Update on Cannabinoids for Epilepsy

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Glossary of Terms:

- *Cannabis* – plant of the *Cannabis* genus, includes *C. sativa*, *C. indica* and *C. ruderalis*
- Hemp – stalk, fiber and sterilized seeds of the cannabis plant, cultivated with low THC content (0.2-0.3%) and low CBD (1-2%)
- Cannabinoids – class of similar molecules found in the *cannabis* plant, termed phytocannabinoids if derived from the plant
- Δ-9 Tetrahydrocannabinol (THC) – the most abundant psychoactive cannabinoid found in *cannabis* plants
- Cannabidiol (CBD) – the most abundant, non-psychoactive cannabinoid found in *cannabis* plants
- Endocannabinoids – molecules produced by the brain that bind to same receptors as THC – CB1 and CB2
- Cannabis Oil/Extract – preparation to extract and concentrate cannabinoids and other compounds using solvents
- Hemp oil – concentrate prepared from industrial hemp plant material
- Hemp seed oil – oil prepared from hemp seeds – no cannabinoids
- Medical marijuana – *cannabis* preparations marketed and distributed for treating human disease
- CBD-rich oil – concentrate made from *cannabis* bred to have low THC, high CBD
- Purified CBD (Epidiolex) – 98+% purified plant-derived CBD manufactured by GW Pharm (UK)
- Synthetic CBD – CBD synthesized in laboratory, structurally identical to plant-derived compound

Cannabis in History

Cannabis sativa – first cultivated ~8,000 BCE in China for rope
First record of medicinal use in China 2700 BCE
Medicinal use also documented in ancient Asian and Middle Eastern world for many conditions including epilepsy
Introduced to UK for medicinal use by W.B. O'Shaughnessy in early 19th century
Interest in purified compounds and prohibitions worldwide, medicinal use of *cannabis* stopped
For much of the 20th centuryMuch of federal research on cannabinoids has targeted adverse effects of recreational use
However, discovery of endocannabinoid system in the brain in 1990s has sparked new research into therapeutic potential of cannabinoids

Friedman D, Sirven JI. Historical perspective on the medical use of cannabis for epilepsy: Ancient times to the 1980s. Epilepsy Behav 2017.

Cannibinoids

85 phytocannabinoids found in *cannabis* species plants
Cannabidiol and Δ9 THC are 2 most abundant neuro-active cannabinoids.

Endogenous Cannabinoids aka Endocannabinoids (eCBs)
Endogenous ligands that target same receptors as THC, discovered in 1990's
Lipid-based, released by the postsynaptic membranes in response to neuronal activity:
Arachidonic acid derivatives produced by neurons and glia, the main 2 are:

- 2-Arachidonoylglycerol (2-AG)
- N-arachidonoylethanolamide/Anandamide (AEA)

Endocannabinoid System:
CB1 Receptors: Located on presynaptic membrane in the central nervous system, G-protein coupled receptor, function to modulate neurotransmitter release
CB2 Receptors: Primarily in peripheral immune cells but also in microglia

Castillo PE, Younts TJ, Chavez AE, Hashimotodani Y. Endocannabinoid signaling and synaptic function. Neuron. 2012;76(1):70-81.

Cannabinoids in Epilepsy
Role of endocannabinoids in epilepsy: Decreased levels of anandamide in CSF of patients with siezures; Decreased level of CBR1 expression in temporal lobe of treatment resistant patients and activation of eCB following seizures
Upregulation of CB1R in patients with epilepsy

Cannabinoids: Animal Models of Seizures
THC, CBD and other synthetic and plant-derived cannabinoids have been tested in multiple in vitro and in vivo models of seizures. THC and CB1 agonists have been shown to have some anticonvulsant properties in some studies but had no effect/worsened seizures in other. CBD has demonstrated anti-seizure effects in most (but not all) models tested. Some anti-seizure effects of Cannabidivarin as well.

Rosenberg EC, Tsien RW, Whalley BJ, Devinsky O. Cannabinoids and Epilepsy. Neurotherapeutics. 2015;12(4):747-68.

Cannabinoids in Epilepsy – Human Evidence

Much of human evidence for the efficacy of cannibinoids for the treatment of epilepsy is anecdotal. Few controlled trials, most small and methodologically flawed.

Devinsky O, Cilio MR, Cross H, Fernandez-Ruiz J, French J, Hill C, et al. Cannabidiol: pharmacology and potential therapeutic role in epilepsy and other neuropsychiatric disorders. Epilepsia. 2014;55(6):791-802.

Recent publication of prospective open-label study of purified CBD (Epidiolex) in 162 patients enrolled in expanded access program at 10 centers. Included patients were 1-30 years old with refractory, severe childhood onset epilepsy. Dravet Syndrome and Lennox Gastaut Syndrome were the most common syndromes included. There was a 36.5% reduction in "motor" seizures over the 12 week observation period. Adverse events were usually mild but common, including somnolence and diarrhea.

Devinsky O, Marsh E, Friedman D, Thiele E, Laux L, Sullivan J, et al. Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial. Lancet Neurol. 2016;15(3):270-8.

Randomized controlled trials of CBD for Dravet Syndrome, Lennox Gastaut Syndrome are completed and have been presented in unreviewed abstract form.

Cross et al, Cannabidiol (CBD) reduces convulsive seizure frequency in Dravet Syndrome: results of a multi-centered, randomized, controlled study (GWPCARE1) Abstract 2.362, American Epilepsy Society Annual Meeting, Houston, TX 2016

Thiele et al, Cannabidiol (CBD) significantly reduces drop seizure frequency in Lennox‐Gastaut syndrome: results of a multi-center, randomized, double‐blind, placebo-controlled trial (GWPCARE4) Abstract 1.377, American Epilepsy Society Annual Meeting, Houston, TX 2016

Trials of CBD and CBDV for refractory focal epilepsy are in progress.

Drug-Drug Interactions

CBD is a potent inhibitor of P450 isozymes *in vitro* and in animal models-CYP2C and CYP3A; CYP3A4 is important for metabolism of many drugs though effects not typically seen in doses used in human studies. Potent inhibition of CYP2C19 may affect clobazam metabolism and lead to increased levels of active metabolite

Geffrey AL, Pollack SF, Bruno PL, Thiele EA. Drug–drug interaction between clobazam and cannabidiol in children with refractory epilepsy. Epilepsia. 2015.

Gaston TE, Friedman D. Pharmacology of cannabinoids in the treatment of epilepsy. Epilepsy Behav 2017.

Safety data for cannabinoids

Much of the safety data for chronic cannabinoid use comes from studies of recreational use; inherently confounded data
Acute side effects: impaired memory, judgment and motor performance. High levels of Δ9-THC are associated with psychosis and increased risk of motor vehicle accidents.
Chronic use: Addiction ~9%; cognitive impairments; decreased motivation; increased risk for psychotic disorders.

Cannabinoids and developing brain

Chronic use can alter brain structures and decrease patterns of activation of frontal lobes.
Adolescent chronic users may have lower than expected IQ scores
Executive dysfunction, impulse and attentional difficulties reported in children exposed *in utero*; Unknown if these effects are mediated solely by THC or what role other cannabinoids may play

Volkow ND, Baler RD, Compton WM, Weiss SR. Adverse health effects of marijuana use. N Eng J Med. 2014;370(23):2219-27.

Safety data from therapeutic cannabinoid studies

Pooled data from cannabinoid use for multiple indications (MS spasticity, pain, dyskinesias): ~1600 exposures in adults for < 6 mo; ~7% stopped drug due to AE's
Common AEs: Nausea, behavioral changes, mood changes, suicidality, hallucinations, dizziness, weakness

More THC = more psychiatric AE's (anxiety, dysphoria, psychosis)
No deaths attributed to cannabinoids

Koppel BS, Brust JC, Fife T, Bronstein J, Youssof S, Gronseth G, et al. Systematic review: efficacy and safety of medical marijuana in selected neurologic disorders: report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology. 2014;82(17):1556-63.

Isolated CBD safety data in humans

CBD has no psychoactive properties. Several studies have demonstrated few adverse effects in oral doses up to 1500 mg/day; some studies were blinded, placebo-controlled assessments; No reported effects on BP, HR, RR, mood or psychomotor function

No human data on long-term use or teratogenicity. Preclinical data suggests long-term use is safe and low teratogenic potential for typical doses
Possible Immunosuppression? Pro-apoptotic in lymphocytes *in vitro;* Inhibits IL8 & IL10 production *in vitro*

Bergamaschi MM, Queiroz RHC, Zuardi AW, Crippa JAS. Safety and side effects of cannabidiol, a Cannabis sativa constituent. Cur Drug Saf. 2011;6:237-49.

Devinsky O, Cilio MR, Cross H, Fernandez-Ruiz J, French J, Hill C, et al. Cannabidiol: pharmacology and potential therapeutic role in epilepsy and other neuropsychiatric disorders. Epilepsia. 2014;55(6):791-802

What's next?

26 states plus D.C. have approved medical marijuana for certain conditions, including epilepsy

Neurologists are often asked to "certify" patients but should you recommend/support MMJ use for patients with epilepsy.

Other reading:

Friedman D, Devinsky O. Cannabinoids in the Treatment of Epilepsy. The New England journal of medicine. 2015;373(11):1048-58.

Vandrey R, Raber JC, Raber ME, Douglass B, Miller C, Bonn-Miller MO. Cannabinoid dose and label accuracy in edible medical cannabis products. JAMA. 2015;313(24):2491-3.

Whiting PF, Wolff RF, Deshpande S, et al. Cannabinoids for medical use: A systematic review and meta-analysis. JAMA. 2015;313(24):2456-73.