canntelligence™

Cannabis and the Brain:
From Plant to Clinical Practice

Educational and Networking Event

Canntelligence will be observing Brain Awareness Month by holding a discussion about the potential of cannabis as a neuroprotective treatment for epilepsy and other neurological disorders.

WHERE

University of Houston Energy Research Park
Center for Innovation and Partnerships Building 4

WHEN

Thursday, March 9th 4.30-6.30pm

Hosted by Ken Jones
Executive Director for the Center for Innovation and Partnerships

Speakers:

Dr. Jokūbas Žiburkus, PhD

Dr. Jaime Claudio-Villamil, MD
Via live video feed from San Juan, PR

Limited seating!

To RSVP or learn more, visit us at:

www.canntelligence.com

canntelligence™

CANNABINOID INTELLIGENCE
EDUCATION·TECHNOLOGY·INNOVATION
Empowerment through Education

www.canntelligence.com

Canntelligence is an education and technology company providing the highest quality educational content in a variety of formats, from in person presentations to virtual reality experiences, about the known benefits and potential harms of natural cannabis and different cannabinoid preparations.

Canntelligence is located at the University of Houston Innovation Center, where the company holds cannabinoid science forums and networking events and is developing new technologies related to cannabinoid industry.

Currently there is a large void of competent, well managed educational sources and technological innovations that make us smarter about cannabis and cannabinoids.

Canntelligence will transform consumers and healthcare practitioners' understanding of the endocannabinoid system and science of cannabis plant.

ABOUT THE SPEAKERS

Dr. Jokūbas Žiburkus, PhD is a neuroscientist with over 20 peer-reviewed publications and book chapters. He is an Associate Professor at the University of Houston where his lab is conducting research on epilepsy and Alzheimer's disease. The laboratory's current focus is on cannabinoid actions in the brain and novel treatments for neurological disorders. Žiburkus is a recipient of both the Global Lithuanian Leader Award for intellectual capital dissemination and the University of Houston's Teaching Excellence Award. He is a recognized public speaker with a widely watched Tedx Talk entitled, "There is something you should know about epilepsy and cannabis." Žiburkus has a proven track record of international leadership and strategic planning, and currently serves on several prestigious boards, including Dravet Syndrome Foundation's Scientific and Medical Advisory Board. Dr. Žiburkus completed his PhD in Lousiana State University Health Sciences Center and did his postdocturate at Johns Hopkins University Zanvyl Krieger Mind/Brain Institute and George Mason University Krasnow Institute for Advanced Studies. ***In person.***

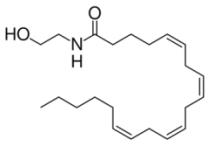
Dr. Jaime Claudio-Villamil, MD is professor of family medicine at the University of Puerto Rico Medical Sciences Campus. He is one of the creators and an active faculty member of the Medical Cannabis Certification Training Program for Physicians, adopted by the College of Physicians of Puerto Rico. He is Director of Education and Formulation Consultant for Academic Sciences of Puerto Rico, a research driven organization for the study of cannabinoids in Puerto Rico and Latin America. Dr. Claudio received undergraduate training in Chemical Engineering at Georgia Institute of Technology and Biochemistry and Psychology at the University of Wisconsin-Madison. He earned his MD in Family Medicine at the University of Puerto Rico School of Medicine. He was awarded a post-graduate fellowship in education and research from the University of North Carolina, Chapel Hill. He created the first Multidisciplinary Clinic for the Management of Obesity in 1989 and the first Telemedicine-Radiology Project in Puerto Rico in 2001. He has participated in more than 20 clinical trials. Dr. Claudio has been a TV, Radio and Newspaper medical news analyst since 1983. His radio program SALU+DEMOS on Science, Philosophy, Medicine and Longevity, has the highest audience rating for a program in this time slot. He is recipient of the Family Physician Award in 2012 and the Humanities in Medicine Award in 2016. His present focus is on creating a Medical Cannabis Practice Paradigm that integrates observational research, precise dosing and formulation of cannabinoids, with endocannabinoid wellness strategies. ***Via live interactive video feed.***

THE ENDOCANNABINOID SYSTEM

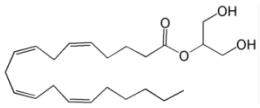
The endocannabinoid system (ECS) is a regulatory body system that consists of cannabinoid molecules synthesized internally and called endocannabinoids, and their target receptors – called cannabinoid receptors (CB) proteins. See Graphic.

Endocannabinoids - Anandamide and 2-Arachidonoylglycerol (2-AG) are endogenous molecules that were discovered in the 1990's. Endocannabinoids are produced and released on demand, during heightened levels of stress on the brain or the body. Endocannabinoids are lipid soluble and are not stored in vesicles, like traditional neurotransmitters. When endocannabinoids are released in the brain, they travel in a retrograde way (from post-synaptic to pre-synaptic side) and target cannabinoid receptors.

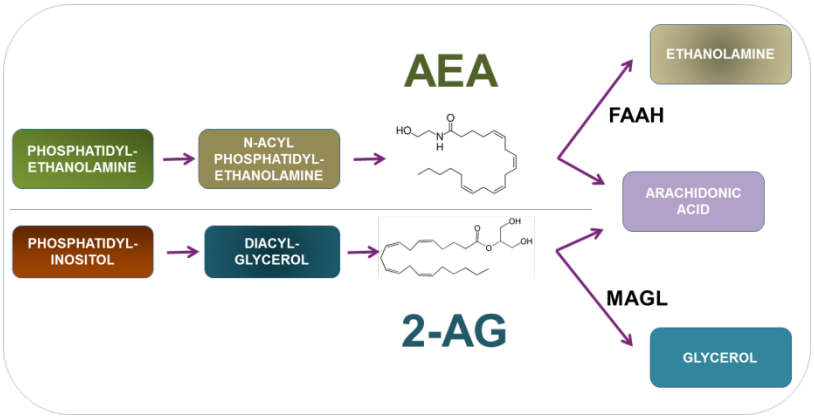
Anandamide (AEA)



2-Arachydonoyl glycerol (2-AG)



Synthesis and degradation of AEA and 2-AG



CB1 receptors are predominantly expressed in the brain. They can also be found in the heart and the digestive system. 2-AG has higher affinity to CB1 receptors. CB1 receptors are the most abundant G-protein coupled receptors in the brain.

CB2 receptors are mostly found in the peripheral body organs and cells that contribute to the normal function of the immune system, such as the spleen and pancreas. Recently CB2 receptors were also found in the brain, but to a lesser extent than CB1.

- Agonist – compounds activate receptors
- Full agonist is more potent than partial
- Affinity – potency of compound binding
- High affinity receptors require lower concentrations of ligands

Endocannabinoid deficiencies are thought to be disorders that stem from the lack of proper ECS functions. These disorders are usually hyperalgesia: Migraines, fibromyalgia, irritable bowel syndrome, neurotransmitter disorders, and epilepsies (Dr. Ethan Russo).

ENDOCANNABINOID SYSTEM

canntelligence™

Brain
Neural regulation
Memory
CB1>>CB2

Lungs
Bronchial response
CB1~CB2

Liver
Metabolism
CB1

Intestines
Inflammatory
Digestive responses
CB1

Kidneys
Inflammatory and Blood vessel response
CB1

Bladder
Bladder control
CB1

Skin
CB1~CB2

Heart
Inflammatory response
Heartbeat
CB1

Stomach
Inflammatory response
Acid reflux
Nausea
CB1

Pancreas
Insulin secretion
CB1~CB2

Spleen
Immune response
CB2

Bone marrow
Immune response
CB2

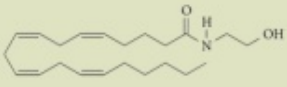
Cannabinoid Receptors

Cannabinoid receptor 1 (CB1)
> Anandamide and THC bind
> THC causes the 'high' effect
> Primarily expressed in the brain

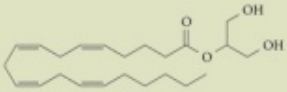
Cannabinoid receptor 2 (CB2)
> Immune system and immune-derived cells
> Greatest density in the spleen

Endocannabinoids

Cannabinoid molecules synthesized endogenously based on demand.



Anandamide or AEA
(arachydonoyl ethanolamide)



2-AG
(2-Arachidonoyl glycerol)

Phytocannabinoids

Cannabinoid molecules synthesized by cannabis plants

THC - Δ9-Tetrahydrocannabinol
THCA - Tetrahydrocannabinolic acid
CBD - Cannabidiol
CBDA - Cannabidiolic acid
CBG - Cannabigerol
CBGA- Cannabigerolic acid
CBDV - Cannabidivarin
CBC - Cannabichromene
CBL - Cannabicyclol
THCV - Tetrahydrocannabivarin

DISEASE DEFINITIONS

Neurodegenerative disease - a condition that results in the progressive loss or death of nerve cells in the brain and spinal cord.

Epilepsy. According to the International League Against Epilepsy, this is what a person is considered to have epilepsy if they meet any of the following conditions: At least two unprovoked (or reflex) seizures occurring greater than 24 hours apart; One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years; Diagnosis of an epilepsy syndrome. Epilepsy is considered to be resolved for individuals who had an age-dependent epilepsy [1, 2]the last 10 years, with no seizure medicines for the last 5 years.

Dravet syndrome is a form of intractable childhood epilepsy, most often associated with the mutation in voltage-gated sodium channels (Dravet Syndrome Foundation).

Alzheimer's disease (AD) is the most common form of dementia in patients over the age of 65. It manifests as a progressive degenerative disorder in the central nervous system. AD is predominantly associated with a progressive decline in cognitive abilities that first manifests as word finding difficulties and impairments in short-term memory. In addition to gross cortical atrophy, the pathological hallmarks used to definitively identify Alzheimer's disease include the presence of insoluble aggregations of extracellular amyloid beta protein and formation of neurofibrillary tangles inside the cells, associated with the accumulation of the Tau protein. (Alzheimer's Association).

Repeated brain injury and dementia. Traumatic brain injuries (TBI) range from mild (concussions) to severe injuries that result in the loss of brain tissue, and other complications, like damage to the micro blood vessels. Repeated brain injuries are most common amongst contact sport athletes and soldiers. Dementias related to head injuries are becoming an important health concern. Multiple head injuries are known to substantially increase the risk for development of chronic traumatic encephalopathy.

Chronic Traumatic Encephalopathy (CTE) is a neurological neurodegenerative disease with a delayed onset that develops in response to repeated mild traumatic brain injury or concussion. CTE can have its onset starting from the teenage years, and has signatures of dementia and Alzheimer's disease.

Migraine is a neurological condition that causes mild to severe head pain, nausea and vomiting, and disturbances in vision and or speech. It can last for hours or days and cab be mentally and physically debilitating.

Fibromyalgia is a widespread pain in muscles and soft tissue and is associated with fatigue, sleep problems, and mood changes.

Neuroinflammation is the protective immune system response to physical damage or viral infection of the brain. Neuroinflammation is common in neurodegenerative diseases and occurs in response to traumatic brain injury.

Neuroprotection is a mechanism by which the brain can protect itself from an ongoing insult, like repeated concussions. Neuroprotective mechanisms in the brain prevent the loss of nerve cells (neurons) and their connections, called synapses.

Inflammation - the succession of beneficial changes which occurs within a living tissue when the tissue is injured and the immune system is engaged. Redness, heat, swelling, pain are all signs of inflammation. Prostaglandins are key mediators of the inflammatory response and they are formed when arachidonic acid is released by the cells.

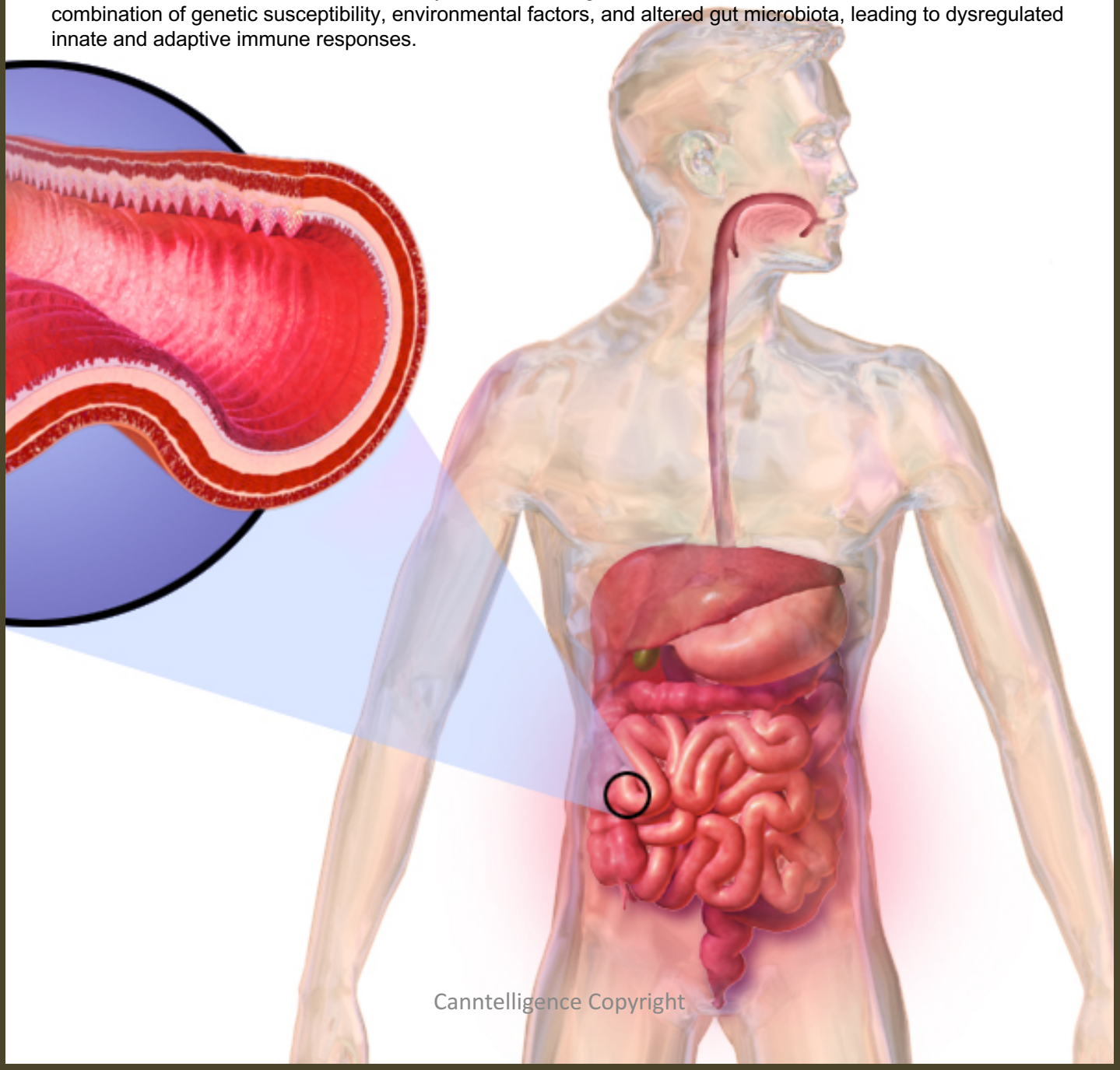
DISEASE DEFINITIONS

Edema or swelling results from increased passage of fluid from dilated and permeable blood vessels into the surrounding tissues, infiltration of cells into the damaged area, and, in prolonged inflammatory responses, deposition of connective tissue.

Rheumatoid arthritis is a chronic inflammatory joint disease, which can cause cartilage and bone damage, chronic pain, as well as disability.

Gout is a chronic disease of deposition of monosodium urate crystals, which form in the presence of increased urate concentrations. This causes pain and inflammation in joints.

Crohn's disease is a chronic inflammatory disease of the gastrointestinal tract. Crohn's disease can stem from combination of genetic susceptibility, environmental factors, and altered gut microbiota, leading to dysregulated innate and adaptive immune responses.



CANNABIS and PHYTOCANNABINOIDS

Cannabis (hemp) is one of the oldest domesticated plants, used for fiber and medical purposes. Cannabis originated in South Central Asia and is largely divided into two main species *cannabis sativa* and *cannabis indica*. There are thousands of different cannabis strains.

Cannabis sativa is associated with cerebral and invigorating effects. Sativas contain lower amounts of tetrahydrocannabinol (THC) and higher amounts of cannabidiol (CBD).

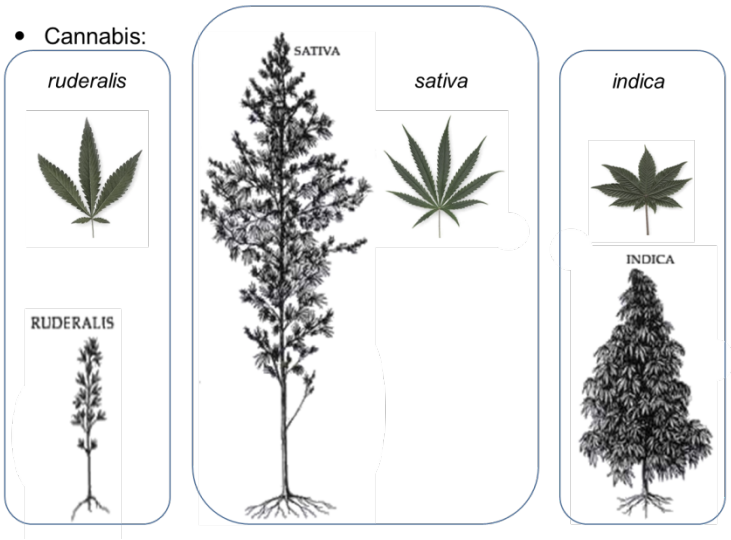
Cannabis indica is known to have stronger physiological effects on the body and be more sedative.

Hybrid strains are genetic crosses of sativas and indicas to perpetuate the best features of the two species.

Medical Cannabis refers to the use of diverse cannabis products in an alternative treatment of a wide variety of symptoms and diseases. Medical marijuana strains contain between 0.3-25% of THC.

Medicinal properties refers to the ability of cannabis and isolated cannabinoids to help with an array of symptoms and disorders ranging from chronic pain, epilepsy to cancer to autoimmune disorders.

Hemp – strains of *cannabis sativa* that have many applications, including industrial and medical uses. According to the regulations in many countries, hemp plants contain 0.3% THC or below. 0.3% THC limit is considered safe and takes into the account high risk population.



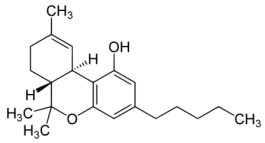
Phytocannabinoids - cannabinoids that are found in cannabis, but also in other plants, like flax. Phytocannabinoids interact with the endocannabinoid and other physiological systems in human brains and bodies. There are over 115 phytocannabinoids found in cannabis plants.

CANNABIS and PHYTOCANNABINOIDS

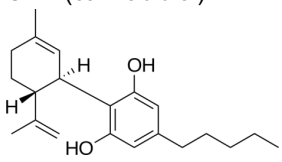
THC binds CB1 receptors by fitting into it like a key into a lock. THC binding to CB1 causes euphoric (intoxicating) effects. THC also targets other receptors, like

CBD also binds CB1 receptors, but in a different location and has taming effects, especially on the negative side effects of THC. However, CBD prefers to bind to other receptors, like serotonin 5HT receptor, instead of CB1.

- THC (tetrahydrocannabinol)



- CBD (cannabidiol)



Acidic cannabinoids are acidic forms of cannabinoids like THC and CBD, known as THCA and CBDA. Over 90% of cannabinoids naturally synthesized by cannabis plants are acidic. THCA is the precursor of THC and has no intoxicating properties until it is heated or decarboxylated. Extracts prepared using low temperatures or 'raw' cannabis formulations contain acidic phytocannabinoids.

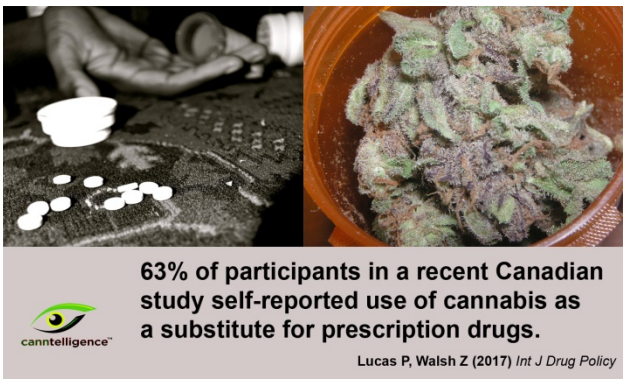
Decarboxylation is a process of turning acidic cannabinoids into neutral forms, like transforming THCA to THC via heating.

Full spectrum hemp or cannabis extracts refers to the whole plant extract, whereby mostly the tops of the plants are used to preserve the full spectrum of phytocannabinoids, terpenes, and other important molecules. Whole plant hemp extracts are usually dominated by CBDs.

Terpenes - volatile odor molecules that give different cannabis strains distinct aromas. Terpenes have known physiological and psychological effects and are also inhaled at lower temperatures than the phytocannabinoids.

Medical cannabis and cannabinoid consumption. Inhalation delivers phytocannabinoid vapor or smoke into the lungs and small blood vessels that distribute it throughout the body. Ingesting cannabis is the second most used way, either by application of oils and concentrates sublingually, in a buccal (cheek) way, or chewing. Suppositories deliver cannabis formulations into vaginal and anal cavities. Topical cannabis preparations are applied externally on the skin, nails, wounds and cuts.

1 in 8 or 13% of US adults use cannabis. This number is almost double of what was reported in 2013 at 7%. Gallup Poll 2016.



REFERENCES

Naftali, T., et al., Cannabis for inflammatory bowel disease. Dig Dis, 2014.
Torres, J., et al., Crohn's disease. Lancet, 2016.
Raymont, V., et al., "Studying injured minds" - the Vietnam head injury study and 40 years of brain injury research. Front Neurol, 2011
Griffin, G.D., The injured brain: TBI, mTBI, the immune system, and infection: connecting the dots. Mil Med, 2011
Plassman, B.L., et al., Documented head injury in early adulthood and risk of Alzheimer's disease and other dementias. Neurology, 2000.
Nemetz, P.N., et al., Traumatic brain injury and time to onset of Alzheimer's disease: a population-based study. Am J Epidemiol, 1999. Mortimer, J.A., et al., Head trauma as a risk factor for Alzheimer's disease: a collaborative re-analysis of case-control studies. EURODEM Risk Factors Research Group. Int J Epidemiol, 1991.
Fleminger, S., et al., Head injury as a risk factor for Alzheimer's disease: the evidence 10 years on; a partial replication. J Neurol Neurosurg Psychiatry, 2003.
Devinsky, O., B.J. Whalley, and V. Di Marzo, Cannabinoids in the Treatment of Neurological Disorders. Neurotherapeutics, 2015..
Friedman, D. and O. Devinsky, Cannabinoids in the Treatment of Epilepsy. N Engl J Med, 2016. 374(1): p. 94-5.
Geffrey, A.L., et al., Drug-drug interaction between clobazam and cannabidiol in children with refractory epilepsy. Epilepsia, 2015.
Katona, I. and T.F. Freund, Endocannabinoid signaling as a synaptic circuit breaker in neurological disease. Nat Med, 2008. Monory, K., et al., The endocannabinoid system controls key epileptogenic circuits in the hippocampus. Neuron, 2006.
Oliveira, C.C., et al., Anticonvulsant activity of beta-caryophyllene against pentylenetetrazol-induced seizures. Epilepsy Behav, 2016.
Tzadok, M., et al., CBD-enriched medical cannabis for intractable pediatric epilepsy: The current Israeli experience. Seizure, 2016.
Ahmed, A., et al., Cannabinoids in late-onset Alzheimer's disease. Clin Pharmacol Ther, 2015.
Dey, A., et al., Natural products against Alzheimer's disease: Pharmaco-therapeutics and biotechnological interventions. Biotechnol Adv, 2016.
Hardy, J., The Discovery of Alzheimer causing Mutations in the APP Gene and the Formulation of the "Amyloid Cascade Hypothesis". FEBS J, 2017.
McKee, A.C., M.L. Alosco, and B.R. Huber, Repetitive Head Impacts and Chronic Traumatic Encephalopathy. Neurosurg Clin N Am, 2016.
Rom, S. and Y. Persidsky, Cannabinoid receptor 2: potential role in immunomodulation and neuroinflammation. J Neuroimmune Pharmacol, 2013.
Lynch, M.E. and F. Campbell, Cannabinoids for treatment of chronic non-cancer pain; a systematic review of randomized trials. Br J Clin Pharmacol, 2011.
Malfait, A.M., et al., The nonpsychoactive cannabis constituent cannabidiol is an oral anti-arthritic therapeutic in murine collagen-induced arthritis. Proc Natl Acad Sci U S A, 2000.
Dalbeth, N., T.R. Merriman, and L.K. Stamp, Gout. Lancet, 2016.
Cahn, R. S. 174. Cannabis indica resin. Part III. The constitution of cannabinol. Journal of the Chemical Society (Resumed), (1932).
RS, C. Cannabis indica resin, Part III. The constitution of Cannabinol. Journal of the Chemical Society, London., 1342-1353 (1932).
Ghosh, R., Todd, A. R. & Wilkinson, S. 264. Cannabis indica. Part V. The synthesis of cannabinol. Journal of the Chemical Society (Resumed), (1940).
Krejci, Z., Horak, M. & Santavy, F. [Hemp (Cannabis sativa)-an antibiotic drug. 3. Isolation and constitution of two acids from Cannabis sativa]. Pharmazie (1959).
Korte, F., Haag, M. & Claussen, U. Tetrahydrocannabinolcarboxylic acid, a component of hashish. 1. Angew Chem Int Ed Engl 4 (1965).
Mechoulam, R. & Gaoni, Y. A Total Synthesis of Dl-Delta-1-Tetrahydrocannabinol, the Active Constituent of Hashish. J Am Chem Soc (1965).
Yamauchi, T., Shoyama, Y., Aramaki, H., Azuma, T. & Nishioka, I. Tetrahydrocannabinolic acid, a genuine substance of tetrahydrocannabinol. Chem Pharm Bull (Tokyo) 1967).
Bicher, H. I. & Mechoulam, R. Pharmacological effects of two active constituents of marihuana. Arch Int Pharmacodyn Ther 172, 24-31 (1968).
串間奉文, 正山征洋 & 西岡五夫. Cannabis. XII. Variations of cannabinoid contents in several strains of Cannabis sativa L. with leaf-age, season and sex. Chemical and Pharmaceutical Bulletin 21980).
Fairbairn, J. W. & Pickens, J. T. Activity of cannabis in relation to its delta'-trans-tetrahydro-cannabinol content. Br J Pharmacol (1981).
Malfait, A. M. et al. The nonpsychoactive cannabis constituent cannabidiol is an oral anti-arthritic therapeutic in murine collagen-induced arthritis. Proc Natl Acad Sci U S A (2000).
Grotenhermen, F. Pharmacokinetics and pharmacodynamics of cannabinoids. Clin Pharmacokinet (2003).
Russo, E. B. & McPartland, J. M. Cannabis is more than simply delta(9)-tetrahydrocannabinol. Psychopharmacology (Berl) (2003).
Dussy, F. E., Hamberg, C., Luginbuhl, M., Schwerzmann, T. & Briellmann, T. A. Isolation of Delta9-THCA-A from hemp and analytical aspects concerning the determination of Delta9-THC in cannabis products. Forensic Sci Int (2005).
Shoyama, Y. et al. Crystallization of Δ1-tetrahydrocannabinolic acid (THCA) synthase from Cannabis sativa. Acta Crystallographica Section F: Structural Biology and Crystallization Communications (2005).
Verhoeckx, K. C. et al. Unheated Cannabis sativa extracts and its major compound THC-acid have potential immuno-modulating properties not mediated by CB1 and CB2 receptor coupled pathways. Int Immunopharmacol (2006).
Eichler, M. et al. Heat exposure of Cannabis sativa extracts affects the pharmacokinetic and metabolic profile in healthy male subjects. Planta Med (2012).
Takeda, S. et al. Cannabidiolic acid, a major cannabinoid in fiber-type cannabis, is an inhibitor of MDA-MB-231 breast cancer cell migration. Toxicol Lett (2012).
Aizpurua-Olaizola, O. et al. Evolution of the Cannabinoid and Terpene Content during the Growth of Cannabis sativa Plants from Different Chemotypes. J Nat Prod, doi: (2016).
Andre, C. M., Hausman, J. F. & Guerriero, G. Cannabis sativa: The Plant of the Thousand and One Molecules. Front Plant Sci (2016).

Canntelligence Evaluation Form

Your feedback is critical to ensure we are meeting your future educational needs. We would appreciate if you could take a few minutes to share your opinions with us so we can serve you better.

Canntelligence Brain Awareness Month: Brain and Cannabis Date: 03/09/2016

Age group 18-25 ❑ 25-35 ❑ 35-45 ❑ 45-55 ❑ 55-65 ❑ 65+ ❑ **Sex** Female ❑ Male ❑

Education level High School ❑ College ❑ Graduate ❑ Postgraduate ❑ Researcher ❑ Healthcare Practitioner ❑

	Strongly agree				**Strongly disagree**
1. The content was as described in publicity materials	1	2	3	4	5
2. The workshop was applicable to my job	1	2	3	4	5
3. I will recommend this workshop to others	1	2	3	4	5
4. The program was well paced within the allotted time	1	2	3	4	5
5. The speakers were good communicators	1	2	3	4	5
6. The material was presented in an organized manner	1	2	3	4	5
7. The speakers was knowledgeable on the topic	1	2	3	4	5
8. I would be interested in attending a follow-up, more advanced workshop on this same subject	1	2	3	4	5

9. Given the topic, was this workshop: ❑ a. Too short ❑ b. Right length ❑ c. Too long

10. In your opinion, was this workshop: ❑ a. Introductory ❑ b. Intermediate ❑ c. Advanced

11. Please rate the following:

	Excellent	Very Good	Good	Fair	Poor
a. Visuals	❑	❑	❑	❑	❑
b. Acoustics	❑	❑	❑	❑	❑
c. Meeting space	❑	❑	❑	❑	❑
d. Handouts	❑	❑	❑	❑	❑
e. The program overall	❑	❑	❑	❑	❑

12. What did you most appreciate/enjoy/think was best about the event? Any suggestions for improvement?

_____

_____

If you would like to be emailed about the future Continuous Medical Education training, please include your contact e-mail address here: _____

Please return this form to Canntelligence. Thank you!