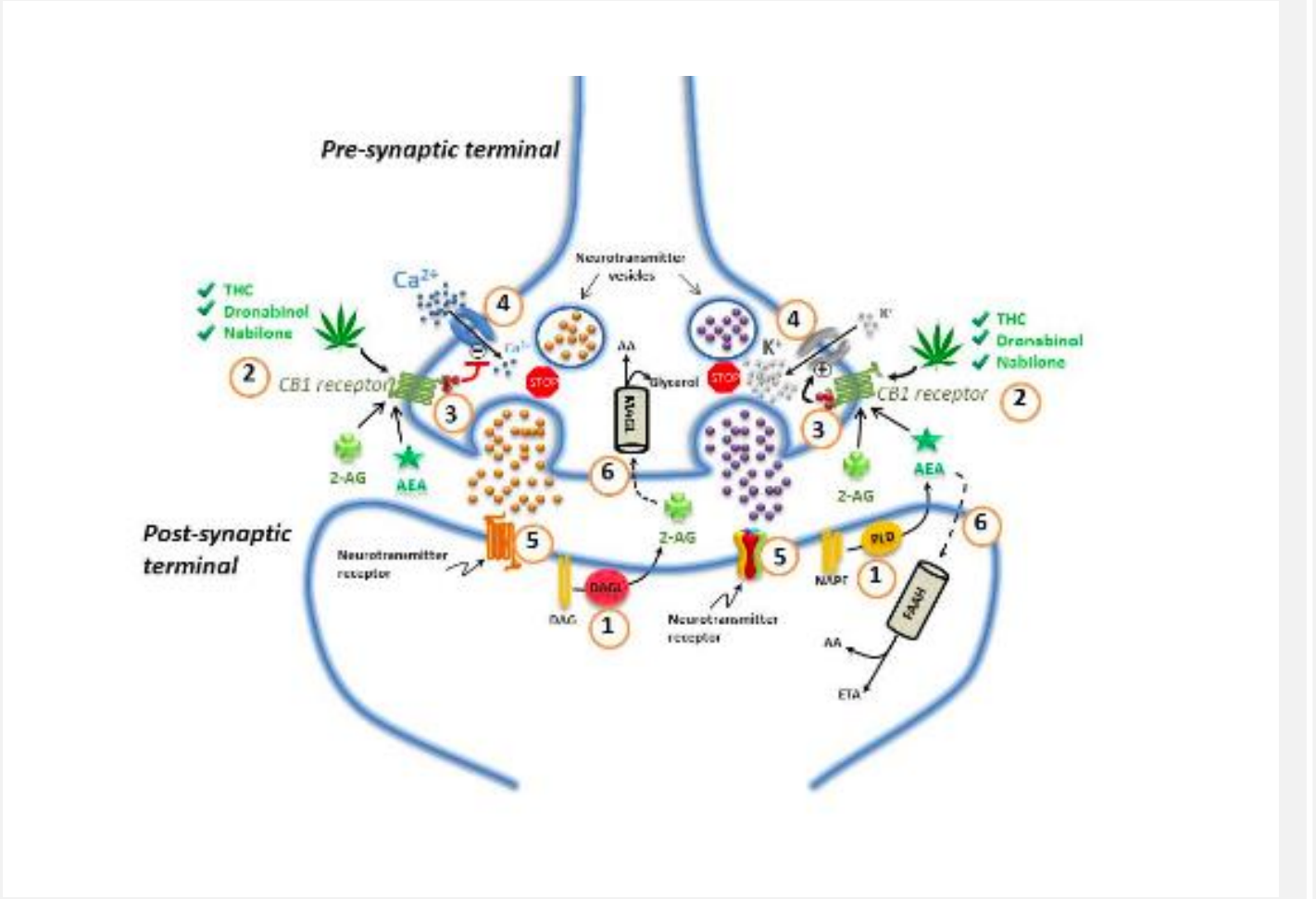
Pharmacol Ther 2011 12;132(1879-016; 0163-7258; 3):215-41
Annu Rev Nutr 2010 08/21;30(1545-4312; 0199-9885):423-40.
Clin J Pain 2012 02/23;29(1536-5409; 0749-8047; 2):162-71.
Handb Exp Pharmacol 2011(0171-2004; 0171-2004; 203):75-104.

THE ENDOCANNABINOID SYSTEM (ECS)

- Endocannabinoid system consists of:
- Cannabinoid 1 and 2 (CB_1 and CB_2) receptors Cannabinoid receptor ligands N-arachidonoylethanolamine ("anandamide") and 2-arachidonoylglycerol (2-AG)
- Endocannabinoid-synthesizing enzymes N-acyltransferase, phospholipase D, phospholipase C-β and diacylglycerol-lipase (DAGL)
- Endocannabinoid-degrading enzymes fatty acid amide hydrolase (FAAH), and monoacylglycerol lipase (MAGL)

Serrano A, Parsons LH. Endocannabinoid influence in drug reinforcement, dependence and addiction-related behaviors. Pharmacol Ther 2011 12;132(1879-016; 0163-7258; 3):215-41

THE ENDOCANNABINOID SYSTEM (ECS) (ECS)



T. R. Deer, M. S. Leong, editors. Comprehensive treatment of chronic pain by medical, interventional, and behavioral approaches: The AMERICAN ACADEMY OF PAIN MEDICINE textbook on patient mana gement. New York: Springer; 2012. ID: 2927; RP: NOTIN FILE.

Nat Rev Cancer 2003 10;3(1474-175; 1474-175; 10):745-55.

Nat Rev Drug Discov 004 09;3(1474-1776; 1474-1776; 9):771-84.

THE ENDOCANNABINOID SYSTEM (ECS) CB1 AND CB2 RECEPTORS

- CB_1 Receptors
  - Most abundant G-protein coupled receptors in the central and peripheral nervous systems
  - Also expressed in:
    - Adipocytes
    - Leukocytes
    - Spleen
    - Heart
    - Lung
    - Gastrointestinal tract
    - Kidney
    - Bladder
    - Reproductive organs
    - Skeletal muscle
    - Bone
    - Joints
    - Skin

Int Immunopharmacol 2010 05;10(1878-1705; 1567-5769; 5):547-55.
Regulation by hydrocortisone. Eur J Pharmacol 1997 05/30;327(0014-2999; 0014-2999; 2-3):227-32.
Immunobiology 2010 08;215(1878-3279; 0171-2985; 8):606-10.
Br J Pharmacol 2011 08;163(1476-5381; 0007-1188; 7):1432-40.
Handb Exp Pharmacol 2011(0171-2004; 0171-2004; 203):75-104.

THE ENDOCANNABINOID SYSTEM (ECS) CB1 AND CB2 RECEPTORS

- CB_2 Receptors
- Most highly concentrated in tissues and cells of the immune system (leukocytes and spleen)
- Also found in bone
- Some found to a lesser degree in liver, nerve cells including astrocytes, oligodendrocytes, microglia, and some neural subpopulations

Mackie K. Signaling via CNS cannabinoid receptors. Mol Cell Endocrinol 2008 04/16;286(0303-7207; 0303-7207; 1-2):S60-5.
Cabral GA. Marihuana and the mmune system. In: G. G. Nahas,K. M. Sutin, D. J. Harvey, S. Agurell, editors. Marihuana and medicine. Totowa: Humana Press; 1999. ID: 2678.

ECS IN PAEDIATRIC POPULATIONS

- ECS present in early development
- Critical for neurodevelopment
- Maintains expression in brain throughout life
- Undergoes dynamic changes during adolescence
  - Significant fluctuations in both levels and locations of CB_1 receptor in brain
  - Significant changes in level of endocannabinoids 2-AG and anandamide
  - ECS changes during adolescence overlap with significant period of neuronal plasticity including neuronal proliferation, rewiring and synaptogenesis, dendritic pruning and myelination that occur at the same time

Chadwick B, Miller ML, Hurd YL. Cannabis use during adolescent development: Susceptibility to psychiatric illness. Front Psychiatry 2013 Oct 14;4:129.
Arain M, Haque M, Johal L, Mathur P, Nel W, Rais A, Sandhu R, Sharma S.Maturation of the adolescent brain. Neuropsychiatr Dis Treat 2013;9:449-61.

MECHANISM OF ACTION OF CBD

- Lacks detectable psychoactivity
- Does not appear to bind to either CB_1 or CB_2 receptors at physiological meaning concentrations
- Emerging evidence suggests CBD may act as a negative, allosteric modulator of CB_1 receptors
- CBD also affects the activity of a significant number of other targets including ion channels, receptors, and enzymes
- Effective CBI molecular targets is associated with anti-inflammatory, analgesic, anti-nausea, antiemetic, antipsychotic, anti-ischemic, anxiolytic, and anti-epileptiform effects

Trends Pharmacol Sci 2009 10;30(1873-3735; 0165-6147; 10):515-27.
Br J Pharmacol 2007 11;152(0007-1188; 0007-1188; 5):567-75.
Br J Pharmacol 2015 Feb;172(3):737-53.
Br J Pharmacol 2010 12/22;163(1476-5381; 0007-1188; 7):1411-22.

CHEMOTHERAPY INDUCED NAUSEA AND VOMITING (CNIV)

- 6 studies of cannabinoids or the treatment of CNIV in children and adolescents
- Double-blind crossover RCT of 23 children showed that nabilone decreased nausea severity and vomiting frequency when compared with domperidone
- Patients were treated with nabilone over 5 days cycle of chemotherapy
- Patients treated with nabilone had an average of 6 episodes of emesis compared with 17 episodes of emesis In patients treated with domperidone
- Nabilone reduced nausea severity rated as a 1.5 on a 5 point scale in comparison with a 2.5 rating in the group treated with domperidone

Dalzell AM, Bartlett H, Lilleyman JS. Nabilone: an alternative antiemetic for cancer chemotherapy. Arch Dis Child. 1986;61(5):502–505

CHEMOTHERAPY INDUCED NAUSEA AND VOMITING (CNIV)

- In a double-blind, crossover RCT of 30 children, nabilone improved retching and emesis by 70% compared with 30% treated with prochloperazine
- During one cycle of chemotherapy patients treated with nabilone had 13 episodes of retching or emesis compared with 27 episodes when treated with prochloperazine

Chan HS, Correia JA, MacLeod SM. Nabilone versus prochlorperazine for control of cancer chemotherapyinduced emesis in children: a doubleblind, crossover trial. Pediatrics. 1987;79(6):946–952

CHEMOTHERAPY INDUCED NAUSEA AND VOMITING (CNIV)

- In 2 double-blind RCTs patients treated with Δ-9-THC had reduced nausea and vomiting when compared with metoclopramide and prochloperazine

Ekert H, Waters KD, Jurk IH, Mobilia J, Loughnan P. Amelioration of cancer chemotherapyinduced nausea and vomiting by delta-9-tetrahydrocannabinol. Med J Aust. 1979;2(12):657–659

CHEMOTHERAPY INDUCED NAUSEA AND VOMITING (CNIV)

In an open-label trial Δ-9-THC prevented vomiting during 480 cycles of chemotherapy in 8 children when given 2 hours prior to chemotherapy and repeated every 6 hours

Abrahamov A, Abrahamov A, Mechoulam R. An efficient new cannabinoid antiemetic in pediatric oncology. Life Sci. 1995;56(23–24):2097–2102

CHEMOTHERAPY INDUCED NAUSEA AND VOMITING (CNIV)

- In a retrospective chart review of 95 children dronabinol treatment was given an average of 3 times over the course of chemotherapy leading to a positive response in 60% of children (0-1 bouts of emesis)
- 95% of the patients received lower dosing than recommended in guidelines (5 mg/m2) with the most common dose given being 2.5 mg/m2 given every 6 hours on a prn basis
- 2/3 of the patients received repeated courses while 62% received a patient prescriptions suggesting good tolerability of the medication
- No studies using CBD oil

Elder JJ, Knoderer HM. Characterization of dronabinol usage in a pediatric oncology population. J Pediatr Pharmacol Ther. 2015;20(6):462–467

EPILEPSY – DEVINSKY ET AL. (2016)

Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial

Orrin Devinsky, Eric Marsh*, Daniel Friedman*, Elizabeth Thiele, Linda Laux, Joseph Sullivan, Ian Miller, Robert Flamini, Angus Wilfong, Francis Filloux, Matthew Wong, Nicole Tilton, Patricia Bruno, Judith Bluvstein, Julie Hedlund, Rebecca Kamens, Jane Maclean, Srishti Nangia, Nilika Shah Singhal, Carey A Wilson, Anup Patel, Maria Roberta Cilio*

Lancet Neurol 2016; 15: 270–78

EPILEPSY – DEVINSKY ET AL. 2016

- Open-label trial, patients (aged 1–30 years) with severe, intractable, childhood-onset, treatment-resistant epilepsy, who were receiving stable doses of antiepileptic drugs before study entry
- Enrolled in an expanded-access programme at 11 epilepsy centres across the USA
- Patients received oral cannabidiol at 2–5 mg/kg/day and up-titrated until intolerance or to a maximum dose of 25 mg/kg or 50 mg/kg per day (dependent on study site)

Lancet Neurol 2016; 15: 270–78

EPILEPSY – DEVINSKY ET AL. 2016

- Primary objective – to establish the safety and tolerability of cannabidiol
- Primary efficacy endpoint was median percentage change in the mean monthly frequency of motor seizures at 12 weeks
- 214 patients were enrolled; 162 (76%) patients who had at least 12 weeks of follow-up after the first dose of cannabidiol were included in the safety and tolerability analysis and 137 (64%) patients were included in the efficacy analysis
- In the safety group, 33 (20%) patients had Dravet syndrome and 31 (19%) patients had Lennox-Gastaut syndrome and the remaining patients had intractable epilepsies of different causes and type

Lancet Neurol 2016; 15: 270–78

EPILEPSY - DEVINSKY ET AL. 2016

- Adverse events were reported in 128 (79%) of the 162 patients within the safety group.
- Adverse events reported in more than 10% of patients:
- Somnolence 25%
- Decreased appetite 19%
- Diarrhea 19%
- Fatigue 13%
- Convulsion 11%

Lancet Neurol 2016; 15: 270–78

EPILEPSY – DEVINSKY ET AL. 2016

- Five (3%) patients discontinued treatment because of an adverse event
- Serious adverse events were reported in 48 (30%) patients, including one death—a sudden unexpected death in epilepsy regarded as unrelated to study drug.
- 20 (12%) patients had severe adverse events possibly related to cannabidiol use - status epilepticus most common side effect 6%
- Median monthly frequency of motor seizures was 30·0 at baseline and 15·8 over the 12 week treatment period
- Median reduction in monthly motor seizures was 36·5%

Lancet Neurol 2016; 15: 270–78

EPILEPSY – DEVINSKY ET AL. 2016

- Conclusion:
  - Cannabidiol might reduce seizure frequency
  - Cannabidiol might have an adequate safety profile in children and young adults with highly treatment-resistant epilepsy
  - RCT needed to characterize safety profile and true efficacy of cannabidiol

Lancet Neurol 2016; 15: 270–78

EPILEPSY – DEVINSKY ET AL. 2017

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 25, 2017 VOL. 376 NO. 21

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*

N Engl J Med. 2017;376(21): 2011–202

DEVINSKY ET AL. (2017)

- Double-blind, placebo-controlled trial
- 120 children and young adults with Dravet syndrome and drug-resistant epilepsy randomly assigned to receive either cannabidiol oral solution at a dose of 20 mg/kg per day or placebo + standard antiepileptic treatment
- Primary end point - change in convulsive-seizure frequency over a 14-week treatment period, as compared with a 4-week baseline period

N Engl J Med. 2017;376(21): 2011–202

DEVINSKY ET AL. (2017)

- 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
- Percentage of patients who had at least a 50% reduction in convulsive seizure frequency was 43% with cannabidiol and 27% with placebo
- 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).
- Frequency of total seizures of all types was significantly reduced with cannabidiol (P=0.03),
- No significant reduction in nonconvulsive seizures

N Engl J Med. 2017;376(21): 2011–202

DEVINSKY ET AL. (2017)

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
- abnormal results on liver-function tests

More withdrawals from the trial in the cannabidiol group

N Engl J Med. 2017;376(21): 2011–202

DEVINSKY ET AL. (2017)

Conclusion:

- In patients with Dravet syndrome, cannabidiol resulted in a greater reduction on convulsive seizure frequency than placebo
- Cannabidiol was also associated with higher rates of adverse events in this group including somnolence and elevation of liver enzyme levels over a 14 week period
- Additional data are needed to determine the long-term efficacy and safety of cannabidiol for Dravet syndrome

N Engl J Med. 2017;376(21): 2011–202

EPILEPSY – GOFSHTEYN (2017)

Journal of Child Neurology
2017, Vol. 32(1) 35-40

DOI: 10.1177/0883073816669450
journals.sagepub.com/home/jcn
SAGE

Cannabidiol as a Potential Treatment for Febrile Infection-Related Epilepsy Syndrome (FIRES) in the Acute and Chronic Phases

Jacqueline S. Gofshteyn, MD[1], Angus Wilfong, MD[2], Orrin Devinsky, MD[3], Judith Bluvstein, MD[3], Joshi Charuta, MD[4], Michael A. Ciliberto, MD[4], Linda Laux, MD[5], and Eric D. Marsh, MD, PhD[1,6]

EPILEPSY – GOFSHTEYN (2017)

Febrile infection-related epilepsy syndrome (FIRES) - devastating epilepsy affecting normal children after a febrile illness.

Presents with an acute phase with super-refractory status epilepticus

All patients progress to a chronic phase with persistent refractory epilepsy.

Outcome is severe encephalopathy or death.

Journal of Child Neurology 2017, Vol. 32(1) 35-40

EPILEPSY – GOFSHTEYN (2017)

Open label case series

7 children from 5 centers with FIRES who had not responded to antiepileptic drugs or other therapies were given cannabadiol (high dose) on emergency or expanded investigational protocols in either the acute or chronic phase of illness

6 of 7 patients' seizures improved in frequency and duration after starting cannabidiol

One patient died due to multiorgan failure secondary to isoflourane

Average of 4 antiepileptic drugs weaned

5 subjects are ambulatory, 1 walks with assistance, 4 are verbal

Cannabidiol as a possible treatment for FIRES

Journal of Child Neurology 2017, Vol. 32(1) 35-40

MCCOY ET AL. (2018)

ANNALS of Clinical and Translational Neurology
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RESEARCH ARTICLE

A prospective open-label trial of a CBD/THC cannabis oil in dravet syndrome

Bláthnaid McCoy[1,2], Laura Wang[3], Maria Zak[1], Sameer Al-Mehmadi[1], Nadia Kabir[1], Kenda Alhadid[1], Kyla McDonald[4], Grace Zhang[4], Rohit Sharma[1], Robyn Whitney[1,2], Katia Sinopoli[4] & O. Carter Snead III[1]

[1]Division of Neurology, the Hospital for Sick Children, Toronto, Canada
[2]Department of Pediatrics, University of Toronto, Toronto, Canada
[3]Department of Pharmacy, Hospital for Sick Children, Toronto, Canada
[4]Department of Psychology, the Hospital for Sick Children, Toronto, Ontario, Canada

Annals of Clinical and Translational Neurology 2018; 5(9): 1077–1088

MCCOY ET AL. (2018)

Primary objective - establish dosing and tolerability of a cannabis plant extract containing 100 mg/mL CBD and 2 mg/mL THC- in children with Dravet syndrome

Secondary objectives were to assess impact of therapy on seizures, electroencephalogram (EEG) and quality of life

Twenty children received add-on therapy – the dose ranged from 2 - 16 mg/kg/day of CBD and 0.04 to 0.32 mg/kg/day of THC

Annals of Clinical and Translational Neurology 2018; 5(9): 1077–1088

MCCOY ET AL. (2018)

- Common adverse events during titration included:
  - Somnolence
  - Anorexia
  - Diarrhea
- Abnormalities of liver transaminases and platelets were observed with concomitant valproic acid therapy

Annals of Clinical and Translational Neurology 2018; 5(9): 1077–1088

MCCOY ET AL. (2018)

- There was a statistically significant improvement in quality of life, reduction in EEG spike activity, and median motor seizure reduction of 70.6%, with 50% responder rate of 63%.
- CBD was safe and well tolerated
- Treatment resulted in a reduction in seizure counts, spike index on EEG, and improved quality of life measures
- This study provides safety and dosing information for THC-containing cannabinoid preparations

Annals of Clinical and Translational Neurology 2018; 5(9): 1077–1088

POST TRAUMATIC STRESS DISORDER (PTSD)

THE JOURNAL OF ALTERNATIVE AND COMPLEMENTARY MEDICINE
Volume 25, Number 4, 2019, pp. 392–397
Mary Ann Liebert, Inc.
DOI: 10.1089/acm.2018.0437

JACM

Cannabidiol in the Treatment of Post-Traumatic Stress Disorder: A Case Series

Lucas Elms, BS,[1] Scott Shannon, MD, FAACAP,[2] Shannon Hughes, PhD,[3] and Nicole Lewis, ND[4]

PTSD – ELMS ET AL. (2019)

Retrospective case series examined the effect of oral CBD administration on symptoms of PTSD in a series of 11 adult patients at an outpatient psychiatry clinic

CBD was given on an open-label, flexible dosing regimen to patients diagnosed with PTSD by a mental health professional

Patients also received routine psychiatric care, including concurrent treatment with psychiatric medications and psychotherapy.

Study was 8 weeks

PTSD symptom severity assessed every 4 weeks by patient-completed PTSD Checklist for the DSM-5 (PCL-5) questionnaires

The Journal of Alternative and Complementary Medicine Volume 25, Number 4, 2019, pp. 392–397

PTSD – ELMS ET AL. (2019)

- 91% (n = 10) experienced a decrease in PTSD symptom severity, as evidenced by a lower PCL-5 score at 8 weeks than at their initial baseline
- Mean total PCL-5 score decreased 28%, from a mean baseline score of 51.82 down to 37.14, after eight consecutive weeks of treatment with CBD
- CBD was generally well tolerated
- No patients discontinued treatment due to side effects

The Journal of Alternative and Complementary Medicine Volume 25, Number 4, 2019, pp. 392–397

PTSD – ELMS ET AL. (2019)

- Administration of oral CBD + routine psychiatric care was associated with PTSD symptom reduction in adults with PTSD
- CBD appeared to offer relief in a subset of patients who reported frequent nightmares as a symptom of their PTSD
- Additional clinical investigation, including double-blind, placebo-controlled trials are needed

The Journal of Alternative and Complementary Medicine Volume 25, Number 4, 2019, pp. 392–397

NEUROPATHIC PAIN

Cochrane Database of Systematic Reviews

Cannabis-based medicines for chronic neuropathic pain in adults

Cochrane Systematic Review - **Intervention** | Version published: 07 March 2018

Am score 220 View article information

Martin Mücke | Tudor Phillips | Lukas Radbruch | Frank Petzke | Winfried Häuser

View authors' declarations of interest

NEUROPATHIC PAIN

- Assessed the efficacy, tolerability, and safety of cannabis-based medicines (herbal, plant-derived, synthetic) compared to placebo or conventional drugs for conditions with chronic neuropathic pain in adults.
- Randomized, double-blind controlled trials of medical cannabis, plant-derived and synthetic cannabis-based medicines against placebo or any other active treatment of conditions with chronic neuropathic pain in adults, with a treatment duration of at least two weeks and at least 10 participants per treatment arm were reviewed

Mücke M, Phillips T, Radbruch L, Petzke F, Häuser W. Cannabis-based medicines for chronic neuropathic pain in adults. Cochrane Database of Systematic Reviews 2018, Issue 3. Art. No.: CD012182. DOI: 10.1002/14651858.CD012182.pub2.

NEUROPATHIC PAIN

- 16 studies with 1750 participants were selected
- Studies were 2 to 26 weeks long and compared an oromucosal spray with a plant-derived combination of tetrahydrocannabinol (THC) and cannabidiol (CBD) (10 studies), a synthetic cannabinoid mimicking THC (nabilone) (two studies), inhaled herbal cannabis (two studies) and plant-derived THC (dronabinol) (two studies) against placebo (15 studies) and an analgesic (dihydrocodeine) (one study).

Mücke M, Phillips T, Radbruch L, Petzke F, Häuser W. Cannabis-based medicines for chronic neuropathic pain in adults. Cochrane Database of Systematic Reviews 2018, Issue 3. Art. No.: CD012182. DOI: 10.1002/14651858.CD012182.pub2.

NEUROPATHIC PAIN

- The potential benefits of cannabis-based medicine (herbal cannabis, plant-derived or synthetic THC, THC/CBD oromucosal spray) in chronic neuropathic pain might be outweighed by their potential harms
- The quality of evidence for pain relief outcomes reflects the exclusion of participants with a history of substance abuse and other significant comorbidities from the studies, together with their small sample sizes

Mücke M, Phillips T, Radbruch L, Petzke F, Häuser W. Cannabis-based medicines for chronic neuropathic pain in adults. Cochrane Database of Systematic Reviews 2018, Issue 3. Art. No.: CD012182. DOI: 10.1002/14651858.CD012182.pub2.

SPASTICITY – CONTIN (2018)

Tetrahydrocannabinol/Cannabidiol Oromucosal Spray in Patients With Multiple Sclerosis: A Pilot Study on the Plasma Concentration-Effect Relationship

Manuela Contin, PharmD,† Luca Mancinelli, MD,*† Alessandro Perrone, MCh,* Loredana Sabattini, MD,* Susan Mohamed, MCh,* Cinzia Scandellari, MD,* Matteo Foschi, MD,† Veria Vacchiano, MD,† Alessandra Lugaresi, MD,*† and Roberto Riva, MD*†*

(Clin Neuropharm 2018;41: 171–176)

SPASTICITY – CONTIN (2018)

- Pilot, single center, open, and prospective study
- Patients were challenged with a morning test dose of 2 THC/CBD sprays at a 15-minute interval
- Venous blood samples collected before the first spray administration and every 30 minutes after the second spray, until 240 minutes postdosing
- Patients rated spasticity on the Numerical Rating Scale (NRS) simultaneously with blood drawings
- Postural and motor tests were performed before the first spray and 90 and 180 minutes thereafter

Clin Neuropharm 2018;41: 171–176

SPASTICITY – CONTIN (2018)

- 12 patients were recruited
- Peak plasma concentrations of THC/CBD largely varied among patients, from 0.60 to 13.29 ng/mL for THC and 0.55 to 11.93 ng/mL for CBD
- Time to peak plasma concentrations ranged from 150 to 240 minutes for THC and 90 to 240 minutes for CBD
- Patients' NRS serial scores decreased after dosing, from a median of 6 to 3.5 ($P < 0.001$)
- Significant inverse correlation observed between median intrasubject repeated NRS scores and corresponding median values of both THC ($P < 0.01$) and CBD ($P < 0.002$) plasma concentrations
- No significant effect of cannabinoids dosing could be appreciated according to posturographic and motor tests

Clin Neuropharm 2018;41: 171–176

SPASTICITY – CONTIN (2018)

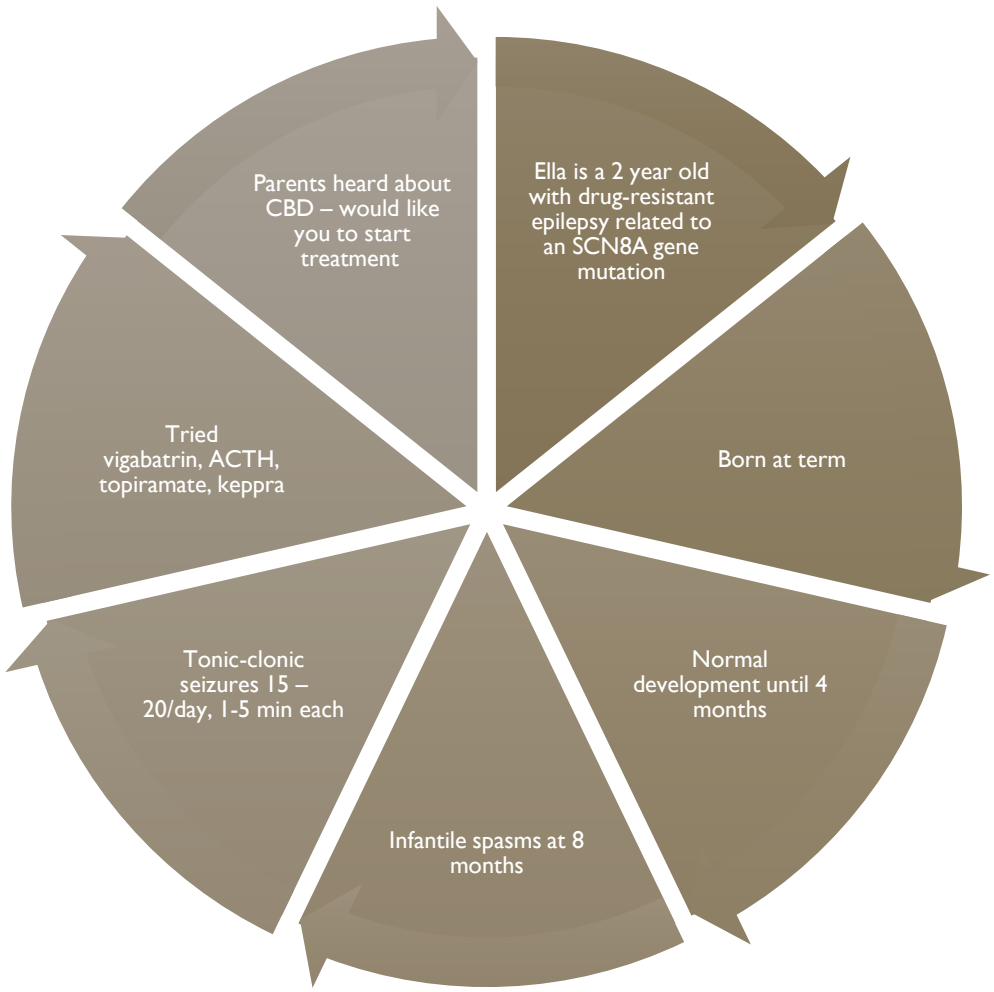
- Kinetic dynamic findings from THC/CBD oromucosal spray were the first obtained in MS patients
- Although preliminary, results suggest subacute dosing might elicit a subjective clinically significant effect on MS-related spasticity, paralleling cannabinoids measurable plasma concentrations

Clin Neuropharm 2018;41: 171–176

SUMMARY

- Only indication that has evidence of efficacy of CBD is epilepsy
- More studies needed for all other conditions including those discussed today

TREATMENT CONSIDERATIONS – CASE STUDY



TO TREAT OR NOT TO TREAT

Is there enough evidence to support your decision in whether to treat Ella with CBD?

How will you dose her CBD?

What will you monitor?

How will you determine which product she should try?

What other considerations must be taken into account before initiating treatment?

RESOURCES

- https://www.canada.ca/en/health-canada/topics/cannabis-for-medical-purposes.html

- Huntsman R, Tang-Wai R, Action B. Cannabis for the treatment of paediatric epilepsy? An update for Canadian paediatricians. *Paediatrics & Child Health*, 2018, 368–373 doi: 10.1093/pch/pxy03

THANK YOU!