Cannabis and Health

Module 11: Neurocognitive/Brain Disorders Part I

Lecture 5: Cannabis and MS and Epilepsy

MS and Cannabis

- Sativex is a 1:1 (THC to CBD) oromucosal preparation from GW Pharma that is approved for the treatment of pain and spasticity in MS patients in Europe, Canada, and elsewhere
- A number or reviews suggest substantial evidence to suggest it has a modest effect on pain and spasticity (see NAS report)
- Almost all of the clinical data is on 1:1 preparation – no evidence to support CBD only

History of Cannabis in the Treatment of Seizures and Epilepsy

- Anecdotally, cannabis has been used for seizure control for many years
- First scientific evidence in 1840: William O'Shaughnessy's publication describing successful treatment of infant seizures with a cannabis tincture
- In 1890, Queen Victoria's personal physician, J. R. Reynolds, said: cannabis is "**the most useful agent with which I am acquainted" in the treatment of "attacks or violent convulsions . . . (which) may recur two or three times in the hour . . . may be stopped with a full dose of hemp**"

Williams, Jones & Whalley, 2014, *Handbook of Cannabis*

Cannabis and Epilepsy

- In the twentieth century the use of cannabis declined somewhat because cultivation of the plant was made illegal in many countries

- Preclinical and clinical research into the potential application of cannabis in the treatment of epilepsy has increased exponentially

- This increasing research interest has largely coincided with the changing legal landscape in the U.S. and increase in medical and recreational cannabis laws

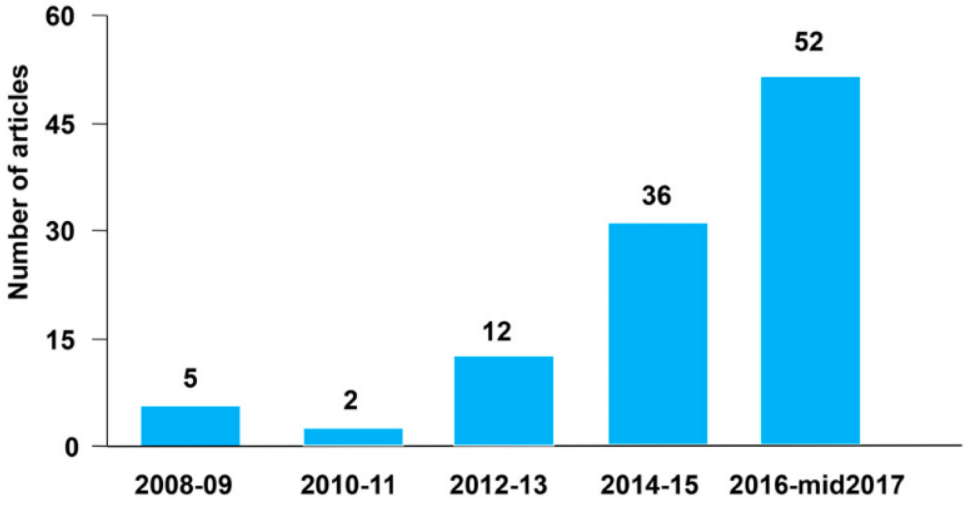

Figure 1. Number of articles retrieved in PubMed by using the search terms 'cannabis and epilepsy', grouped by year of publication.

Perucca 2017, *Journal of Epilepsy Research*

Anticonvulsant Properties of THC

- THC shows some anticonvulsant effects in certain seizure models
- There have also been studies suggesting proconvulsant effects
- THC may contribute to anti-seizure activity reported for medical cannabis
- However, adverse psychotropic properties and inconsistent activity in seizure models render it undesirable for development for treatment of epilepsy
- Most cannabinoid research efforts in epilepsy focus on the non-psychoactive agents
  - particularly CBD

Perucca 2017, *Journal of Epilepsy Research*

CBD Treatment Potential—Preclinical Data

- Compared with THC, cannabidiol (CBD) shows a better defined anticonvulsant profile in animal models
- In preclinical studies, CBD has been found to be active in a variety of seizures models
- NINDS-funded Epilepsy Therapy Screening Program:
  - CBD produced a dose-dependent protection against electroshock-induced seizures in mice
  - effects were observed at doses that did not cause motor impairment

NIH National Institute of Neurological Disorders and Stroke

Perucca 2017, *Journal of Epilepsy Research*

CBD Treatment Potential in Humans

- CBD is largely devoid of adverse psychoactive effects and abuse liability
- Molecular actions involved in CBD anti-seizure activity do not appear to be mediated by a direct effect on cannabinoid receptors
- Recent human placebo-controlled **adjunctive therapy** trials:
  - purified CBD in patients with Dravet syndrome and Lennox-Gastaut syndrome
  - CBD superior to placebo in reducing frequency of convulsive seizures in patients with Dravet syndrome, and the frequency of drop seizures in Lennox-Gastaut syndrome
  - unclear whether improved seizure control related to direct action of CBD or mediated by drug interactions with concomitant medications

Perucca 2017, *Journal of Epilepsy Research*

CBD: Safety and Side Effects

- 2017 review of the literature on CBD
  - Favorable safety profile of CBD in humans was confirmed
  - Most commonly reported side effects were tiredness, diarrhea, and changes of appetite/weight
  - Future research should examine whether CBD has any effect on hormones
  - Also need to determine whether there are any negative effects of chronic CBD administration

Iffland & Grotenhermen, 2017, *Cannabis and Cannabinoid Research*

Important Interactions Between CBD and Other Drugs

- There may be important effects of co-administration of CBD with other drugs
  - Especially drugs that interact with cytochrome P450 enzymes
  - The cytochrome P450 family of enzymes metabolizes potential toxins (e.g., drugs/medications)
- CBD metabolized by CYP3A4 enzyme, which is inhibited by certain drugs such as antifungal medications, HIV drugs and antibiotics
  - can lead to lower CBD degradation, thus higher CBD doses that are active in the body for longer periods of time
- Other common drugs, particularly anticonvulsants, cause reduced CBD bioavailability

Case Report: Charlotte Figi

- Widely publicized story of Charlotte, a little girl with Dravet
- Started having seizures at 3 months old
  - Multiple severe seizures per day as she got older
- Seizures did not respond to traditional treatments
- Experienced remarkable improvement in seizures after being switched to CBD-enriched extract
- Increased popularity of CBD oils, other CBD products
- Sparked development of Epidiolex by GW Pharma

CBDV Treatment Potential

- Cannabidivarin (CBDV) has been the focus of recent studies
- Like CBD, CBDV is virtually devoid of psychoactive effects
- Some promising preclinical evidence
  - shows protection *in vitro* against seizure-inducing electrical activity potentials in rat hippocampal slices
  - shows protection *in vivo* against seizures induced by electroshock and other electrical stimulation in rodent models
- Little is known about the pharmacology of CBDV
  - Mechanisms responsible for anti-seizure effects of CBDV do not seem to involve action on cannabinoid receptors

Perucca 2017, *Journal of Epilepsy Research*

Recent Legal/Policy Developments: Epidiolex

- GW Pharma has developed an oral formulation of purified cannabidiol (CBD), approved as Epidiolex® in the U.S. by the U.S. Food and Drug Administration (FDA) (June 25, 2018)
  - To treat seizures associated with Lennox-Gastaut syndrome or Dravet Syndrome
  - FDA advisory committee meeting: unanimous vote to approve Epidiolex for seizures

First cannabis plant-derived medicine ever approved by the FDA

- One downside: Epidiolex is expensive

Conclusions

- Cannabis extracts were thought to be helpful for seizures hundreds of years ago
- In 2018, the FDA approved a purified form of plant-derived CBD (epidiolex)
- From this evidence, it is clear that CBD has a beneficial effect with epilepsy