

**Caring for the Endocannabinoid System**

**Today's Dietitian**  
 SPRING SYMPOSIUM  
 2020  
 #TDVIRTUALSYMPOSIUM

**PRESENTER**  
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**Disclosures**

Bonnie Johnson, MS, RDN:

- Editorial Board and Contributor to **CRx Magazine** (Great Valley Publishing)

Janice Newell Bissex, MS, RDN:

- Editorial Board and Contributor to **CRx Magazine** (Great Valley Publishing)
- Owner, Jannabis Wellness and Jannabis Wellness (hemp CBD products)

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**Getting Familiar with the ECS:**  
*Learning Objectives*

At the end of this session, participants will be able to:

1. Identify 2 receptors and 2 ligands of the endocannabinoid system (ECS).
2. Discuss the role of the endocannabinoid system in the etiology of migraine, fibromyalgia, irritable bowel syndrome, and other conditions.
3. Explain the role of cannabis and CBD in the regulation of the ECS.
4. Discuss the different methods of cannabis or CBD administration, and why some might be more effective than others based on potential drug interactions, condition, and lifestyle.

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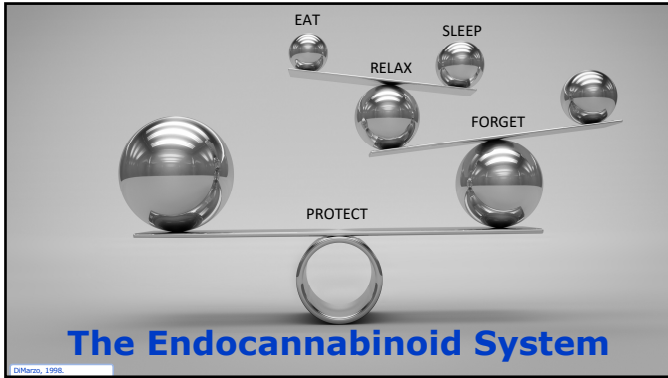
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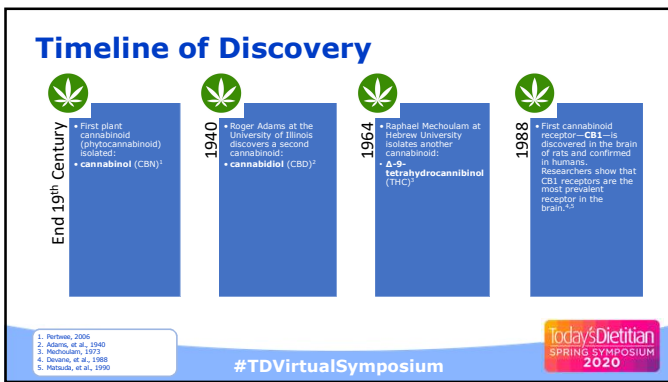
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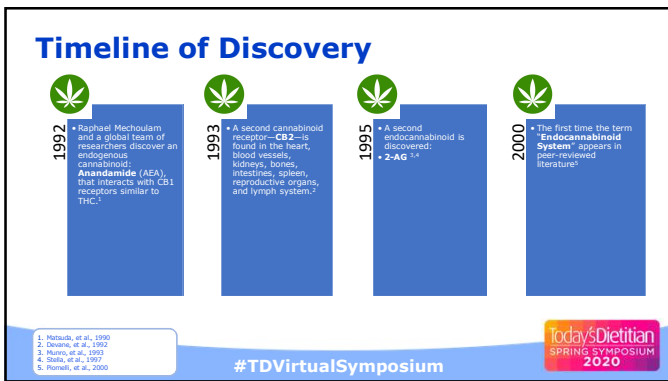
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## Timeline of Discovery



**2008**

- Endocannabinoid Deficiency proposed as underlying cause of Migraine, Fibromyalgia, Irritable Bowel Syndrome.<sup>1</sup>



**2017**

- The National Academies of Sciences, Engineering, Medicine publish book: *The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research.*<sup>2</sup>

1. Russo, 2008  
2. National Academies of Sciences, 2017  
Image Credit: VectorStock 1783376

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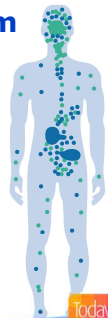
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## The Endocannabinoid System (ECS)

- Receptors
  - CB1
  - CB2
- Messengers
  - Anandamide (AEA)
  - 2-AG
- Enzymes
  - FAAH
  - MAGL



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## Endocannabinoid Receptors



- G Protein-Coupled Receptors (GPCR)
  - The "inbox" for messages sent between cells.
- Cannabinoid receptor 1 (CB1)
  - The most abundant G protein-coupled receptor (GPCR) expressed in the brain.
  - Also found in the peripheral nervous system, fat cells, liver & musculoskeletal tissues<sup>1</sup>
- Cannabinoid receptor 2 (CB2)
  - A G protein-coupled receptor primarily located on immune cells
  - Also found on the spleen, tonsils, and thymus glands
  - Are found localized on monocytes, macrophages, B-cells and T-cells<sup>2</sup>
  - CB2 receptors are also found in the peripheral nervous system, GI tract, and central nervous system.<sup>3</sup>
- GPCR are an important drug target.<sup>4</sup>

1. Combl, et al., 1997  
2. Ohnishi, 2011  
3. Lapin, et al., 2010

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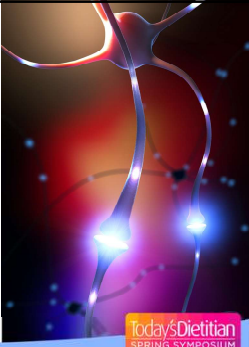

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## Endocannabinoids<sup>1</sup>

- Messengers:
  - The endocannabinoids (also called ECS ligands) are the messengers that connect with receptors and start biochemical cascades to maintain homeostasis.
- Anandamide
  - also known as N-arachidonyl ethanolamide
  - AEA
- 2-AG
  - also known as sn-2-arachidonoylglycerol
- AEA and 2-AG are released from phospholipids embedded in cell membranes and released **on-demand** or only when they are needed.
  - AEA and 2-AG cannot be packaged and stored for later use unlike other biological messengers.

1. DiMarzio, 1998

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## Endocannabinoid Enzymes

- Enzymes that breakdown the two main cannabinoids are embedded in the cell membranes
- Fatty Acid Amide Hydrolase (FAAH)
  - Breaks down anandamide (AEA)<sup>1</sup>
- Monoacylglycerol Lipase (MAGL)
  - Breaksdown 2-AG<sup>2</sup>
- Because endocannabinoids function in homeostatic fashion, they are **broken down** as soon as they deliver their messages to the receptors

1. Bonner, et al., 2002  
2. Zorr, et al., 2002

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## ECS Deficiency Syndrome<sup>1</sup>

- All humans have a personal "endocannabinoid tone":
  - Production of the endocannabinoids AEA and 2AG
  - Metabolism of endocannabinoids by FAAH and MAGL
  - The number and sensitivity of cannabinoid receptors CB1 and CB2
- ECS tone can be genetic or affected by external factors
- When ECS tone becomes deficient, it can produce symptoms like:
  - Hypersensitivity to pain
    - Associated with symptoms of migraine (photo and phonophobia)
  - Reduced threshold for pain
    - Associated with chronic pain in fibromyalgia
  - Chronic inflammation
    - Associated with changes in GI tract anatomy and secretions

1. Russo EB, 2016

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## Three Ways to Regulate the ECS



- Increase ECS messenger biosynthesis (↑ AEA and 2-AG)
  - Short term steroid use may ↑ AEA in the brain.<sup>1</sup>
  - Exercise may ↑ AEA and 2-AG in short term.<sup>1</sup>
  - Arachidonic Acid supplements may ↑ synthesis of AEA.<sup>2</sup>
  - Obesity may ↑ AEA and 2-AG.<sup>2</sup>
- Decrease ECS metabolic enzyme activity (inhibit FAAH and MAGL)
  - NSAIDS + Acetaminophen may block FAAH which stops the breakdown of AEA which may influence pain perception.<sup>3,4</sup>
- Increase/decrease number of and/or sensitivity of cannabinoid receptors
  - Probiotics/prebiotics may ↑ CB1 and CB2 receptors and have been shown to reduce pain behavior in mice.<sup>5</sup>
    - L.acidophilus, Bifidobateriam and oligofructoses
  - Weight loss by calorie restriction may ↓ CB1 receptors in the brain.<sup>2</sup>
  - Long term and binge drinking (alcohol) likely ↓ CB1 receptors.<sup>6</sup>
  - Long term use of steroids may ↓ CB1 receptors in the brain.<sup>1</sup>

McPartland, et al., 2014  
 Auerin, et al., 2012  
 Fowke, et al., 1999  
 Horgan, et al., 2005  
 Rousseau, et al., 2007  
 Gonzalez et al., 2002

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## CBD & Cannabis Impact on ECS

Janice N. Bissex, MS, RDN



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## CBD & Cannabis: *Impact on ECS*



- CBD does not bind to receptors<sup>1</sup>
  - ↓ FAAH ↑ anandamide (AEA) ↑ CB1 activation
- THC activates CB1 and CB2 receptors
- THC binds tighter to CB1 receptors and has longer half life than AEA
- Pharmaceutical isolates do not have same impact. Whole plant = entourage/ensemble effect<sup>2</sup>

1. Salibaery 2018  
 2. Russo 2011

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### Cannabidiol (CBD)



- Pain relief
- Anti-inflammatory<sup>1</sup>
- Anti-bacterial<sup>1</sup>
- Anti-seizure<sup>2</sup>
- Anti-nausea
- Anti-depressant
- Anti-anxiety
- Neuroprotective<sup>3,4</sup>
- Bone health<sup>5,6</sup>

1. Espinosa, 2013  
2. Guadaño 2016  
3. National Academies of Sciences 2017  
4. NIH 2003  
5. Rosen 2015  
6. Siva 2009

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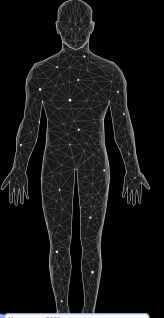
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### How Cannabis & CBD Relieve Pain



- NAS 2017 report- conclusive evidence for ↓ pain
- Inhibits release of pro-inflammatory molecules
- Cannabis activates CB1 & CB2 receptors to ↓ pain signals
- CBD
  - Inhibits FAAH↑AEA→CB1 activation
  - ↓ transmission of pain signals
  - Activates serotonin receptors to ↓ pain perception

Marcavalle 2006

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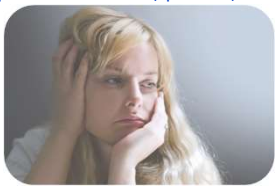
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### CBD & Mental Health

- CBD reduces fear and drug memory processes in PTSD, phobias, addiction<sup>1</sup>
- Anxiety and depression<sup>2</sup>
  - ↑AEA
  - ↑serotonin
  - ↑GABA inhibitory neurotransmitter
  - ↓cortisol stress hormone
- Synergy with SSRIs



Lee, 2017  
Pretzsch, 2019

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## Cannabis vs Hemp



- Both from cannabis sativa L plant
- Hemp contains < 0.3% THC
- Cannabis contains up to 30% THC
- Cannabis federally illegal
- 33 states + DC allow medical and 11 states + allow medical and adult "recreational" use
- Hemp production legalized in 2018 but no FDA decision on CBD Generally Recognized as Safe (GRAS) status

fda.gov, 2020

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## Modes of Administration

- Sublingual tinctures
- Topical Creams
- Transdermal Patches
- Capsules/softgels
- Inhalation
- Edibles
- Suppositories
- Raw juice



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## Onset and Duration

Format/Method	Onset (minutes)	Duration (hours)
Ingested (capsules, edibles, drinks)	30-120	6-12
Inhaled (vapor or smoke)	1-3	1-3
Sublingual (drops, lozenges, spray)	15-30	2-4
Topical (salves, roll-ons, creams)	30-60	2-4
Transdermal (patch, gels)	15-30	6-12
Suppositories	15-30	6-8

Montemayor, M. Holistic Cannabis Academy, 2016

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### Dosing: Start Low and Go Slow!



- Therapeutic ranges of CBD and THC are large
- Individual personalization – keep journal
- May take 2 weeks to see effect
- THC tolerance – take a break!

Montenayor, M. Holistic Cannabis Academy 2016

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### Possible Drug Interactions



- May ↑ effect of some drugs
- Be cautious taking meds contraindicated with grapefruit when ingesting cannabis<sup>1</sup> - CYP450 enzyme system
- Synergy with some meds (SSRIs)
- Tricyclics: possible enhanced sedation, hypotension, tachycardia<sup>2</sup>
- Alcohol - THC may increase central nervous system (CNS) impairment<sup>3</sup>
- Check with cannabis practitioner

1. Griesson 2018  
2. Devitt-Lee 2015  
3. Kozmin 2017

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### Potential Side Effects of CBD

- Vivid dreams
- Fatigue
- Low blood pressure
- Dry mouth

2018 WHO Report on CBD:

*"Across a number of controlled and open label trials of the potential therapeutic effects of CBD, it is generally well-tolerated with a good safety profile."*



WHO. Cannabidiol (CBD): Critical Review Report 2018

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# Potential Downside of Cannabis



- Short term effects<sup>1</sup>
- Increased heart rate, distorted perception, loss of coordination, issues with memory and learning
- Cannabis Use Disorder (CUD)<sup>2</sup>
- 8 to 12% of heavy users
  - More common with early age onset of use
  - Impairment affecting behavior, health, relationships
  - 4.2M in U.S. w CUD & 14.4M w alcohol use disorder<sup>3</sup>
  - Cannabinoid hyperemesis syndrome
- Long term effect on cognition? Twin study<sup>4</sup>
- Psychotic disorders<sup>5,6,7</sup>
  - Adolescent/heavy use may be risk for earlier onset
  - Correlation = causation?

1. MIDA 2019  
2. Droney 2018  
3. SAMHSA.gov  
4. Chen 2016  
5. Conry, Child Mind Institute  
6. Singh 2019  
7. Di Forti 2019

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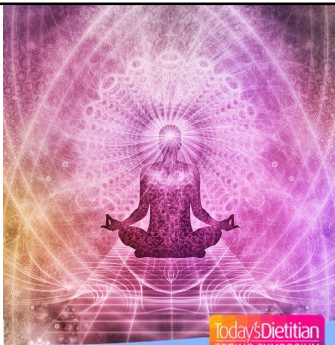
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# Conclusions

- The ECS is relatively new to most healthcare professionals and can contribute to homeostasis in the body
- We can influence our ECS with lifestyle modifications, food, and plant-derived medicines like cannabis and CBD
- It's important to work with knowledgeable professionals when using plants as medicine



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# Questions?

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