Learning Objectives

1. Discuss assessment protocols to determine level of endocannabinoid deficiencies of the endocrine system.
2. Discuss therapeutic strategies to address endocannabinoid deficiencies of the endocrine system.
3. Discuss patient care guidelines to implement cannabinoid therapy with standard of care pharmaceutical regimens pertaining to the endocrine system.
4. Discuss educational guidelines for patients to monitor clinical outcomes when implementing cannabinoid protocols for endocrine disorders.

The Endocannabinoid System and Cannabidiol (CBD) - Introduction

The endocannabinoid system (ECS) is a lipid-derived signaling system discovered within the past decade. Cannabinoids, which are homeostatic regulators, circulate throughout human and animal systems continuously, affecting all physiological processes. The endocannabinoid system is comprised of CB1 and CB2 receptors, which bind directly or indirectly to cannabinoids and phytocannabinoids. CB1 receptors are excitatory and are located in the central nervous system, lungs, liver, and kidney. CB2 receptors regulate immunological responses and are located in the immune and circulatory systems. Endogenous compounds, such as anandamide and arachidonylglycerol (2-AG), are made by mammals from lipids and bind directly to the CB1 and CB2 receptors, serving as neurotransmitters for cannabinoids.

Cannabidiol (CBD) is a non-psychotropic cannabinoid naturally occurring in human and animal species, derived from the industrial hemp plant. While CBD does not bind directly with receptors, it does affect stress genes, such as Soat2 and Cyp27a1, which control sterol (i.e., cholesterol) metabolism. CBD increases the amount of anandamide and other vital lipids, thereby indirectly increasing the availability of circulating cannabinoids to bind with CB1 and CB2 receptors.

Research has shown that cannabidiol, in the form of CBD oil, has therapeutic benefits individually and adjunctively with other interventions. Cannabidiol (CBD) made from legal, industrial hemp contains less than .3% THC, rendering it non-psychoactive. CBD oil has antiemetic, anxiolytic, antitumoral, and immunologically inhibitory properties. Three categories differentiate the types of clinical endocannabinoid deficiency (CECD), which are associated with different disease processes and disorders: genetic, acquired, and idiopathic autoimmune. Many disorders have a combination of CECD origins, and supplementation with cannabidiol (CBD) requires ongoing assessment to facilitate optimal benefit for the individual.

The Human Endocannabinoid System

The human endocannabinoid system is responsible for memory networks in the brain, both excitatory and inhibitory, including the neurogenesis of hippocampal granule cells, which regulate the timing of the endocannabinoids in accordance with the brain’s needs, pain perception, mood, synaptic plasticity, motor learning, appetite and taste regulation, and metabolic function, which regulates the storage of energy and transport of cellular nutrition. Cannabinoid receptor binding sites are located in the forebrain areas associated with higher cognitive function, forebrain, midbrain, and hindbrain areas associated with movement control, and hindbrain areas associated with motor and sensory functions attributed to the autonomic nervous system. The endocannabinoid system affects the lipocytes and fat cells, collectively...
known as adipocytes, hepatocytes, in the gastrointestinal tract, musculoskeletal system, and endocrine system. The endogenous arachidonate-based lipids, anandamide and 2-arachidonoylglycerol (2-AG) are physiological ligands for the cannabinoid receptors. Cannabinoid receptors CB1 and CB2, two G-protein-coupled receptors, facilitate the responses of the endocannabinoid system in the body, which are critical to maintaining homeostasis. CB1 receptors are located in the central and peripheral nervous systems as well as the lungs, kidneys, and liver. CB2 receptors are predominantly expressed in the immune system and hematopoietic cells.

The direct effect of the endocannabinoid deficiency (CECD) correlates with multisystemic clinical outcomes in such conditions as hyperinsulinemia, osteoporosis, diabetes, dementia, cardiovascular disease, multiple sclerosis, and obesity. Three primary categories are herein defined to discuss endocannabinoid deficiency (CECD): genetic, acquired, and idiopathic autoimmune. Genetic endocannabinoid deficiency relates to hereditary acquisition of a disorder, acquired refers to an infectious or traumatic origination, and idiopathic autoimmune refers to etiologies for endocannabinoid deficiencies (CECD) which do not have direct associations.

Diseases and disorders are assigned to one or more of these categories because often secondary disorders arise with physiological changes associated with the primary diagnosis. For example, endocrine disease has been associated with endocannabinoid deficiency (CECD) and the disease is categorized as genetic, originating from a hereditary source. The presentation of primary multifocal leukoencephalopathy (PML), which affects the neurological system, supports adding the category of idiopathic autoimmune as well to the assessment. Because the endocannabinoid system facilitates communication and coordination between various cell types, deficiencies directly affect physiological homeostasis.

Cannabidiol (CBD), a non-psychotropic cannabinoid naturally occurring in human and animal species, occurs as a phytocannabinoid, CBD oil, which is derived from the industrial hemp plant. The restorative effects of cannabidiol (CBD oil), which increases anandamide and other lipid neurotransmitters, thereby restoring the endocannabinoid system, are of interest in the medical management of multiple disorders, including disorders of the endocrine system, which is directly affected by the immunological and neurological systems. Indeed, research supports that plant-derived cannabidiol (CBD) has neuroprotective and anti-inflammatory benefits.

**Cannabidiol (CBD)**

Cannabidiol (CBD) is a non-psychotropic and non-toxic compound that has been demonstrated to positively affect the human endocannabinoid system. Cannabidiol (CBD), derived from the hemp plant, demonstrates anti-inflammatory and immune-modulating properties. Cannabidiol (CBD) has a low affinity for CB1 and CB2 receptors in the human body, but acts as an indirect antagonist of their agonists. (Antagonists are defined as substances that stop or inhibit the effects of another substance on the cellular surface, producing the same effect as a substance which would normally bind to the receptor. Agonists are chemicals that bind to receptors and elicit a biological response.) Therefore, cannabidiol (CBD) may enhance the therapeutic effects of THC, possibly by increasing the density of the CB1 receptors. Cannabidiol (CBD) has been demonstrated to cross the blood-brain barrier and exert antioxidant, antimicrobial, and neuroprotective properties, rendering it valuable in the prevention and treatment of oxidative endocrine disorders and diseases.
Human Endocrine System
The endocrine system refers to the collection of glands of an organism that secrete hormones directly into the circulatory system to be carried towards a distant target organ. The major endocrine glands include the pineal gland, pituitary gland, pancreas, ovaries, testes, thyroid gland, parathyroid gland, hypothalamus, gastrointestinal tract and adrenal glands. The endocrine system is in contrast to the exocrine system, which secretes its hormones using ducts. The endocrine system is an information signal system like the nervous system, yet its effects and mechanism are classifiably different. The endocrine system’s effects are slow to initiate, and prolonged in their response, lasting from a few hours up to weeks. The nervous system sends information very quickly, and responses are generally short lived. In vertebrates, the hypothalamus is the neural control center for all endocrine systems. The field of study dealing with the endocrine system and its disorders is endocrinology, a branch of internal medicine.

Special features of endocrine glands are, in general, their ductless nature, their vascularity, and commonly the presence of intracellular vacuoles or granules that store their hormones. In contrast, exocrine glands, such as salivary glands, sweat glands, and glands within the gastrointestinal tract, tend to be much less vascular and have ducts or a hollow lumen.

In addition to the specialized endocrine organs mentioned above, many other organs that are part of other body systems, such as bone, kidney, liver, heart and gonads, have secondary endocrine functions. For example the kidney secretes endocrine hormones such as erythropoietin and renin. A number of glands that signal each other in sequence are usually referred to as an axis, for example, the hypothalamic-pituitary-adrenal axis.

As opposed to endocrine factors that travel considerably longer distances via the circulatory system, other signaling molecules, such as paracrine factors involved in paracrine signaling diffuse over a relatively short distance.

Cannabidiol (CBD) and Endocrine Disorders and Diseases: Diabetes
Diabetes is an endocrine disorder with a strong hereditary component, affecting children and adults throughout the lifespan. The development of insulin resistance and glucose dysregulation characterizes diabetes mellitus, affecting the cardiovascular, immunological, and neurological systems as well as the endocrine system. Clinical endocannabinoid deficiency (CECD), characterized as genetic and acquired, affects excitatory CB1 receptors and immune-responsive CB2 receptors in the endocrine system. Research supports the benefit of cannabidiol (CBD) in reducing insulin resistance and as a hypoglycemic agent. Preventatively in individuals at risk for diabetes mellitus, and as adjunctive therapy under physician supervision in management of serum glucose, cannabidiol is suggested to improve disease management and prevent secondary manifestations of the disease, such as diabetic neuropathy.

Hypothyroidism
Hypothyroidism is a disease which affects the thyroid glands ability to secrete associated hormones, leading to weight gain, fatigue, immune dysfunction, and internal temperature regulation dysfunction. Medical management includes hormonal supplementation, and cannabidiol (CBD) has been shown to improve symptoms of hypothyroidism as adjunctive therapy. CB1 receptors are directly affected in hypothyroidism, which is considered idiopathic autoimmune and genetic
in relation to clinical endocannabinoid deficiency (CECD). In individuals at risk for the development of hypothyroidism, preventative administration is warranted to improve the function and receptivity of CB1 receptors to anandamide, the lipid neurotransmitter which is increased by CBD oil.

**Thyroid cancer**
Malignant tumors of the thyroid affect hormonal function, rendering the individual with profound symptoms of fatigue and depression. Clinical endocannabinoid deficiency (CECD) in thyroid cancer affects CB2 receptors, reducing the ability of the immune system to eradicate malignancy. The anti-tumoral benefits of cannabidiol (CBD) are well documented and administration is suggested as adjunctive therapy in the management of thyroid cancer. In patients at risk for developing thyroid cancer associated with hypothyroidism, prophylactic use of cannabidiol may be considered to prevent thyroid dysfunction. Metastatic disease associated with cancer has been inhibited by the use of cannabidiol in human studies, suggesting beneficial use in diagnosed metastatic disease.

**Endocannabinoid Deficiency (CECD) Classification: Endocrine Disorders**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Origin of CECD</th>
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<tbody>
<tr>
<td>Diabetes</td>
<td>Genetic</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Genetic</td>
</tr>
<tr>
<td>Thyroid cancer</td>
<td>Idiopathic Autoimmune</td>
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**CEN Medical Cannabis Pharmacological Prescription and Coding System**

**Endocrine Disorder Application**
The CEN Medical Cannabis Pharmacological Prescription and Coding System (CEN/MCPPCS) provides language that enables the health care practitioner to communicate with the dispenser of medical cannabis. The first two letters of the system refer to the cannabis type: cannabis sativa, cannabis indica, or cannabis hybrida. The numerical value in percentage to the right of the colon refers to the recommended THC content in percentage, and the numerical value in sequence to the right of the THC percentage refers to the recommended CBD content.

(CEN/MCPPCS): Cannabis type (sativa, indica, hybrida; THC percentage or range/CBD percentage or range) or Hemp Cannabidiol (CBD)

**Example:** Cannabidiol (CBD oil) is recommended for the patient. The concentration of the CBD oil is 19.5% and the patient is to ingest 50 mg. of CBD oil four times each day every six hours, as adjunctive therapy in the treatment of thyroid cancer, (ICD-9: 193). The prescription would therefore read:

Nancy Hershel  
Date of Birth: 11-01-1979.  
Diagnosis: Thyroid cancer, ICD-9 code: 193  
CBD: 0.00%/ 19.5%. Take 50 mg. of CBD oil by mouth four times daily, every 6 hours. Use dropper as indicated.  
Eli Oster, M.D.
The patient would then be able to purchase the CBD oil online or at a dispensary, offering the prescription to the pharmacist or technician.

**Composition Assignments:**

1. Please suggest a plan of care based upon the following patient information. Discuss if CBD oil would be indicated with rationale and the type of endocannabinoid deficiency(s)(CECD) for the endocrine disease process.
   a. A 40-year-old African American female complains of fatigue, weight gain, and difficulty concentrating. Recent lab studies indicate hypothyroidism.

2. Please choose an article from the CEN library on an aspect of cannabidiol (CBD) and the reproductive system. Write a two-hundred-word critical analysis paper on this research article and determine the following in your paper:
   a. Author and affiliation
   b. Study population
   c. Purpose
   d. Outcome of the study
   e. Importance of the research
Bibliography


