Cannabinoids and Diabetes Management

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Faculty/Presenter Disclosure

I am a nurse practitioner in primary care. I am currently employed fulltime as a consultant with Apollo Applied Research, where I assess patients via telemedicine.

Apollo Applied Research is a partner clinic of Canopy Growth Corporation (CGC), the parent company for Spectrum Cannabis – however, I do not refer patients to Spectrum Cannabis exclusively.

I am a member of the speaker panel for CGC and frequently give educational presentations on their behalf, for which I receive financial compensation.

I have no other conflicts to disclose
# Objectives

<table>
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<th>History of Medical Cannabis in Canada</th>
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<td>Why patients access medical cannabis</td>
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<td>Brief review of the endocannabinoid system (ECS) and the major cannabinoids</td>
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<td>Hemp CBD – a cautionary tale</td>
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“Researchers from the Hebrew University of Jerusalem have discovered that CBD receptors are highly prevalent in the pancreas (where insulin is made). Preliminary studies have suggested that feeding these receptors with high doses of CBD oil may stimulate insulin production.”

Source: Diabetes UK, 2015 (unpublished study)

“Of the participants in our study sample, 579 were current marijuana users and 1975 were past users. In multivariable adjusted models, current marijuana use was associated with 16% lower fasting insulin levels and 17% lower HOMA-IR (insulin resistance). We found significant associations between marijuana use and smaller waist circumferences.”

Source: AJM, 2013
Medical Cannabis – a Timeline

- 2014: Marijuana for Medical Purposes Regulations (MMPR) allowed sale of dried product through Licensed Producers through mail.
- Legalization of recreational use in Oct 2018 may affect medicinal use - the need for a separate medical stream remains a "hot topic."

Medical Cannabis Registrations

The latest data suggest that by the end of Sept 2018, almost 350K patients had registered with Health Canada through ACMPR, up from fewer than 100 in 2001.

Source: Health Canada, 2019
The new “Grey Market”

Older adults (50+) represent the fastest growing demographic of medical cannabis users.

Usage estimates range from 7% to more than 33% (depends on the country).

A 2013 US study revealed that more than 90 percent of medical marijuana patients (of around 7,500 surveyed) say that medical marijuana has helped treat their conditions. Seniors were the largest age group in the study (more than 2,300 respondents).

The National Counsel on Aging (US) supports the use of medical cannabis in older adults (aging.com).
Medical vs Recreational

**MEDICAL**
- Older, less experienced users (40+)
- Prefer high CBD/low THC
- Prefer oils/caps vs smoked
- Interested in topicals, suppositories, SL sprays
- Use cannabis as an alternative to Rx opioids or mood stabilizers
- May have medical conditions which require guidance regarding choices of strains

**RECREATIONAL**
- Young users
- High THC (rosins, shatter, BHO, hash oil)
- In search of euphoric effects
- Tend to be resistant to non-inhaled routes of use
**Patient Diagnoses**

1. Mood > 85%
2. Pain > 65%
3. Sleep > 30%

(many co-morbid conditions)

Wan et al, J Pain Manage 2017;10(4)

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**Table 4. Patient medical conditions**

<table>
<thead>
<tr>
<th>Medical Condition</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety Disorder</td>
<td>732 (31.7%)</td>
</tr>
<tr>
<td>Depression</td>
<td>729 (31.4%)</td>
</tr>
<tr>
<td>Pain</td>
<td>681 (29.5%)</td>
</tr>
<tr>
<td>Sleep disorder</td>
<td>589 (25.5%)</td>
</tr>
<tr>
<td>PTSD</td>
<td>502 (21.8%)</td>
</tr>
<tr>
<td>Migraines</td>
<td>336 (14.6%)</td>
</tr>
<tr>
<td>Degenerative Disk Disease</td>
<td>278 (12.1%)</td>
</tr>
<tr>
<td>Irritable bowel syndrome</td>
<td>247 (10.7%)</td>
</tr>
<tr>
<td>Fibromyalgia</td>
<td>214 (9.3%)</td>
</tr>
<tr>
<td>Spinal Disk Herniation</td>
<td>194 (8.4%)</td>
</tr>
<tr>
<td>ADHD</td>
<td>169 (7.3%)</td>
</tr>
<tr>
<td>Cancer</td>
<td>142 (6.2%)</td>
</tr>
<tr>
<td>Restless Leg Syndrome</td>
<td>137 (5.9%)</td>
</tr>
<tr>
<td>Asthma</td>
<td>128 (5.5%)</td>
</tr>
<tr>
<td>GERD</td>
<td>120 (5.2%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>116 (5.0%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>96 (4.2%)</td>
</tr>
<tr>
<td>Obsessive Compulsive Disorder</td>
<td>74 (3.2%)</td>
</tr>
<tr>
<td>Bipolar</td>
<td>71 (3.1%)</td>
</tr>
<tr>
<td>Diverticulitis</td>
<td>50 (2.2%)</td>
</tr>
<tr>
<td>Total Responses</td>
<td>2307</td>
</tr>
</tbody>
</table>

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**Green and Silver Report (October, 2018)**

Primary Conditions:

1. Back pain (67%)
2. Anxiety (63%)
3. Arthritis (58%)
Why patient request medical cannabis

1. They do not feel that their current medication is working well enough
2. They are experiencing side effects from their current medication and wish to discontinue it
3. They have been recommended a specific medication (ex. opioid for pain) which they do not wish to take (ex. due to the risk of addiction)
4. A friend told them cannabis could help them manage their condition and “it’s safer”
5. They are currently self-medicating using cannabis
6. They have complex health issues and wish to have a formal medical assessment and recommendations for which products to take (and how)
7. They have read that high dose cannabis may help treat their condition (ex. cancer)

Cannabis Use - A Cautionary Tale

- **Unstable heart disease** (chest pain, recent history of heart attack, poorly controlled atrial fibrillation, heart failure)
- **History of stroke** (CVA) or “mini” stroke (TIA)
- **Serious lung or liver disease** (asthma, COPD, cirrhosis, chronic Hep C)
- **History of schizophrenia, bipolar disorder or psychosis**
- **History of drug or alcohol abuse or dependency**
- **Currently taking high doses of opioids, sedatives or benzodiazepines** (ex. Ativan)
- **Because cannabis crosses into the placenta and is excreted in breast milk, women who are pregnant or breastfeeding should not use cannabis.**
Cannabinoids and the Endocannabinoid System

The Human Endocannabinoid System

The endocannabinoid system (ECS) consists of cannabinoid receptors, endocannabinoids, and their metabolic enzymes. Two major cannabinoid receptors, CB1 and CB2, two major endocannabinoids, anandamide (AEA) and 2-arachidonoyl glycerol (2-AG), have been identified. Humans, endocannabinoids and plant cannabinoids, such as THC and CBD, bind to cannabinoid receptors with great specificity, much like a lock and key. Activation of the cannabinoid receptors leads to the release of neurotransmitters. The ECS plays a key role in homeostasis and regulates many physiological processes such as inflammation and pain perception, immunity, appetite and metabolism.

Receptors
CB1 receptors are mainly located in the brain and central nervous systems and are also found in other tissues.

Ligands
THC and CBD are the main ligands for CB1 and CB2 receptors.

CB1 receptor

CB2 receptor

THC

CBD

Presynaptic (sending neuron)

Postsynaptic (receiving neuron)

MedReleaf: The Medical Grade Standard

All bind to the CB1 receptor with greater affinity than CBD; whereas, CB1 and CB2 bind to the CB1 receptor with equal affinity. THC binds the CB1 receptors with greater affinity than the CB2 receptors and has been suggested that binding affinity of THC to CB1, CBD has been proposed that binding affinity of CBD is similar to CB1.
Evidence suggests a role for the Endocannabinoid System in:

- Immune function
- Inflammation
- Appetite
- Metabolism and energy homeostasis (blood sugars)
- CV function
- Digestion
- Bone development and bone density
- Pain (including neuropathy)
- Reproduction
- Psychiatric conditions
- Psychomotor behaviour
- Memory
- Sleep/wake cycles
- Regulation of stress and emotional state
- Learning

Role of the Endocannabinoid System (ECS) in DM

(Horvath et al, 2012)

TYPE 1: Lack of insulin due to autoimmune destruction of the islet cells
- CB1 and CB2 receptors are both expressed in islet cells (their role is unclear)

TYPE 2: Insulin resistance (obesity is the main risk factor for development)
- Dysregulation of the peripheral ECS is linked to the development of obesity (DiMarzo, 2008)
- Development of insulin resistance linked to CB1 receptor activity
- Rimonabant (RIO) is a peripheral CB1 receptor antagonist
- Patients with Type II DM show higher serum levels of AEA and 2-AG than non-diabetics
- Suggests a role for ECS in DM
- Exact mechanisms unclear
What Is in Cannabis?

C. sativa and C. indica
Most varieties are hybrids

Isolated pure compounds
More than 500 chemical compounds

Non-cannabinoids:
Terpenes & Flavonoids

Phytocannabinoids
More than 120 have been identified

Psychoactive/euphoric
• Δ9-tetrahydrocannabinol (THC)
• Δ8-THC
• Cannabinol (weak)

Psychoactive but non-euphoric
• Cannabidiol (CBD)
• THCV

To be determined...
• More than 60
• other compounds

ENTOURAGE EFFECT


Cannabis: Two Main Active Compounds

1. Responsible for many of the pharmacological effects of cannabis, including its psychoactive effect or “high”

2. Varieties with high concentrations of THC can cause anxiety, disorientation, and intoxication in some patients.

Interacts with cannabinoid receptors (mostly CB1) to induce:

- Analgesia (low dose)
- Antispasmodic activity
- Reduction of chemotherapy-induced nausea and vomiting
- Appetite stimulation
- Decreased intestinal motility

THC (Delta-9-tetrahydrocannabinol)
Cannabis: Two Main Active Compounds

1. Indirect effects on CB1 and CB2 (i.e. does NOT bind)
2. Affects the activity of a significant number of other targets including ion channels, receptors, and enzymes

Research has indicated CBD has the following effects:
- Anti-inflammatory
- Analgesic
- Antiemetic
- Antipsychotic
- Anxiolytic
- Anti-convulsant

Entourage Effect

Refers to the combined effect of the cannabinoids, terpenes, and other active ingredients work together to produce an effect that is greater than the sum of their parts

A 1981 study found that whole plant extracts produced 330% more activity than THC alone. The researchers hypothesized that cannabis contains “synergist” and “inhibitor” compounds (now known to be cannabinoids and terpenes) – “plant-based medicine”

CBD has a well-documented synergy with THC, reducing its negative effects (ex. paranoia) and amplifying its benefits (lower doses required)
Hemp CBD vs Cannabis CBD

CBD IS CBD....EXCEPT....

Hemp CBD vs Cannabis CBD

• Hemp is mainly grown for industrial purposes (growing conditions not regulated)
• Hemp = 3-5% CBD, require a large amount of plant to produce a small amount of hemp CBD oil (increased risk of contaminants)
• CBD oil created by licensed producers = 18-20% CBD (or higher)
• Hemp CBD oil is extracted from seeds, has little medicinal value
• Cannabis CBD oil is extracted from flowers, leaves, and the stalk of the plant
• By law, hemp oil can't contain more than 0.3% THC (0.3%) or zero % CBD and can only being used for non-medicinal purposes
How Patients use Medical Cannabis

Modes of Administration

<table>
<thead>
<tr>
<th></th>
<th>INHALED</th>
<th>INGESTED</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ONSET</strong></td>
<td>5-10 minutes</td>
<td>1-3 hours</td>
</tr>
<tr>
<td><strong>DURATION</strong></td>
<td>2-4 hours</td>
<td>6-8 hours</td>
</tr>
<tr>
<td><strong>STARTING DOSE</strong></td>
<td>1/2 teaspoon (0.1 g) of dried flowers</td>
<td>2.5 mg of THC and equal amount CBD</td>
</tr>
<tr>
<td><strong>HOW IT’S ABSORBED</strong></td>
<td>through the lungs directly into the bloodstream</td>
<td>from the GI tract, metabolized in liver before entering bloodstream</td>
</tr>
</tbody>
</table>
Inhalation (smoking, vaping) vs oral (oils, softgels/capsules)

Cannabis Oils & Capsules

- Taken by mouth
- Variable concentrations of THC and CBD
- 50% of THC content is metabolized to
- 11-hydroxy THC (4x more potent!)
- Onset of effect = 90 min
- Peak: 2-6hrs
- Duration of effect = 4-12 hrs
Typical Cannabis Regime for Chronic Pain
(Product Authorization: 1gm/day)

**CBD**
- Starting dose: 5mg OD
  (Spectrum Yellow oil = 0.4mL)
- May increase dose to BID-TID PRN
- No max dose per se but if no relief at doses > 30mg per dose then reconsider regime

**THC:CBD**
- Dosing based on THC content
- Starting dose: 1.25mg-2.5mg HS (Spectrum Blue oil = ~0.1-0.2 mL)
- Typical dose 0.3-0.4mL (3-4mg THC, 4.5-6mg CBD)
- Typical THC dose to experience euphoria = 10mg

Source: MacCallum and Russo, 2018

Typical consumption:
1-3gm/day

<table>
<thead>
<tr>
<th>Side-effect</th>
<th>Most common</th>
<th>Common</th>
<th>Rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drowsiness/Fatigue</td>
<td>✔</td>
<td>✔</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>✔</td>
<td>✔</td>
<td></td>
</tr>
<tr>
<td>Dry mouth</td>
<td>✔</td>
<td>✔</td>
<td></td>
</tr>
<tr>
<td>Cough, phlegm, bronchitis</td>
<td>✔</td>
<td>✔</td>
<td></td>
</tr>
<tr>
<td>(smoking only)</td>
<td>✔</td>
<td>✔</td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>✔</td>
<td>✔</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>✔</td>
<td>✔</td>
<td></td>
</tr>
<tr>
<td>Cognitive effects</td>
<td>✔</td>
<td>✔</td>
<td></td>
</tr>
<tr>
<td>Euphoria</td>
<td>✔</td>
<td>✔</td>
<td></td>
</tr>
<tr>
<td>Blurred vision</td>
<td>✔</td>
<td>✔</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>✔</td>
<td>✔</td>
<td></td>
</tr>
<tr>
<td>Orthostatic hypotension</td>
<td>✔</td>
<td>✔</td>
<td></td>
</tr>
<tr>
<td>Toxic psychosis/paranoia</td>
<td>✔</td>
<td>✔</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>✔</td>
<td>✔</td>
<td></td>
</tr>
<tr>
<td>Ataxia/dyscoordination</td>
<td>✔</td>
<td>✔</td>
<td></td>
</tr>
</tbody>
</table>
Possible Medication Interactions (CYP450)

- Opioids (ex. morphine, hydromorphone, codeine)
- Benzodiazepines (ex. lorazepam, clonazepam)
- Hypnotics (ex. zopiclone, sublinox)
- SSRIs (especially fluoxetine – Prozac)
- Warfarin (Coumadin) – newer blood thinners are safe (Xarelto, Eliquis)
- NSAIDs (ex. Celebrex, Diclofenac)
- Azole antibiotics
- Statins (atorvastatin, rosuvastatin)
- St. John’s Wort, 5-HTP
- Clobazam (if taken with high dose CBD)
- Valproic acid medications (ex. Divalproex) - can increase liver enzymes three-fold – monitor with concomitant use
- Azole antibiotics

Medical Cannabis and Diabetes Mellitus (DM)
Cannabis users exhibit 16% lower levels of fasting insulin and 17% lower insulin resistance than subjects who do not use cannabis (Penner, 2013)

The Endocannabinoid System and Plant-Derived Cannabinoids in Diabetes and Diabetic Complications (Horvath, et al. 2012)

- Oxidative stress and inflammation play critical roles in the development of diabetes and its complications
- The endocannabinoid system is a lipid-based signaling system which may significantly influence reactive oxygen species production, inflammation and subsequent tissue injury
- Both micro and macrovascular complications of diabetes are related to damage to the vascular wall (process is thought to be mediated by reactive oxygen and nitrogen species)
- Primary mechanism of Type II DM relates to the development of insulin resistance
  - Obesity is a key factor
  - Dysregulation of the ECS may contribute to excessive visceral fat accumulation and reduced adiponectin release from this tissue (DiMarzo, 2008)
Phytocannabinoids and DM

**THC**

*Excellent immunosuppressive activity*
- CB1 receptors play a key role in vascular smooth muscle proliferation (underlying patho in atherosclerosis)
- THC binds to CB1 receptors to mediate this effect
- THC use preserves pancreatic insulin content and lowers BG levels in patients with DM1 (Penner, 2013)
- Interaction with CB1 receptors has shown to increase metabolism and promote weight loss.
- Psychotropic effects limit its usefulness

**CBD**

*Similar immunosupressive effects without euphoria*
- Reduced the incidence of type 1 DM in non-obese mice (Weiss, et al, 2006, 2008)
- Emerging interest in THCV (∆9-tetrahydrocannabivarin) as an anti-inflammatory agent in DMII (also lacks psychotropic effects)
- A 2016 study found that THCV and CBD decreased blood glucose levels and increased insulin production in people with type 2 diabetes, indicating a “new therapeutic agent for glycemic control” (Jadoon et.al, 2016)
- CBD can help to suppress appetite and help individuals to re-balance the endocannabinoid system by increasing the fat breakdown, increase the mitochondria activities and promote metabolism, and decrease fat storage

Diabetic Complications and Cannabis

**CARDIOVASCULAR**
- Role of ECS in the regulation of vascular inflammation and oxidative stress is well established
- THC treatment reduces the development of atherosclerotic plaques through activation of CB2 receptors (Steffens, et al, 2005)
- CBD treatment reduces the inflammation associated with atherosclerosis (numerous studies)

**NEUROPATHY**
- 60-70% incidence
- Very difficult to treat effectively
- Neuropathic pain is one of three conditions with high grade evidence to support treatment with cannabis (Health Canada, 2018)
- “Balanced” products with both THC and CBD appear to be most effective (Iskedjian, et al., 2007)
**Co-Morbidities in Neuropathic Pain**

Percentage of patients with moderate-to-severe discomfort due to symptoms (n = 126)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor Appetite</td>
<td>18</td>
</tr>
<tr>
<td>Anxiety</td>
<td>27</td>
</tr>
<tr>
<td>Depression</td>
<td>33</td>
</tr>
<tr>
<td>Concentration Difficulties</td>
<td>36</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>39</td>
</tr>
<tr>
<td>Lack of Energy</td>
<td>55</td>
</tr>
<tr>
<td>Difficulty Sleeping</td>
<td>60</td>
</tr>
</tbody>
</table>


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**Diabetic Complications and Cannabis**

**NEPHROPATHY**

- Diabetes is a leading cause of renal failure, accounting for 45-50% of new cases annually
- Hyperglycemia stimulates ROS generation, which ultimately leads (via diverse pathways) to mesangial expansion, thickening of the glomerular basement membrane, and glomerular sclerosis
- Both CB₁ and CB₂ receptors are expressed in the kidneys
- CB₁ receptor blockade and CB₁ receptor agonism may be possible therapeutic targets for the management of diabetic nephropathy (Ho et al., 2019)

**RETINOPATHY**

- Diabetes is the leading cause of new cases of blindness and preventable blindness among adults
- Vascular inflammation and endothelial cell death caused by oxidative and nitrative stress are characteristics of diabetic retinopathy.
- The ECS is present in the retina (AEA, 2-AG, metabolizing enzymes)
- CBD reduces oxidative stress, inflammation, cell death, and vascular hyperpermeability associated with diabetes.
Diabetes and Cannabis – Summary

1. It helps reduce the pain associated with Type I Diabetes
2. It shows promise for reversing early stage Type I Diabetes by preserving pancreatic cells.
3. It helps reduce insulin resistance
4. It helps regulate body fat, which also leads to reduced insulin resistance
5. It promotes the production of HDL cholesterol
6. It contains compounds found in its essential oils (terpenes) that help reduce the risk for diabetic neuropathy
7. Regular cannabis users have been shown to exhibit a 16-17% lowered risk for key diabetic indicators than their non-using counterparts, even if they take in more calories than they did prior to using this therapeutic supplement

Source: Strainprint, 2018

A Final Word

“The use of cannabis in patients with diabetes may help with stabilizing blood sugars, preventing nerve inflammation, lowering blood pressure over time, reducing atherosclerotic changes and improving circulation” (Horvath, et al., 2012)
Referring a Patient for Assessment

Patients may self refer:
1. Online: https://apollocannabis.ca/
2. Phone: 1-877-560-9195

Providers may refer via fax or by email request:
1. Fax: 1-647-729-4766
2. Email: homecare@apolloresearch.ca

Educational Resources for Professionals
1. Spectrum e-Learning
   https://spectrumcannabis.canopygrowthlearning.com
2. TMCI Global
   https://themedicalcannabisinstitute.org/
3. Advancing Practice Medical Cannabis Certificate
4. The Canadian Consortium for the Investigation of Cannabinoids
   http://www.ccic.net
5. Monthly webinars
   https://cannabiseducation.com/#webinar