Pharmacology of Medical Marijuana for Optometrists

1. Survey origins of cannabis for medical purposes.
2. Review the diverse strains, compounds, and varied responses on individuals with the use of cannabis.
3. Describe the pharmacology of the effects of cannabis on the human body with a focus on the pharmacodynamics of tetrahydrocannabinol (THC) and cannabidiol (CBD).
4. Explain and compare the various methods of cannabis administration
5. Review how the human body manages Cannabis in the body including absorption, distribution, metabolism and excretion (pharmacokinetics).
What is the Endocannabinoid system?
How Does the System Work and Its Role in Disease?
Where and What are Endocannabinoid Receptors?

What Does the Endocannabinoid System (ECS) Do and How Does it work?
This is Crucial for Homeostasis.
The body's predisposition to balance, monitor and maintain internal states
Homeostasis involves three key features:
1. A clear set point
2. The ability to detect deviations from this set point
3. Behavioral and physiological responses designed to return the body to the set point

What do Endocannabinoid Receptors do?
- They are REGULATORS
- Cannabinoids regulate every system in our bodies –
  - Nervous
  - Digestive
  - Reproductive
  - Immunological
  - Endocrine system.
- They are essential for MAINTAINING THE BODY’S HOMEOSTASIS
What is the Endocannabinoid system (ECS)?

The ECS itself is made up of three parts:

1. Endocannabinoids
2. Cannabinoid Receptors in the nervous system and around your body that endocannabinoids and cannabinoids bond with
3. Enzymes that help break down endocannabinoids and cannabinoids

Where are Cannabinoid Receptors?

Marijuana’s effects can be understood by knowing where in the brain it acts, or where in the brain cannabinoid receptors are found.

• In your brain and body, there are groups of cannabinoid receptors

• These cannabinoid receptors have an effect on mental and physical activities.

Where are Cannabinoid Receptors?

These cannabinoid receptors have an effect on mental and physical activities to regulate functions such as:

- Appetite
- Digestion
- Immune function
- Inflammation, including neuroinflammation
- Mood
- Sleep
- Motor control
- Temperature regulation
- Memory
- Pain
- Pleasure/reward
Where are Cannabinoid Receptors

**CB1 Receptors** are found in the central nervous system (in the brain they are found mostly in the hippocampus, cerebellum, hypothalamus, substantia nigra, mesolimbic dopamine pathways, cerebral cortex, brain stem) and in peripheral tissues.

**CB2 Receptors** are found in the periphery, mostly in lymphoid tissue but also in immune cells of the CNS.

What are the Neurotransmitters called for Cannabinoids that Trigger the Receptors?

- Group of >82 chemicals found in leaves and flowering tops of female cannabis plant
- Common cannabinoids are:
  - CBD (Cannabidiol)
  - CBN (Cannabinol)
  - Anandamide

<table>
<thead>
<tr>
<th>From CANNABIS plant: (exogenous)</th>
<th>In your body NATURAL (endogenous):</th>
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<tbody>
<tr>
<td>Δ9 – THC</td>
<td>2-arachidonylethanolamine (2–AE)</td>
</tr>
<tr>
<td>CBD (non-psychoactive)</td>
<td>Anandamide</td>
</tr>
<tr>
<td>CBN (psychoactive)</td>
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What are Endogenous and Exogenous cannabinoids?

The Brain's Natural Marijuana

What is Anandamide?

- **ANANDAMIDE** shares most but not all of the pharmacologic properties of THC.

- **ANANDAMIDE** (highest level) found in the HIPPOCAMPUS (anandamide) is an endogeneous agonist for the brain cannabinoid receptor.

  Effect in memory: Role in memory and induces forgetfulness.

- **ANANDAMIDE** – Chocolate contains small quantities of anandamide, an endogenous cannabinoid found in the brain.
What is Anandamide?
What about the Runner’s High?

Runners and Bicyclists

*80% more anandamide in their blood after exercising, with the greatest increase among the runners.

*Reported physical feelings similar to marijuana use, such as relaxation, regulated mood, and increased appetite.

What is the Pharmacological Mechanism of the CB receptors and Endocannabinoid (ECS) system?

Endocannabinoids (endocannabinoids):
Retrograde Signaling, a previously Unknown Form Of Communication between Neurons In The Brain!!

What is the Pharmacology of the CB receptors and Endocannabinoid system?

Endogenous cannabinoids (endocannabinoids)

Retrograde Signaling, 2. Endocannabinoids work backward, traveling from the postsynaptic cell to the presynaptic one as NEUROMODULATORY neurotransmitters involved in many of Physiological Processes
WHAT IS NEUROMODULATION?
Neuromodulation is technology that acts directly upon nerves. It is the alteration or modulation of nerve activity by delivering electrical or pharmaceutical agents directly to a target area.

Uses of Neuromodulation:
- Chronic pain relief (TENS units)
- Deep brain stimulation (DBS) treatment Parkinson's disease
- Vagus (Vagal) Nerve Stimulation
- Sacral nerve stimulation for pelvic disorders and incontinence
- Cardiac pacemaker

How Do Cannabinoids Work Differently From Other Neurotransmitters?
- The CB1 receptor are PRESYNAPTIC and NEUROMODULATE and can control what happens next when these cells are activated.
- Cannabinoids function like a “dimmer switch” for presynaptic neurons, limiting or increasing the amount of neurotransmitter released.
- This affects how messages are sent, received, and processed by the cell.
- Acts to Modulate and ALTER the release of other neurotransmitters eg. glutamate, GABA, Serotonin.

Cannabinoids – METHOD OF ACTION
1. This can cause a reduction in GABA release on the neuron. Inhibiting This GABA Inhibitor.
2. THC INCREASES the amount of DOPAMINE produced and the amount of pleasure felt.
3. The amount of DOPAMINE in the REWARD PATHWAY INCREASES dramatically.
Not Just a Weed - Pharmacology of Medical Marijuana
for Optometrists ©

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Normal Pre to Post Neuron Stimulation

THC and CBD Cannabinoids – METHOD OF ACTION

GABA “Slows Down”

Glutamate “Speeds Up”

Endocannabinoids stimulated receptors work backward, traveling from the postsynaptic cell to the presynaptic one as NEUROMODULATORY.

INHIBITING The INHIBITOR

DOWN REGULATION of cannabinoid receptors may cause THC to produce inhibition (BLOCK) rather than activate (EXCITE).

UP REGULATION is expected to enhance the ability to activate cannabinoid receptors.
UP AND DOWN REGULATION

When some disorders are present, it will trigger an UP REGULATION of cannabinoid receptors. This leads to NEUROMODULATION in these receptors to create symptom relief and/or inhibition of disease progression when activated by exogenously administered cannabinoids, e.g., 9THC and CBD.

Exogenous cannabinoids

9THC resembles Anandamide in its CB1 action.

Anandamide

THC

What are the Active Components of Medical Cannabis?
What are the Active Components of Medical Marijuana?

- ∆9-tetrahydrocannabinol (THC), the most psychologically active compound in cannabis.
- 483 different identifiable chemical constituents found in cannabis. Many are non-psychoactive components.
- More than 70 of these constituents—called cannabinoids—are unique to the Cannabis plant.

Why Tested Cannabis is Important!
There are over 100 known cannabinoids!
These are known to effect you the most!

D 9 THC
Tetrahydrocannabinol (THC) The most abundant and widely known cannabinoid in cannabis, THC is the cannabinoid responsible for the main psychoactive effects patients are familiar with. THC is believed to interact with parts of the brain normally controlled by the endogenous cannabinoid neurotransmitter anandamide.
THCV
Tetrahydrocannabivarin (THCV) is found in largest quantities in Cannabis varieties indigenous to central Africa. It is currently being researched as a treatment for metabolic disorders including diabetes, as well as serving as a potential appetite suppressant.

THCA
Tetrahydrocannabinolic Acid (THCA) THCA is the main constituent in raw cannabis. THCA holds much of the anti-inflammatory properties, as well as anti-proliferative (inhibiting the cell-growth in tumors/cancer cells,) as well as anti-spasmodic (suppresses muscle-spasms.)

CBDa
Cannabidiolic Acid (CBDa) CBDA, similar to THCA, is the main constituent in cannabis that has elevated CBD levels. THCA and CBDa hold most of the anti-inflammatory properties that cannabis has to offer.

CBDa also stimulates 5-HT1A.
CBN
Cannabinol (CBN) A mildly-psychoactive cannabinoid that comes about from the degradation of THC. (very little CBN in a fresh plant).
CBN potentiates the effects of THC. CBN may also cause drowsiness.

CBG
Cannabigerol (CBG) A non psychoactive cannabinoid.
CBG has antibacterial effects, anti-inflammatory, and anti-cancer properties.
CBG can alter the overall effects of Cannabis.

CBC
Cannabichromene (CBC) Research suggests that CBC includes: anti-inflammatory, analgesic, bone stimulant, and anti-cancer properties.
CBD
Cannabidiol (CBD) may hold the most promise for many serious conditions. CBD is a non-psychoactive cannabinoid that is believed to reduce the psychoactive effects of THC. Smokers of cannabis with a higher CBD/THC ratio are less likely to experience anxiety.

What is the Pharmacology of CBD?

How Does CBD Affect the Endocannabinoid System?

CBD General Pharmacology

Routes of administration and dosage
- Orally as either a capsule, or dissolved in an oil
- Administered through sublingual or intranasal routes.
- Oral doses have been from 100-800mg/day.
CBD Pharmacodynamics

- CBD does not appear to act directly at CB1 receptors
- CBD does not produce the behavioral effects associated with CB1 as THC does when CB1 is activated.
- CBD has effects which are generally opposite to those of THC
- CBD has no effect on heart rate or blood pressure under normal conditions, but in animal models of stress it reduces heart rate and blood pressure.

**CBD Pharmacodynamics**

CBD quite possibly interact with the **ENDOCANNABINOID SIGNALING SYSTEMS**:

Enhanced action of the natural internal Cannabinoid anandamide
(by blockade of anandamide reuptake inhibitor)

**CBD Pharmacodynamics**

CBD has been shown to adjust several **NON-ENOCANNABINOID SIGNALING SYSTEMS**:

- The 5-HT1A receptor is the most widespread of all the 5-HT receptors
- 5-HT1A receptor agonists are involved in neuromodulation.

**CBD Pharmacodynamics**

CBD has Enhanced activity at the 5-HT1a receptor.

Drugs that act 5-HT1A receptor agonists

- Anxiolytic, (Buspar)
- Antidepressant (Viibryd)
- Antipsychotic (Clozapine medications)
CBD Pharmacokinetics

- ORAL absorption of CBD from the gastrointestinal tract is erratic
- Aerosolized CBD has been higher bioavailability than oral administration.
- CBD is extensively metabolized in the liver and has been shown to inhibit CYP enzymes in liver (Drug Interaction Concern - Dosage dependent)
- CBD may preferentially accumulate in fatty tissues

What is the difference between CBD and THC?

- CBD (Cannabidiol) and THC work best together.
- CBD and THC interact to enhance each other’s therapeutic qualities.
- CBD enhances THC’s painkilling and anticancer properties
- CBD lessens THC’s psychoactivity.

What is the difference between CBD and THC?

- CBD can also take the edge off adverse effects caused by too much THC, such as anxiety and rapid heartbeat.
- CBD will lower the ceiling on the THC high while prolonging its duration. (“Relaxing but not intoxicating”)
- CBD broadens the range of conditions treatable with cannabis
- CBD and THC both stimulate neurogenesis, the creation of new brain cells, in adult mammals.
What is the difference between CBD and THC?

Key Misunderstanding
- CBD is Medical, THC is Recreational
- CBD is Most Effective Without THC
- Designed Pharmaceuticals Are Superior To ‘Crude’ Whole-Plant Medicinals
- THC Is The Bad Cannabinoid. CBD Is The Good Cannabinoid
- Psychoactivity Is Inherently An Undesirable Side Effect of THC
- CBD Is Legal In All 50 States
- CBD Is CBD—It Doesn’t Matter Where It Comes From

General Pharmacology

How is Cannabis metabolized in the body?

General Pharmacology

Routes of administration
- Inhalation
- Oral
- Other methods
  - tablets,
  - extracts,
  - tinctures
Human Metabolism of THC

- Pharmacokinetics-

Cannabis is a slurry of over 421 chemicals that each exert different effects on the body.

A bit of biochemistry

When cannabis is consumed, the liver breaks down the main psychoactive ingredient delta-9-THC into other molecules.

Metabolic pathway of THC

**Inhalation**

**Metabolic pathway of THC**

**Ingestion**

- delta-9-THC
- 11-OH-THC
- 11-COOH-THC
Bioavailability

How much of the consumed THC actually makes it into the bloodstream?

Cannabinoid Pharmacokinetics Are Different For Everyone!

One of the major sources of variability in cannabinoid response is Pharmacokinetics.

Bioavailability

What influences bioavailability?

1. Method of inhalation, e.g. vaping or smoking, smoking in a joint or pipe.
2. Infrequent or regular user.
   1. Technique matters, as depth of inhalation, puff duration and breath hold increase bioavailability.
   2. Regular users inhale more efficiently and therefore show a 50-70% higher bioavailability of delta-9-THC.
3. The bioavailability for inhaled delta-9-THC is between 10-35%.

Which produces stronger effects, inhalation or ingestion?

Problems with assuming inhalation is better?
1. Bioavailability fluctuating wildly between users.
2. THC blood levels are a terrible indicator for the magnitude of a psychological high or impairment.
   1. When cannabis is inhaled, blood tests show a 10:1 ratio between delta-9-THC and 11-OH-THC.
   2. When cannabis is ingested, however, blood tests show this same ratio being 1:1.
Which produces stronger effects, inhalation or ingestion?

1. 11-OH-THC passes the blood-brain-barrier more easily than delta-9-THC. Better High!
2. 11-OH-THC has shown to be three to SEVEN TIMES MORE POTENT THAN DELTA-9-THC, (7X better binding to the CB1 receptors in the brain.)

What are the different methods of cannabis administration and how do they compare?

What Is a Proper Dosage of Medical Marijuana, and How Can Patients Control Their Dose?
Administering Medical Marijuana: Methods of Taking Cannabis

- Inhalation
- Oral
- Other methods
  - tablets,
  - extracts,
  - tinctures

Inhalation
Vaporize vs Igniting their plant matter.

How Does The Vaporizer Work?
- CBD or THC is usually taken orally as a cannabis-based concentrate or extract.
- Smoking or vaporizing is favored over ingesting cannabinoids orally because of its quicker effect.

Edible Marijuana

- Medical cannabis can be heated and made into oils, butters, and tinctures.
- Many cannabis dispensary or clubs carry pre-made cookies, brownies, lollipops, and teas
- Eating or drinking marijuana’s active ingredient, THC, is certainly preferable to many patients than smoking it
Cannabis Tincture

Tinctures - designed to address the problems of rapid medicine delivery without smoking and maintaining consistent dosing.
- Alcohol Cannabis Tincture
- Glycerin Alcohol Free Cannabis Tincture

EDIBLE and Oral Cannabis

Raw Cannabis and Juicing
AVOIDS decarboxylation

Problem of Quantity?

Delta-9 THC is absent in the raw, fresh leaf.

*Active* ingredients in raw cannabis:
- Cannabinol (CBN)
- Cannabidiol (CBD)
- Cannabigerol (CBG)

What Is a Proper Dosage of Medical Marijuana, and How Can Patients Control Their Dose?
Minimum Effective Dose (MED)

Coming up with the right minimum effective dose (MED) is a matter of trial and error. Bioavailability fluctuates wildly across individuals and gender. The enzymes in the liver of a man and a woman work differently (Age, Gender).

How Much Does a Patient need or Eat?

A general rule is,
1. Cut the edible product into four pieces and eat one piece to start.
2. Wait at least one hour.
   If you feel the effects of the medication, do not eat any more. If you do not feel the effects of the medication, you can eat another piece.

What are drug interactions and side effects of Cannabis on the systemic and ocular systems?

Does cannabis/THC interact with other drugs used for the treatment of diseases?

Cannabis Interaction
Cannabis Interaction

- Opiates: Enhancement of sedation and pain reduction.
- Anti-depressants (selective serotonin reuptake inhibitors): THC may increase the effect of fluoxetine (prozac)
- Tranquilizers (Valium, Xanax): Respiratory depression and depression of the brain function may be increased. Includes muscle relaxants, etc.

- Non steroidal antiinflammatory drugs (NSAID): Indomethacin, acetylsalicylic acid (aspirin), and other NSAIDs antagonize THC effects: reduced subjective "high" and acceleration of heart frequency.
- Anti-cholinergics: Atropine and scopolamine may increase the acceleration of heart frequency by THC.
- Sympathomimetics: Amphetamines and other sympathomimetics enhance the acceleration of heart rate and the increase of blood pressure.
- Theophylline: The metabolism of theophylline is accelerated by THC.

Are there Specific Pharmaceutical Drugs Based on Cannabis
Pharmaceutical Drugs Based on Cannabis

1. Sativex
   Manufacturer: GW Pharmaceuticals
   Cannabis spray whose chemical compound is derived from natural extracts of the cannabis plant. Sativex contains two cannabinoids: THC (delta-9-tetrahydrocannabinol) and CBD (cannabidiol).
   Suggested Medical Use: Treatment of neuropathic pain and spasticity in patients with Multiple Sclerosis (MS); Analgesic treatment in adult patients with advanced cancer who experience moderate to severe pain.

2. Dronabinol / Marinol
   Manufacturer: Unimed Pharmaceuticals, a subsidiary of Solvay Pharmaceuticals
   Synthetic Delta-9 THC.
   Suggested Medical Use: Treatment of nausea and vomiting for patients in cancer treatment; appetite stimulant for AIDS patients; Analgesic to ease neuropathic pain in multiple sclerosis patients.

3. Nabilone / Cesamet
   Manufacturer: Valeant Pharmaceuticals International (VRX on NASDAQ)
   Synthetic cannabinoid similar to THC.
Rimonabant / Acomplia

Manufacturer: Sanofi-Aventis

Rimonabant was the first selective CB1 receptor blocker and is an anorectic antiobesity drug.

Cannabis-Related Properties

Synthetic chemical that blocks endocannabinoids from being received in the brain, and, as a result, suppresses appetite.

Suggested Medical Use

Anti-Smoking
Anti-obesity (appetite reducer)

SUICIDAL THOUGHTS?