OBJECTIVES

- To briefly discuss the role of the endocannabinoid system in the response to cannabinoids
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- To examine the evidence for the use of cannabinoids for the treatment of seizures/epilepsy

Definitions (NIDA)

- **Cannabinoids**
  - Chemicals derived from the Cannabis plant (or manufactured)
  - Dronabinol (pill and liquid) and Nabilone – synthetic FDA-approved ∆-9 THC products

- **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
  - MMJ (marijuana/marihuana) – in the US this term is somewhat pejorative as it was first used by law enforcement to demonize the use of MMJ by immigrants ("something used by others")
  - "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..."
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: CB₁ and CB₂
  - CB₁ – “central” and CB₂ – “peripheral” (mainly located on blood cells and in immune tissue)
  - 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)

ECS: “Relax, eat, sleep, forget, and protect”

Modified after Ethan Russo, MD
Clinical Endocannabinoid Deficiency (CED)

- All humans possess underlying "endocannabinoid tone" that reflects the levels of AEA and 2-AG
- Brain disorders are associated with endocannabinoid neurotransmitter deficiency(ies)
- CED manifests as a
  - Hyperalgesic state
  - Elevated anxiety/depression
- They (FBM, migraine, and IBS) are comorbid
- Diagnoses of exclusion
- Theory expanded to include many unexplained conditions e.g., neonatal failure to thrive, causalgia, phantom limb pain, etc.

Cannabinoids in epilepsy: experimental evidence

ECS and its role in epilepsy

- Seizure increase with SR141716A (CB1 antagonist) suggests that cannabinoids decrease hyperexcitability

- Increased CB1R indicates compensatory mechanism of seizure manifestation
Cleeren et al., Epilepsia (2018)

- 2 rhesus monkeys
- TLE model (electrical amygdala kindling)
- [18F]-MK-9470 (CB1R)
- Red – increase in CB1R binding

Human data

- New onset TLE – patients had lower levels of CSF AEA compared to HCs
- Patients undergoing ATL had lower CB2-RNA for DAGL-alpha compared to non-epilepsy controls (less “on demand” production of 2-AG)
- PET – Increased availability of CB1 receptor in TL compared to HCs ([18F]-MK-9470 (CB1R))

Overall MOA CBD and Δ-9 THC

- Δ-9 THC
  - CB1R and CB2R
- CBD
  - ECS modulation (allosteric CB1R and CB2R)
  - Transient receptor potential (TRP) of vanilloid type-1 (TPRV1)
  - G-protein coupled receptor (GPR55)
  - A1R and A2R
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>500 compounds in cannabis but potency always judged based on THC content

- Tested: marijuana, sinsemilla (proportion of sinsemilla to marijuana is increasing), kilobrick, Thai stacks, hashish, hash oil, and ditchweed
- THC:CBD ratio has increased from 14:1 in 2001 to 80:1 in 2014

Cannabis Intoxication

- Euphoria
- Relaxation
- Jocularity
- Rare:
  - Deperonalization
  - Subjective “time slowing”
  - Memory impairment
  - Unsteadiness
  - Conjunctival injection
  - Tachycardia with postural hypotension
  - Increased appetite
  - Paranoia, confusion, and panic lasting for hours
  - Death

ElSohly et al., 2016 Biological Psychiatry
Cannabis Withdrawal

- Abrupt withdrawal may cause:
  - Jitteriness/irritability
  - Anorexia, cravings, and GI upset
  - Anxiety
  - Insomnia

- Testing for use:
  - Plasma half-life is ~56 hours in occasional users and ~28 hours in chronic users
  - THC can be tested in blood, urine, hair, saliva or sweat
  - Concentration obtained via HPLC techniques can be helpful in distinguishing passive exposure and active use
  - Screening for use via Duquenois-Levine test – sensitive but not very specific (many false positives and e.g., zinc supplements can mask the presence of THC); HPLC is a confirmatory test

Epigenetic effects

- Epigenetic – modulating gene expression without altering the genetic code
- DNA methylation
- Histone modifications
- Noncoding RNAs (gene expression regulation at a transcriptional and post-transcriptional level)
- Sperm epigenome (DNA methylation) different between Cannabis users (active vs. abstinent) and non-users

Youth and Cannabis

- Results from this 2016 Barometer indicate that states such as Utah (4.5%), Alabama (5.2%), and Iowa (5.3%) had the lowest percentage of past-month marijuana use among youth aged 12-17 compared to the corresponding national annual average of 7.2%.
- However, states such as Colorado (11.1%), Vermont (10.9%), and Alaska (10.6%) had the highest percentage of past-month marijuana use among youth.
Children and Adolescents

- In animal models exposure to THC or analogues (WIN or CP-55):
  - Alterations in maturation of the ECS and dysregulation of neurotransmitter systems maturation (GABA and glutamate)
  - May predispose to psychotic-like symptoms in adulthood
  - Long-term impairment in learning and memory
  - Effect on anxiety is unclear
  - Negative effect on social behavior and emergence of depression-like signs
  - End-product: picture resembling the one present in schizophrenia patients (schizophrenia-like symptoms)

Rubino et al., 2016 Biological Psychiatry

Children and Adolescents

- Short-term use
  - Impairment of memory and judgement
  - Decreased coordination (i.e., accidents)
  - Paranoia and psychosis

- Long-term and heavy use
  - "Gateway drug": 17% of adolescent users develop addiction to other drugs
  - Cognitive impairment including loss of IQ points
  - Diminished lifetime satisfaction and achievement
  - Increased risk of anxiety and depression
  - Increased risk of psychosis and schizophrenia-like symptoms in persons with predisposition

Volkow et al., 2014 NEJM

Neurologic complications of Cannabis

- Cognition and behavior
  - Controversial in adults but there is mounting evidence that marijuana use in children and adolescents damages the brain
  - In-utero exposure can cause long-lasting executive dysfunction

- Stroke
  - 98 (13 synthetic e.g., spice or K2) marijuana-related strokes reported with 5x higher incidence in men; there were 8 hemorrhagic and 5 undetermined strokes
  - Only one study suggested the relationship may be coincidental b/o prevalence of marijuana use
  - Vascular events within 30-60 minutes of marijuana use are likely not coincidental
  - Mechanism: likely reversible cerebral angiopathy (or vasocostriction syndrome; RCVS)
    - RCVS – thunderclap HA with or without other neurological symptoms, resolves gradually over 1-3 months

- Seizures
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”

CBD vs. THC

- Effects on mood are divergent (2008)
  - Hair samples of 54 individuals who screened (+) for cannabis
  - 3 groups THC only; THC+CBD; negative hair testing
  - THC only showed higher schizophrenia-like symptoms than THC+CBD or negative group

- Effects on memory are divergent (2010)
  - 134 cannabis smokers (own supply)
  - THC:CBD content measured in own supply and saliva
  - Independent of THC content, high CBD content was associated with no memory impairment

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**Anti-seizure drugs (ASDs)**

- 7777 – cannabis
- 1857 – bromides
- 1912 – phenobarbital (PB)
- 1937 – phenytoin (PHT)
- 1944 – trimethadione
- 1954 – primidone
- 1958 – ACTH
- 1959 – levetiracetam (LEV)
- 1960 – ethosuximide (ESM)
- 1963 – diazepam
- 1974 – carbamazepine (CBZ)
- 1975 – clonazepam (CZP)
- 1978 – valproate (VPA)
- 1993 – felbamate (FBM), gabapentin (GBP)
- 1995 – lamotrigine (LTG)
- 1997 – topiramate (TPM), zonisamide (ZNS)
- 1999 – levetiracetam (LEV)
- 2000 – oxcarbazepine (OXC)
- 2005 – pregabalin (PGB)
- 2008 – lacosamide (LAC), zonisamide (ZNS)
- 2011 – rufinamide (RUF)
- 2013 – eslicarbazepine (ESL)
- 2016 – brivaracetam (BRV)
- 2018 – cannabidiol (CBD)

**Drug Development: Industry vs. MMJ**

**Early history**

- ~12,000 BCE
- 2000 BCE
- 200

- 2000 BCE – Use of cannabis for convulsions and other conditions in Sumerian and Akkadian civilizations
- 2000 BCE – Therapeutic use of cannabis in ancient Egypt
- 2000 BCE – Use of cannabis to treat multiple conditions in ancient India
- 2000 BCE – Use of cannabis as medicine throughout Middle East, Far East and North Africa
- 2000 BCE – Emperor Shen Nung (China): cannabis and other herbal remedies for disease
- 2000 BCE – hemp for rope and fiber in ancient China
Synthesis of CBD and ∆9-THC

1990

1200
1800
1900

1619 King James I ordered colonists to grow 100 hemp plants

1842: O'Shaughnessy promotes cannabis for treatment of numerous conditions including seizures

1881: Gowers describes use of cannabis for epilepsy

Discovery of cannabinoid receptor and endocannabinoid signaling system

Synthesis of CBD and ∆9-THC

Human trials of MMJ and CBD for epilepsy

Risk Factors for Epilepsy

LVH = left ventricular hypertrophy.
*Protective.
Opinion: Safety of Cannabis in Epilepsy

Summary of efficacy data prior to 2015

- 69/102 patients received Cannabis products
- 42/69 were “responders” (61%)
- Cochrane Review – “no reliable conclusions can be drawn […] regarding the efficacy of cannabinoids for the treatment of epilepsy”

A case for a pharmaceutical grade product

- Dispensaries in San Francisco, Los Angeles, Seattle (randomly selected)
- 75 edible products of different brands
- 17% labelling of content was accurate
  - 23% under-labelled
  - 60% over-labelled
- For non-THC content:
  - 17% were labelled as (+)
  - 59% had non-THC content
A case for a pharmaceutical grade product

<table>
<thead>
<tr>
<th>Cannabinoid Extract Products</th>
<th>THC (mg/mL)</th>
<th>CBD (mg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>0.20</td>
<td>0.03</td>
</tr>
<tr>
<td>#2</td>
<td>0.25</td>
<td>0.05</td>
</tr>
<tr>
<td>#3</td>
<td>0.30</td>
<td>0.06</td>
</tr>
</tbody>
</table>

Perspective

- US: 3.4M people have epilepsy (1.2%)
  - ~1M are medically intractable despite best medical and surgical treatment
- Worldwide, ~70M people have epilepsy
  - ~20-30M medically intractable
- Intractable epilepsy is under-recognized and under-treated
- Efficacious treatments are needed
  - Is there a role for Cannabinoids?

Available Medical Cannabis Products

- THC/CBD spray/aerosol/pill products
  - Sativex (GW Pharma – several countries)
  - Nabiximol (Italy)
  - Marinol/Nabilone (USA – THC only)
- THC/CBD dry products
  - Bediol – proportional THC/CBD
  - Bedrocan – high THC / low CBD
- CBD oils
  - Canebe Oil – 4% CBD/<0.2THC (Holland)
  - Cibdol – 4% CBD only (Holland)
  - Epidiolex - >99% CBD
  - Endoca – various concentrations – 3, 5, 15, 20, and 30% CBD
Artisanal Cannabis Products

<table>
<thead>
<tr>
<th>Reference</th>
<th>Number of Participants</th>
<th>Age of Participants</th>
<th>Diagnosis</th>
<th>Preparation</th>
<th>Dosage</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Artisanal Oral Cannabis Extracts (OCES)</td>
<td>75 children</td>
<td>51% improvement, 33% responders</td>
<td>RRF 22% “locals” vs. 47% “transplants”</td>
<td>71% terminated use</td>
<td>11.7 months (0.3-57)</td>
<td>Relocation to CO associated with perceived benefit (65% vs. 38%; p=0.01)</td>
</tr>
</tbody>
</table>

Treatment duration and expectation of efficacy

- Artisanal Oral Cannabis Extracts (OCES)
  - Press et al.
    - 75 children (51% improvement, 33% responders)
    - RRF 22% “locals” vs. 47% “transplants”
  - Treat et al.
    - Of 119 children 71% terminated use
    - Average treatment duration – 11.7 months (0.3-57)
    - Relocation to CO associated with perceived benefit (65% vs. 38%; p=0.01)
  - Espay et al.
    - FMRI PD study
    - Expectation of efficacy was associated with 28% improvement (not different from levodopa response)
“CBD products”

- Porcari et al., 2018 (Tennessee)
  - "CBD-containing product"
  - 39% >50% improvement (N=133)
  - No difference between patients on CBD vs. CBD+CLB
- Pietrafusa et al., 2019 (Italy)
  - Crystalline CBD (98-99%)
  - 37% >50% improvement (N=29)
  - No difference between patients on CBD vs. CBD+CLB

McCoy et al., 2018

- Pharmaceutical grade CBD:THC (50:1)
- Tilray (The Little Rocky Project)
- 20 patients with DS
- Dose
  - CBD 2 to 16 mg/kg/day
  - THC 0.04 to 0.32 mg/kg/day
- 19/20 completed
- Improved QOL, EEG biomarker, motor seizure frequency (70.6%) with 50% RR of 63%

RCT – Dravet Syndrome

- First CBT Phase III RCT reported
- 120 patients (61 received CBD at 20 mg/kg/d vs. 60 PCBO)
  - Added to current regimen of up to 3 AEDs
  - Average age 9.8 ± 4.9 years
  - Average number of previously failed AEDs = 4.6 ± 3.8 and concurrent 2.9 ± 1.0
- Reduction in convulsive seizures over the treatment period compared to placebo
  - Baseline 12.4 vs. 14.9
  - Treatment period 5.9 vs. 14.1
  - Percentage change p<0.01
- 84% reported mild side effects
<table>
<thead>
<tr>
<th>End Point</th>
<th>Change from Baseline or End Point</th>
<th>Difference (95% CI)</th>
<th>PCBO</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total seizure (recurrent or non-recurrent)</td>
<td>Total seizure</td>
<td>7.5 (0.46, 14.5)</td>
<td>0.10</td>
<td></td>
</tr>
<tr>
<td>Tonic clonic seizures</td>
<td>Tonic clonic seizures</td>
<td>0.30 (0.0, 0.60)</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>Atypical seizures</td>
<td>Atypical seizures</td>
<td>1.25 (0.74, 1.76)</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>Epileptic auras</td>
<td>Epileptic auras</td>
<td>1.87 (0.92, 2.82)</td>
<td>0.20</td>
<td></td>
</tr>
<tr>
<td>Overall outcomes</td>
<td>Overall outcomes</td>
<td>2.07 (0.64, 3.50)</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>Other partial seizures</td>
<td>Other partial seizures</td>
<td>0.00 (0.0, 0.0)</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>Change from Baseline (other variables)</td>
<td>Change from Baseline (other variables)</td>
<td>0.56 (0.50, 0.62)</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>Seizure frequency score</td>
<td>Seizure frequency score</td>
<td>3.3 (0.24, 6.3)</td>
<td>0.06</td>
<td></td>
</tr>
<tr>
<td>Quality of life in childhood epilepsy</td>
<td>Quality of life in childhood epilepsy</td>
<td>3.3 (0.24, 6.3)</td>
<td>0.06</td>
<td></td>
</tr>
<tr>
<td>Inpatient hospitalization due to epilepsy</td>
<td>Inpatient hospitalization due to epilepsy</td>
<td>0.00 (0.0, 0.0)</td>
<td>0.00</td>
<td></td>
</tr>
</tbody>
</table>

**RCT - LGS**

20 mg/kg/d vs. PCBO

![Graph showing statistical data](image)

**RCT - LGS**

![Graph showing statistical data](image)
Sustained treatment response

Treatment response rates for the (A) efficacy analysis set and (B) LOCF analysis

### A.
- ≥ 50% Reduction
- ≥ 75% Reduction
- 100% Reduction

#### Week 12 (n=343)
- Percentage of Patients: 52

#### Week 24 (n=331)
- Percentage of Patients: 49

#### Week 48 (n=224)
- Percentage of Patients: 48

#### Week 72 (n=157)
- Percentage of Patients: 51

#### Week 96 (n=112)
- Percentage of Patients: 44

### B.
- ≥ 50% Reduction
- ≥ 75% Reduction
- 100% Reduction

#### Week 12 (n=575)
- Percentage of Patients: 50

#### Week 24 (n=575)
- Percentage of Patients: 48

#### Week 48 (n=575)
- Percentage of Patients: 48

#### Week 72 (n=575)
- Percentage of Patients: 48

#### Week 96 (n=575)
- Percentage of Patients: 47

Response rates are based on data collected since the previous visit compared to the baseline period.

LOCF, last observation carried forward.

Szaflarski et al., 2018 Epilepsia

Is response related to interactions?

- Dravet Syndrome RCT (Devinsky et al. NEJM 2017)
  - 65% received Clobazam
  - 42% received Stiripentol
  - Both raise nCLB levels; Stiripentol also CLB levels
  - Both inhibit CYP2C19
  - CBD results in 1.7-2.6 fold increase
- But, in subsequent letter they avoid addressing whether there were differences

Word of caution

- CBDV IV trial (Greenwich Pharmaceuticals) – not efficacious – phase I
- Synthetic CBD patch (Zynerba, Inc) – phase III not efficacious
  - STAR I
  - STAR II
- Synthetic CBD (INSYS Therapeutics) – phase I only (interactions results only)
Is the response related to interactions?

- **UAB data**  114/132 at 12 weeks
  - 45 on Clobazam (24 adults/21 children)
  - No significant difference in
    - Seizure reduction (% frequency or absolute reduction)
    - Seizure severity (Chalfont) was different between groups (regression p=0.03) but paired samples T-test was not significant
  - Overall conclusion: Concomitant Clobazam has no effect on seizure frequency

Drugs – drug interactions: UAB Data

- CBD T1/2 ~24 hours
- Interactions were seen between CBD and topiramate, clobazam, and rufinamide in adults and children, and zonisamide and eslicarbazepine in adults.
- Adult subjects reported sedation more frequently with higher N-desmethylclobazam levels (CYP2C19 and CYP2C9 interactions).
- AST and ALT were higher in VPA and CBD (though the average values were still within the normal range).

Summary (Epilepsy)

- CBD has clear efficacy in the treatment of epilepsy
- Effect is likely due to modulation of the ECS
- Efficacy of THC or THC/CBD combinations is still unclear
- Stay tuned…. 