Cannabinoids & CBD
Moving Mainstream

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Colonel (Retired), U.S. Army

Brain Health
Education & Research Institute
a 501(c)(3) nonprofit organization

Louisiana Psychiatric Medical Association: Feb 2019
Learning Objectives

1. Describe the role our endogenous cannabinoid system plays in our bodies

2. Understand how phytocannabinoids interact with our endogenous cannabinoid system

3. Understand the clinical use of Cannabidiol (CBD) in maintaining/obtaining brain health including its use in anxiety/mental health
We All Have Cannabinoid Receptors

The cannabinoid receptors are further divided into 2 main subtypes, known as cb1 and cb2.

CB1 is found mostly in the brain.

CB2 receptors are mostly found within the immune system.
- Cerebral cortex (thought, planning)
- Basal ganglia (movement)
- Thalamus (gateway to cortex)
- Cerebellum (coordination & balance)
- Hypothalamus (regulates body function)
- Amygdala (emotion)
- Hippocampus (memory)
- Medulla oblongata (cardio-resp fxn)
Endogenous Cannabinoids

• Endocannabinoids are “messengers”

• Involved in direct regulation of appetite, metabolic health, pain, inflammation, thermoregulation, sensation, muscle control, motivation, reward, mood, memory

• Involved in learning and synaptic plasticity
Endocannabinoids

Arachidonoylethanolamide (anandamide)

2-arachidonoylglycerol (2-AG)
Arachidonoyl ethanolamide (Anandamide or AEA)

• Discovered 1992 by Raphael Mechoulam

• “Ananda–mide” means bliss–molecule

• Activity CB1>>CB2 receptors

• Short half-life (minutes)

• Broken down by Fatty Acid Amide Hydrolase (FAAH) into arachidonic acid
Anandamide - Functions

• Pleasure/happiness/euphoria
• Ability to cope with stress
• Decrease/relieve anxiety
• Enhances libido
• Reduces pain levels, cortisol levels, and inflammation
• May inhibit cancer cell growth
2-arichidonyl glycerol (2-AG)

- 200 times more 2-AG than anandamide
- Full agonist for CB1R & CB2R
- Main activator of CB2 receptors
  - Immune system and brain glial cells
- Broken down into Arachidonic Acid
Functions of 2-AG

- Regulates immune function
- Reduces inflammation
- Neuroprotective
- Suppresses seizure activity
- Communication: gut flora to brain
- Regulates vascular system
Endocannabinoid System

Neuromodulators that mediate the intensity of neurotransmission
Endocannabinoid Tone

• Most important physiologic system involved in establishing and maintaining human health

• Various lifestyle factors including diet and aerobic activity affect the overall ECS function or ‘endocannabinoid tone’

• Keeps internal bodily functions stable and controls how we think, feel, and react
Balanced Effects of Endocannabinoids

- Metabolic syndrome
- Obesity & over-eating
- Increased inflammation
- Insulin resistance/diabetes
- Mental health instability
- Migraines
- Chronic pain
- Fibromyalgia
- IBS
- Depression
- PTSD

Ideally, if the ECS is functioning normally, a person might enjoy a normal mental state, without pain, have good digestive function, etc.
Nature and the Endocannabinoid System

Cannabinoid Receptors
[CB1, CB2, TRPV1, 5-HT1A]

Phyto-
Cannabinoids
[THC, CBD]

Endogenous
Cannabinoids
[Anandamide (AEA),
2-arachidonoylglycerol (2-AG)]

Regulatory Metabolic/
Catabolic Enzymes
[fatty acid amide hydrolase
(FAAH), monoacylglycerol
lipase (MAGL), and others]
Endocannabinoids

Arachidonoylethanolamide (anandamide) (AEA)  2-arachidonoyletylercol (2-AG)

Phytocannabinoids

Cannabidiol (CBD)  \( \Delta^9 \)-tetrahydrocannabinol (\( \Delta^9 \)-THC)
Beware! Young All Will

This may be handled by the friendly stranger

"Marihuana" - a powerful

Murder

WARNING

Dope peddling

put some of your in the use for details.

Address: THE INTER-STATE

53 W. Jackson Blvd.

"REEFER MADNESS"

WOMEN CRY FOR IT - MEN DIE FOR IT!

"The Sweet Pill" that makes life bitter!

ADULTS ONLY!

SEE

YOU CRAZED ABANDON

YOUTHFUL MARIHUANA VICTIMS

WHAT ACTUALLY HAPPENS...
What do these men have in common?

- **Aiden Hampson**, a neuropharmacologist at the Natl Inst for Mental Health (NIMH). Now Health Science Administrator, Natl Inst of Drug Abuse (NIDA), Medications Research Grants Branch

- **Julius Axelrod** (1912-2004), Professor Emeritus, NIH, pharmacologist and neuroscientist who shared the 1970 Nobel Prize in Physiology or Medicine for his discovery of the actions of neurotransmitters in regulating the metabolism of the nervous system

- **Maurizio Grimaldi**, professor of neurology/neuropsychopharmacology and toxicology, NIMH. Now with Natl Inst on Aging, Scientific Review Branch
ABSTRACT

Cannabinoids have been found to have antioxidant properties, unrelated to NMDA receptor antagonism. This new found property makes cannabinoids useful in the treatment and prophylaxis of wide variety of oxidation associated diseases, such as ischemic, age-related, inflammatory and autoimmune diseases. The cannabinoids are found to have particular application as neuroprotectants, for example in limiting neurological damage following ischemic insults, such as stroke and trauma, or in the treatment of neurodegenerative diseases, such as Alzheimer’s disease, Parkinson’s disease and HIV dementia. Nonpsychoactive cannabinoids, such as cannabidiol, are particularly advantageous to use because they avoid toxicity that is encountered with psychoactive cannabinoids at high doses useful in the method of the present invention. A particular disclosed class of cannabinoids useful as neuroprotective antioxidants is formula (I) wherein the R group is independently selected from the group consisting of H, CH₃, and COCH₃.
This study reports that CBD and other cannabinoids such as THC are potent antioxidants that protect neurons from glutamate-induced death without cannabinoid receptor activation. Nonpsychoactive CBD was found to prevent both glutamate neurotoxicity and ROS-induced cell death.
US Govt: Who’s Right about Cannabis?

**FDA & DEA**

- Schedule I Drug:
  - (a) high potential for abuse;
  - (b) no currently accepted medical use;
  - (c) lack of accepted safety for use of the drug or other substance under medical supervision

**HHS - NIH**

- Holds a patent for CBD:
  - Neuroprotectant, anti-epileptic, anxiolytic
  - “For use in prophylaxis and treatment of disease”
  - “No signs of toxicity or serious side effects have been observed following chronic administration... even when given in large acute doses”
History: Cannabis as Medicine

- 2900 BC: Chinese Emperor Fu His - popular medicine that possessed both yin and yang
- 1450 BC: Book of Exodus (30:22-23)
- 1213 BC: Egyptians Use for glaucoma, inflammation
- 1000 BC: Used in India as anesthetic
- 700 BC: Documented use in Persia
- 200 BC: Used in Ancient Greece for inflammation
- 1762: farming of hemp *required* by law in Virginia
- 1745-1824: grown by Presidents GW, TJ, JM, others
- 1942: USDA film “Hemp for Victory” to support the war effort, encourages growing hemp
Cannabis Americana

As active as Indian Cannabis

We are marketing Cannabis Americana, a fluid extract
containing the active principles of Cannabis Indica
and Cannabis Sativa, also known as Indian Cannabis.

Our product is physiologically and pharmaceutically
equivalent to the fluid extract obtained from
the plants indigenous to India.

Fluid Extract Cannabis Americana is marketed
as a powerful and effective remedy for
infants relief, with a formulation of
Dr. P. D. Fahnrey.

It contains per fluid ounce:
- Solvent: 45 cc.
- Cannabis Indica: 11-4 grains
- Sweet Spirits of Nitre: 20 minims
- Chloroform: 5 minims

For all looseness of bowels.

Serial No. 519

Parke, Davis & Co.
Home Offices and Works, Detroit, Michigan, U. S. A.

Cannabis Indica
(Catalogue No. 171)

Physiologically: strength is 25
doors from American's solid extract.

Dosage: 1/8 grain (.043 g)

For the
Laboratory of
W. S. Merrell
Cincinnati, U.S.A.

Victor

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Formula of Dr. P. D. Fahrney

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Cannabis

Marijuana
- THC content 5-30%
- Female plant cultivated for THC from buds
- Grown under controlled conditions
- Classified as illegal drug
- Use: Recreational/medical drug

Hemp
- THC content <0.3%
- Male plant/crop: tall, thick, fast growing
- Grown outside >20 ft
- Classified as food, legal to import into U.S.
- Use: Foods, oils, textiles, rope, fabrics
CBD

Antibacterial
Inhibits cancer cell growth
Neuro-protective
Promotes bone growth
Reduces seizures and convulsions
Reduces blood sugar levels
Reduces function in the immune system
Reduces inflammation
Reduces risk of artery blockage
Reduces small intestine contractions
Reduces vomiting and nausea
Relieves pain
Relieves anxiety
Slows bacterial growth
 Suppresses muscle spasms
Tranquilizing
Treats psoriasis
Vasorelaxant
Cannabinoids in the Body

80+ cannabinoid compounds are found in cannabis plants

THC (Delta-9-tetrahydrocannabinol)
- Psychoactive
- Creates the characteristic marijuana "high"
- Can relieve pain and inflammation

CBD (Cannabidiol)
- Non-psychoactive
- Can reduce negative psychoactive effects of THC
- Responsible for many of the medical benefits of cannabis
Side Effects

**THC**
Anxiety and paranoia are well-known potential side effects
May have acute and long-term adverse effects on parts of brain for learning and memory

**CBD**
Immediate and long-term side effects appear to be minimal
The alterations in thinking and perception caused by THC are not observed with CBD. The different pharmacological properties of CBD give it a different safety profile from THC.

A review of 25 studies on the safety and efficacy of CBD did not identify significant side effects across a wide range of dosages, including acute and chronic dose regimens, using various modes of administration.

Nora D. Volkow, Director, National Institute on Drug Abuse
Testimony on June 24, 2015, to Senate Caucus on International Narcotics Control
Hemp-derived CBD is NOT Marijuana

- 2014 U.S. Farm Bill allows states to regulate and permit commerce in hemp and hemp products
- 2016 Omnibus Law prohibits federal agencies (and $$) from interfering with hemp pilot programs
- Nov-2017, WHO issued report that CBD is safe, well-tolerated, without negative public health outcomes including physical dependence or abuse potential
- 1-Jan-2018, WADA drops CBD from Banned Substance list and no longer tests for it
- 2018 U.S. Farm Bill: Includes Hemp Act 2018
Agricultural Hemp Is Amazing

• Non-psychoactive/toxic

• Whole plant is incredibly useful: Food, fiber, rope, textiles, building materials, fuels, >25K uses

• Nutrient rich: EFAs, amino acids, Vitamin E, phosphorus, potassium, sodium, magnesium, sulfur, calcium, iron, zinc

• Eco-friendly: Sequesters CO2, no herbicides, repletes soil
<table>
<thead>
<tr>
<th>FATTY ACIDS</th>
<th>CANNABINOIDS</th>
<th>TERPENES</th>
<th>PLANT STEROLS</th>
<th>CHLOROPHYLL</th>
<th>VITAMIN E</th>
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<tr>
<td>α-Linolenic Acid 18:3N-3</td>
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* Most abundant terpenes
** Less than 0.3% THC in bulk oil and considerably less in the finished product
*** Contains all naturally-occurring forms of Vitamin E
Raw Hemp Extract
CBDA: Herbal Ibuprofen

- Cannabidiolic Acid → “Acid form” of CBD
- Least blood-brain barrier penetration
- Least likely to cause any CNS effects
- More specific in inflammation management →
  Blocks COX-2 enzyme more than CBD
  - Inflammation
  - Arthritis
  - Exercise recovery
  - Headache pain
  - Gut modulation, leaky gut, IBS
  - Balm excellent for acne, eczema, skin irritation
Decarboxylation of CBDA
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Refined Hemp Extract
Neurogenic Support

- Mental Health, Stress Resilience
- Anxiety, Depression
- Chronic pain perception > sensory pain
- Neuroprotection → Alzheimer’s, Parkinson’s, Stroke, Trauma, Concussions
- Clinical Endocannabinoid Deficiency: Fibromyalgia, Migraines, IBS
- Metabolic Health, Appetite Control
- Balm for muscle and joint discomfort
**Stages of CBD Oil Processing**

**RAW FORMULA**
- 10% PHYTOCANNABINOIDs
- 90% PLANT MATERIAL
- 10% PHYTOCANNABINOIDs → CBDA

**TOTAL PLANT COMPLEX**
- 15% PHYTOCANNABINOIDs
- 85% PLANT MATERIAL

**GOLD FORMULA**
- 25% PHYTOCANNABINOIDs
- 75% PLANT MATERIAL

**ISOLATE**
- 99% CBD

**Potent Peripheral Anti-inflammatory Benefits → CBDA**

**Total Body Support With Both Systemic Anti-inflammatory & Neurogenic Benefits**

**High-intensity Support For Both Central & Peripheral Neurogenic Dysfunction**

**Concentrated Vape CBD For Rapid Absorption**
EPIDIOLEX – 100mg CBD/mL

99% CBD
Among patients with the Dravet syndrome, cannabidiol resulted in a greater reduction in convulsive-seizure frequency than placebo.

20 mg per kilogram of body weight per day \(\rightarrow\) average 1400 mg per day dose.
Patients treated with CBD-rich extracts lower average dose (6.1 mg/kg/day) than purified CBD (27.1 mg/kg/day).

Mild/severe adverse effects less with CBD-rich extracts than products containing purified CBD.

CBD-rich extracts seem to present a better therapeutic profile than purified CBD...likely due to synergistic effects of CBD with other phytocompounds (Entourage Effect).
Overcoming the Bell-Shaped Dose-Response of Cannabidiol by Using *Cannabis* Extract Enriched in Cannabidiol

**Ruth Gallily¹, Zhannah Yekhtin¹, Lumír Ondřej Hanuš²**

¹The Lautenberg Center for General and Tumor Immunology, The Hadassah Medical School, The Hebrew University of Jerusalem, Jerusalem, Israel
²Department of Medicinal and Natural Products, Institute for Drug Research, The Hadassah Medical School, The Hebrew University of Jerusalem, Jerusalem, Israel

Email: ruthg@ekmd.huji.ac.il
CBD-rich Hemp Extracts

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<th>Anti-inflammatory Effect</th>
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<tr>
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**Purified CBD**
Common Effects:
- euphoria
- relaxation
- anxiety
- short term memory impairment
CBD's Therapeutic Impact

- Activates 5-HT1A serotonin receptor. Helps with anxiety, addiction, appetite, sleep, nausea, vomiting.
- Binds to TRPV1 receptors. Moderates pain, inflammation, body temperature.
- Blocks G protein receptor GPR55. May decrease bone reabsorption and the spread of cancer cells.
- Activates peroxisome proliferator activated receptors (PPARs). Has been shown to produce anti-cancer effect and help with Alzheimer's.
CBD, FAAH, and Anandamide

- CBD has little affinity for CB1R and CB2R
- ↑↑ FAAH $\rightarrow$ low anandamide levels
- CBD blocks FAAH keeping anandamide around longer
Chronic Inflammation

CRH (Stress)

Prostaglandin E2

Peripheral Tissue

COX-2

AEA

FAAH

AA

细胞

另一个细胞

核

CBD

NF-κB

PPARγ
INDIRECT INTERACTION

OUTSIDE CELL

THC

INSIDE CELL

CBD

Cannabinoid

AILMENTS CBD MAY DECREASE:
- side effects of THC, e.g. anxiety
# CBD Mechanisms of Action

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<tr>
<th>Agonist</th>
<th>Antagonist</th>
<th>Receptor-Independent</th>
<th>Regulates</th>
<th>Serotonin 5HT1A</th>
<th>Vanilloid TRVP-1</th>
<th>Adenosine 2A2</th>
<th>GPR55</th>
<th>FAAH inhibition</th>
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- Agonist
- Antagonist
- Receptor-Independent
- Regulates: depression, sleep, appetite, pain, inflammation, body temperature, cardiovascular, other neurotransmitters, bone density, blood pressure, cancer cell proliferation, ECB tone, neuroprotection
- Serotonin 5HT1A
- Vanilloid TRVP-1
- Adenosine 2A2
- GPR55
- FAAH inhibition
- Antioxidant

Martin A. Lee (O’Shaughnessy’s – Autumn 2011)
Cannabinoids and Mental Health

• CBD is emerging as potential treatment for:
  • Depression
  • Psychosis
  • Addictive behavior
  • Anxiety disorders
  • PTSD

CBD as an Antidepressant

• Study results demonstrate that CBD exerts *fast and maintained* antidepressant-like effects

• 5-HT1A receptor-dependent mechanism

• CBD significantly enhanced serotonin and glutamate levels

“Results showed a single dose of CBD dose-dependently induced antidepressant-like effect in... 30 minutes following treatment. ...These effects may be related to rapid changes in synaptic plasticity...”
Psychosis

- Acute schizophrenia RCT in 33 patients over 4 weeks
  - CBD worked better, had superior safety profile, without amisulpride's side-effects
- In fMRI studies, CBD improves limbic and neocortical function that are abnormal in schizophrenia
  - Δ⁹-THC worsens those areas in the brain associated with schizophrenia

Addictive Behavior

- Animal models show CBD reduces drug-seeking behavior:
  - Cocaine & Amphetamines
  - Heroin-seeking behaviors up to 2 weeks suggesting long-term impact to drug relapse
- In 94 cannabis smokers, higher CBD:THC decreased drug seeking behavior versus high THC cannabis users
- In human observational studies, CBD being used as a therapeutic for cannabis withdrawal and nicotine dependence

Anxiety/Stress Can Be Good! Or Not
How CBD Treats Anxiety

• Blocks FAAH enzyme from breaking down anandamide increasing its levels in the brain
• Partial agonist of Serotonin 5-HT1A receptor
  • Results in increased serotonin, dopamine
• Hippocampal neurogenesis
  • Stimulation of CB1/CB2 receptor sites upregulates endocannabinoid signaling leading to growth
CBD and Anxiety Disorder

10 pts with generalized social anxiety disorder

CBD significantly decreased anxiety (p<0.001)

Effected activity in limbic/paralimbic areas
Cannabidiol in Anxiety and Sleep: A Large Case Series

Main Outcome Measures: Sleep and anxiety scores, using validated instruments, at baseline and after CBD treatment.

Results: The final sample consisted of 72 adults presenting with primary concerns of anxiety (n = 47) or poor sleep (n = 25). Anxiety scores decreased within the first month in 57 patients (79.2%) and remained decreased during the study duration. Sleep scores improved within the first month in 48 patients (66.7%) but fluctuated over time. In this chart review, CBD was well tolerated in all but 3 patients.

Conclusion: Cannabidiol may hold benefit for anxiety-related disorders. Controlled clinical studies are needed.
PTSD: PCL-5 Scores
28% Decrease over 8 Weeks (n=11)
75% Reduction in PTSD Symptom Scores (n=80)

PTSD symptom reports of patients evaluated for the New Mexico Medical Cannabis Program.

Greer GR, Grob CS, Halberstadt AL.

Abstract

BACKGROUND: New Mexico was the first state to list post-traumatic stress disorder (PTSD) as a condition for the use of medical cannabis. There are no published studies, other than case reports, of the effects of cannabis on PTSD symptoms. The purpose of the study was to report and statistically analyze psychometric data on PTSD symptoms collected during 80 psychiatric evaluations of patients applying to the New Mexico Medical Cannabis Program from 2009 to 2011.

METHODS: The Clinician Administered Posttraumatic Scale for DSM-IV (CAPS) was administered retrospectively and symptom scores were then collected and compared in a retrospective chart review of the first 80 patients evaluated.

RESULTS: Greater than 75% reduction in CAPS symptom scores were reported when patients were using cannabis compared to when they were not.

CONCLUSIONS: Cannabis is associated with reductions in PTSD symptoms in some patients, and prospective, placebo-controlled study is needed to determine efficacy of cannabis and its constituents in treating PTSD.
My Clinical Experience with CBD

• Clinical practice focused on helping people recover from TBI/concussions
• Very effective for anxiety, depression
• Improves ability to focus
• Concentrated 15mg gelcaps once/twice a day and as needed throughout the day
• Raw CBD great for athletic recovery and inflammatory problems
Patient Feedback: 4.5yrs post-TBI

“I’m feeling really good overall. I feel like I’m able to move easier which has been the most noticeable change for me thus far. Most importantly, I started the CBD oil Saturday morning. I can’t begin to tell you how life changing this little pill has been for me. I am actually relaxed and not anxious. However, I’m so much more focused than I have been and get a lot done.”
Patient Feedback: Anxiety

“...introduced me to the benefits of CBD oil – those who know me know I am a skeptic and not easily convinced... My personal results have been truly life-changing – reduced anxiety, less aches on the tennis court, overall sense of calm – but most importantly, no side effects that pharmaceuticals cause.”
The story of Bobby

Case Report

Therapeutic use of omega-3 fatty acids in severe head trauma

Abstract

Traumatic brain injury (TBI) has long been recognized as the leading cause of traumatic death and disability. Tremendous advances in surgical and intensive care unit management of the primary injury, including maintaining adequate oxygenation, controlling intracranial pressure, and ensuring proper cerebral perfusion pressure, have resulted in reduced mortality. However, the secondary injury phase of TBI is a prolonged pathogenic process characterized by neuroinflammation, excitatory amino acids, free radicals, and ion was intentionally treated with substantial amounts of omega-3 fatty acids (n-3FA) to provide the nutritional foundation for the brain to begin the healing process following severe TBI.

In March 2010, a teenager sustained a severe TBI in a motor vehicle accident. After prolonged extrication, he was resuscitated at the scene and flown to a Level I Trauma Center. His Glasgow Coma Scale score was 3. Computerized tomography revealed panhemispheric right subdural and small temporal epidural hematomas and a 3-mm midline shift (Fig. 1). The patient underwent emergency craniotomy and intracranial pressure monitor placement. The patient was rated at Rancho Los Amigos Cognitive Scale Level I, and the attending neurosurgeon’s impression was that the injury was likely lethal.
Fish oil helped save our son

By Stephanie Smith, CNN

updated 1:40 PM EDT, Mon October 22, 2012

Bobby Ghassemi was just 17 years old when he was in a horrific car accident.
Update on Bobby

• Started on hemp-derived CBD oil June 2015
• Phone call two weeks later....
  • No longer depressed
  • Stopped taking SSRI’s
  • Anxiety levels completely vanished
  • Asked a girl for her phone number
  • Set goal to walk without assistance
• 10 months later, an email...
Dr. Lewis,

Thank you so much for giving me CBD oil. It drastically changed my life, I cannot begin to describe it with words. Thanks to CBD oil, I'm feeling much more comfortable in my own skin, I'm being more social, I'm making BIG noticeable changes. I'm doing stand-up comedy now, I have my own place, I got a raise at my job, and I'm feeling VERY optimistic about the future! A friend I made when I was doing improv comedy told me, and I've also been told repeatedly this, that I have a great personality and a great ZEST for life!!!

I can't wait to see what adventures up next in life

All the best,
Bobby Ghassemi aka DJ Sh8oon
Practical Notes on Using CBD

• Rule #1: low doses – start low and gradually ↑
• High doses may overwhelm CB1 receptors and ↑ spaciness and anxiety
• Very safe: no receptors in Respiratory & C-V nuclei
• Positive interaction with the Limbic system: stress, anxiety, fear, emotions
• Good quality CBD in measured doses is important
• Synergistic with The Omega-3 Protocol
Summary: Cannabis/CBD

- Cannabis has a long tradition in the healing arts.
- The Endocannabinoid system plays a central role in most biological systems.
- CBD is well tolerated and has a calming effect.
- Hemp CBD is a useful tool for a range of psychiatric disorders in the future including those as a result of TBI.