The Science of Medical Cannabis

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Disclaimer

• We are members of the faculty at the University of Vermont

• Materials presented here represent our own research, views and opinions and are in no way a reflection of the legal views or opinions of the University of Vermont

• Conflict of Interest: Pharmaceuticals will be presented according to their FDA approvals. We have no financial interests to disclose.
A Brief History of Cannabis

Cultivation for food and fiber
Sacramental use
Medicinal use
Documented in first Herbals
Cannabis sativa classified
Harrison Narcotics Tax Act
Controlled Substances Act
Marinol approved
CB1 & CB2 discovered
Endogenous Cannabinoids
Compassionate Use Act
Genome sequenced
Gains popularity as a therapeutic drug

10,000 BCE - 0
100
1500
1700
1930
1964
1970
1985
1988
1992
1996
2011
2014
23 medical states

Used as a therapeutic drug
The Medicinal Use of Plant-based Chemicals

Crude drugs as dried, unprepared plant material have been used for medicine since the dawn of mankind.
All plants produce chemical compounds as part of their normal metabolic activities.

These *phytochemicals* are divided into

1. **primary metabolites** such as sugars and fats, which are found in all plants;

Carotenoids from natural foods, such as the primrose, are considered healthy dietary Supplements.
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(1) **primary metabolites** such as sugars and fats, which are found in all plants;

(2) **secondary metabolites**—compounds which are found in a smaller range of plants, serving a more specific function.

Morphine, the active principle of opium
All plants produce chemical compounds as part of their normal metabolic activities. These **phytochemicals** are divided into
(1) **primary metabolites** such as sugars and fats, which are found in all plants;
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**Mate de Coca**, an herbal tea made from raw leaves of the coca plant. 

![Cocaine](image)

Cocaine, the active principle of coca.
The chemical components of the Cannabis plant
## Constituents of *Cannabis sativa*

<table>
<thead>
<tr>
<th>No.</th>
<th>Groups</th>
<th>Number of Known Compounds</th>
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<tbody>
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<td>1</td>
<td>CBG type</td>
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<tr>
<td>2</td>
<td>CBC type</td>
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<td>Miscellaneous</td>
<td>22</td>
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<tr>
<td>12</td>
<td>Total cannabinoids</td>
<td>104</td>
</tr>
<tr>
<td>13</td>
<td>Total noncannabinoids</td>
<td>441</td>
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<td>Total</td>
<td>545</td>
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Although the plant synthesizes a variety of compounds in the root system, stem and leaves, it is the female flowers that secrete the highest amounts of cannabinoids through glandular trichomes.
Trichomes on a cannabis plant
Capitate stalked trichomes have two main parts: the stalk and the gland head.
The Main Biologically Active Cannabinoids

- Delta-9-tetrahydrocannabinol (THC)
  - Partial Agonist CB1/CB2 receptors
  - Psychoactive
  - Anti-pain, anti-nausea
  - Anti-spasm, anti-immune

- Cannabidiol (CBD)
  - Antagonist CB1/CB2 receptors
  - Not psychoactive
  - Anti-seizure activity
  - Possible non-receptor activities

- Activated by heating the plant (smoking, vaping, baking, heat extraction)
A wide range of cannabinoid chemotypes found in Cannabis plants and extracts of different strains in Vermont

* #45 (1:1 CBD to THC oil); #46 (2:1 CBD to THC oil); #47 (hash) Courtesy of Dr. Kalev Freeman
Chemical Phenotype: Chemotype

Some species of plants have the **genetic ability** to generate different chemical constituents due to the environment in which they reside (geographical location, weather conditions, etc.).

These different chemical compositions within the same plant species are called chemical phenotypes, or “chemotypes.”

![Diagram of Cannabis Sativa and Cannabis]

Cannabis Sativa

Cannabis
Chemical phenotype: Chemotype

• Minor genetic changes with little effect on morphology may produce large changes in the chemical phenotype.

• Chemotypes are often defined by the most abundant chemical produced.

Good examples of plants with many polymorphic chemotypes are Thyme, Rosemary and Cannabis.
Notable Strains: Chemotypes of *Cannabis Sativa*

- Acapulco Gold
- Bubba Kush
- Charlotte's Web
- Diesel
- G-13
- Granddaddy Purple
- Haze
- Northern Lights
- Malawi Gold
- Purple Urkle
- Skunk Shot
- Sour Diesel
- White Widow
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Terpenes and Terpenoids: The non-psychoactive chemical constituents of Cannabis

- Also called essential oils, Cannabis produces a wide variety of terpenes and terpenoids found in many plant species.

- Myrcene
- Limonene
- Linalool
Terpenes and Terpenoids: The non-psychoactive chemical constituents of Cannabis

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Pinene

Humulene

Caryophyllene Oxide
The “Entourage Effect” of Terpenes

In 1998 Shimon Ben-Shaba and Raphael Mechoulam introduced the concept of a novel molecular mechanism of cannabinoids:

The concerted biological activity of cannabinoids in the presence of inactive compounds.
Dr. Mechoulam not only discovered and synthesized Δ9-THC, he also discovered Anandamide and the brain’s endocannabinoid system.
The Endocannabinoid system

• Humans naturally produce cannabinoids
• These compounds interact with specific receptors found on nerve cells (neurons) and immune cells
• They act to reduce excess nerve activity and suppress inflammation
• When humans are exposed to plant cannabinoids, the receptors respond in the same way
Endocannabinoids act to reduce nerve impulses
Effects of THC on the brain depend on where cannabinoid receptors are located

- Note: Cannabinoid receptors are NOT highly expressed in the medulla oblongata of the brain stem that regulates breathing
Cannabis Intoxication: Enjoyable Experiences

• **Attributed to THC action in the brain**

• Head rush and euphoria

• Relaxed calm

• Altered Perceptions
  • Awareness of the senses and of music may be increased
  • Distorted sense of time

• Giggles

• Appetite increase
Cannabis Effects on Attention: Impaired ability to drive

- Peripheral attention reduced
  - A person who is high may become absorbed in an object, event, or process to the exclusion of everything else

- Memory
  - Both short-term and long-term memory impairment

- Color/Image Perception
  - Hallucinogenic effects

- Motor Coordination
  - Impaired, but much less than alcohol or opioids

States with legalized recreational use have seen increased car accidents in the population that has combined alcohol and cannabis.
Possible Negative Consequences of Chronic Use

• Dependence and Addiction
  • THC stimulates the reward pathway and is mildly addicting (physical withdrawal and craving)
  • Heavy use at young age increases risk of dependence (~9% of chronic users become dependent)

• Lung Effects
  • Smoking cannabis actually improves lung function
  • Smoke contains combustible toxins and carcinogens
  • Heavy use is linked to bronchitis

• Psychiatric Illness
  • Some limited evidence for link with heavy use
Overall Toxicity of Cannabis: Why the Big Difference?

Annual Causes of Death From Drugs in the US

- Tobacco: 435,000
- Alcohol: 85,000
- Prescription drug reactions: 32,000
- Illicit drug use: 17,000
- Cannabis: 0

Medicalnewstoday.com
Cannabis has Low Toxicity: No Effects on Breathing Center

• Cannabinoid receptors are not found at significant levels in the breathing center of the brain

• Opioids and Ethanol depress the activity in the breathing center, thus breathing slows even when asphyxiating

• Opioids and Ethanol also increase vomiting risk, death due to aspiration

Opioids suppress multiple controls of breathing
Toxicity of Different Drugs of Abuse

By a wide margin, cannabis is the least risky recreational drug

Ratio between toxic dose and typical human intake

Margin of exposure (MOE): ratio between toxicological threshold and estimated human intake based on individual/population scenarios (akin to Therapeutic Index)

Medical Uses of Cannabis

• Severe and Chronic Pain
• Chemo-induced Nausea
• Seizures
  • Spasticity (MS and Cerebral Palsy)
  • Eating Disorders
  • Glaucoma
  • Anxiety Disorders (OCD, PTSD)
• Addiction
• Parkinson’s/Alzheimer’s
• Inflammatory Diseases
• Cancer
Cannabinoids Reduce Pain and Inflammation

- Cannabinoid Receptors
  - Found in both pain-conducting nerves and in the brain where pain is processed
  - Found in immune cells that cause inflammation
- Activation of receptors by either synthetic THC or by cannabis reduces nerve stimulation and inflammation
- Pain relief from cannabis is strongly supported by clinical trials

Inhibiting the breakdown of endogenous opioids and cannabinoids to alleviate pain, 2012
http://www.nature.com/nrd/journal/v11/n4/full/nrd3673.html
Advantage of adding cannabinoid to opioid regimen for pain

• Enhances pain control
  • Different mechanism
• Reduced opioid side effects
  • Nausea and constipation
• Reduced dose of opioid needed
  • Additive pain relief
• Reduced risk of dependence
  • Can reduce withdrawal pain
Cannabis offers relief from multiple cancer-related problems

• **Pain**: reduces pain signaling, anti-inflammatory activity
  • reduce the amount of opioids needed to control pain

• **Nausea/Vomiting**: inhibits the vomiting reflex at multiple levels, stimulates appetite
  • reverses side effects of opioids

• **Anxiety**: reduces anxiety, calming effect

• **Anti-cancer Activity**: Potential in pre-clinical studies
Cannabinoids Reduce Chemotherapy-induced Nausea by Inhibiting the Vomiting Reflex

- Effectiveness supported by several clinical trials
- Patients report better results with whole plant cannabis compared with THC
- Fewer side effects than other anti-nausea medications

CTZ=chemoreceptor trigger zone

Courtesy Mike Harlos, University of Manitoba
Cannabis for Seizure Disorders

Sanjay Gupta and Joel Stanley

Charlotte Figi: Charlotte’s Web namesake

Sanjay Gupta CNN Medical Marijuana
https://www.youtube.com/watch?v=oxrKyjeC1Tk
Cellular Mechanisms of Seizure Generation

• Excitation (too much)
  • Sodium (Na+) ions are not regulated properly
  • Leads to excess nerve impulses
  • Drug Treatment: reduce sodium ion entry into cells

• Inhibition (too little)
  • Inhibitory chloride (Cl⁻) ions are not regulated properly
  • Drug Treatment: Enhance inhibitory chloride signaling
How to keep the cannabinoid effect in childhood seizures without causing developmental/psychoactive problems with THC?

- **Cannabidiol (CBD)**
  - A component of cannabis
  - Not psychoactive
  - Anti-seizure activity

Strong evidence indicates the anticonvulsant activity of CBD compounds (Wallace et al., 2001; Blair et al., 2015)
Pharmaceutical Cannabinoids

- FDA Approved: Synthetic THC
  - Dronabinol (Marinol™) for Pain or Nausea
  - Nabilone (Cesamet™) for Pain or Nausea
Dronabinol (Marinol™)

- Synthetic delta-9-THC
- US FDA approved for nausea due to cancer chemotherapy in 1986
- Marketed by AbbVie
- Approved for HIV-AIDS associated weight loss
- Marinol is an FDA approved Schedule III drug, although dronabinol (THC) is Schedule I (no medical use)
- Some patients do not tolerate as well as cannabis – entourage effect!
Cannabis vs. Synthetic/Extracted Cannabinoids

• Advantages
  • Low Cost
    • Pharmaceuticals cost over a billion dollars to get FDA approval, they will need to make up that cost
  • “Entourage Effect”
    • Other cannabinoids and terpenes contribute to effects and may reduce side effects (especially CNS side effects)
• Delivery
  • Inhalation gives faster relief
  • Metabolism profile is different

• Disadvantages
  • Illegal in many states (patients hesitant to use)
  • Few clinical trials to determine effectiveness or drug interactions
  • Difficult to standardize dose
    • Different strains, processing, etc.
Future Cannabinoid Research: Cannabis Extracts in Development

- In Phase III Clinical Trials: Plant-derived cannabinoids
  - 1:1 THC/CBD (Sativex™) sublingual spray for Multiple Sclerosis
  - CBD (Epidiolex™) oral solution for Epilepsy
GW pharmaceuticals phase 3 trials

Epidiolex® (plant-derived CBD) proprietary platform has Orphan Drug Designation and Fast Track Designation from the U.S. Food and Drug Administration (FDA) in the treatment of Dravet syndrome.

The capitalized cost to develop a new drug, on average, is about $1.3 billion, adjusted to 2009 dollars. (Forbes magazine, Shocking Secrets of FDA Clinical Trials Revealed, Jan 24 2014).
Future Cannabinoid Research: Other Targets

Plant-derived cannabinoid

$\Delta^9$-Tetrahydrocannabinol (THC)

Endogenous cannabinoids

Anandamide (AEA)

2-Arachidonoylglycerol (2-AG)

Fatty Amino Acid Hydrolase

Presynaptic neuron

$\downarrow$Ca$^{2+}$, K$^+$

CB$_1$

AEA or 2-AG

Precursor

FAAH

Et, AA

Postsynaptic neuron

mR

iR

$\uparrow$Ca$^{2+}$

NT
Cannabis Regulation in Vermont

• **1967**: Cannabis simple possession dropped to misdemeanor

• **1981**: Vermont Cannabis Therapeutic Research Program established

• **2004**: VT is the 9th state to legalize Medical Cannabis

• **2011**: Four dispensaries permitted to provide Medical Cannabis

• **2013**: 1oz. Cannabis decriminalized

• **2016**: Legalization bill passes VT Senate, fails
Vermont Medical Marijuana Law: Eligible Medical Conditions

• The treatment of these conditions if the disease or the treatment results in severe, persistent, and intractable symptoms

  • Cancer
  • Acquired immune deficiency syndrome (AIDS)
  • Positive status for human immunodeficiency virus (HIV)
  • Multiple sclerosis (MS)
  • Glaucoma

• Or a disease, medical condition, or its treatment that is chronic, debilitating and produces severe, persistent, and one or more of the following intractable symptoms:

  • Cachexia (wasting syndrome)
  • Severe and/or Chronic pain
  • Nausea
  • Seizures

Statutes:
H.245 expanded conditions (2016)
Why Do Vermonters use Medical Cannabis?

- Results of patient surveys - target symptoms
- Patients were asked to report the primary symptom for which they were using medical *Cannabis*
Becoming a Patient on the Vermont Marijuana Registry

• Registration forms are available at the Vermont Marijuana Registry Website http://vcic.vermont.gov/marijuana-registry/library

• Complete the Registered Patient application

• Ask your doctor to sign and complete the Physicians Medical Verification Form. The doctor must be licensed to practice in Vermont, New Hampshire, Massachusetts or New York

• When all sections of the form are completed you will need to have it notarized.

• Enclose with the form:
  • A digital photograph
  • A check or money order for $50

• Mail the application package to:
  • Marijuana Registry, Department of Public Safety, 103 South Main Street, Waterbury, Vermont 05671
Because of the Federal Law
Physicians cannot:

• Provide cannabis or information about how to obtain cannabis
• Offer individualized patient advice concerning appropriate dosage timing, amount and route of administration for cannabis
  • Information provided to the Department of Public Safety is only related to the patient’s diagnosis and the existence of a physician-patient relationship.
Summary

• Cannabis has a jaded Legal and Medical History
• Endocannabinoid system is affected by compounds in *Cannabis sativa* (THC, CBD etc)
• Neurologic effects have the potential to lead to addiction in adolescents, but low risk of overdose
• Cannabis has proven medical uses in treating pain, nausea, and seizure disorders, among many others
  • CB1 and CB2 receptors act as negative modulators of excess neuronal signaling
• Current Prescriptions: THC, THC/CBD, CBD
  • Advantages and disadvantages to using whole cannabis
• Vermont’s Medical Marijuana Program is restrictive, but is a step in the right direction