PAST, PRESENT AND FUTURE OF MEDICAL CANNABIS

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Outline

• Medical History of Cannabis
• Pharmacology of Cannabinoids
• Endocannabinoid System Physiology
• Safety and Adverse Effects of Cannabis
• Impairments from Cannabis
• Future of Cannabis in Medicine
HISTORICAL USE OF CANNABIS IN MEDICINE
Historical Use of Cannabis in Medicine

- 2700 BC Emperor Shen-Nung
  - Analgesia, rheumatism, beriberi, malaria, gout and poor memory
- 1839 William O’ Shaughnessy
  - Introduced medical cannabis to England
- 1854 Cannabis enters Dispensatory of US
  - Sir William Osler on migraine…“cannabis Indica is probably the most satisfactory remedy.”
- Empirical Medicine of the 19th Century
  - Combined morphine, cannabis and capsicum
  - Provided-phyto-opiod, Phytocannabinoids and phytovanilloid in one prep
  - Better outpatient pain relief than is currently available in 21st century
Historical Use of Cannabis in Medicine

- 19th and 20th Century
  - US Pharmacopoeia 1850-1942
  - Restrictions of sale and use 1937
  - Boggs 1951 and Narcotic Control Act of 1956 – legal penalties
- 1996 - California permits cannabis use for medicine
  - Compassionate Use Act
- 2017 - 28 states as well as Washington, DC, Guam and Puerto Rico
  - 21 states decriminalized
  - 8 states allow recreational use (AL, CA, CO, MN, MA, NV, OR, WA, DC)

Cannabis and Medicine

- Seizures, Schizophrenia, Graft vs Host Disease, NFL
- FDA approved medical cannabis since 1980
- Marinol
- Sativex: combination of CBD:THC
- Rimonabant
- Epidiolex (June 25, 2018)
- BUT cannabis remains a Schedule I drug since 1970
  - No medical benefit, high abuse potential
  - Restrict research and funding

https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm611046.htm accessed 6/29/18
Cannabis and Medicine History

- 1997 US National Institute of Health and British Medical Association release report on potential therapeutic effect
- 2017 Health Effect of Cannabis and Cannabinoids: Current Evidence
- 89.5% of residents and fellows felt unprepared to prescribe cannabis
- 35.3% felt ready to answer cannabis questions
- 9% of US medical schools have cannabis in their curricula
- PubMed search of “Endocannabinoid”
  - 1993: 10 citations
  - 2018: 9,032 citations

PHARMACOLOGY OF CANNABINOIDS
Cannabinoids

- Cannabinoids are compounds produced by cannabis plants which interact with the mammalian Endocannabinoid system.
- Cannabis contains more than 200 cannabinoids (THC, CBD, CBG, CBN).
- Terpenes
- Flavonoids
- Sativa vs. Indica
3 Types of Cannabinoids

01
Phytocannabinoids: terpenophenolic 21-C compounds found in the genus Cannabis (e.g. THC, CBD)

02
Endocannabinoids: natural endogenous compounds binding cannabinoid receptors (anandamide and 2-arachidonylglycerol)

03
Synthetic cannabinoids: Ajulemic acid
Nabilone
Dronabinol
Phytocannabinoids

- Cannabis contains more than 200 cannabinoids (THC, CBD)
- Terpenes
- Flavonoids
- Sativa vs. Indica

Pharmacologic Actions of Non-psychotropic Cannabinoids
Source: Izac et al., 2009.

Most Common Cannabinoids found in Cannabis

- Tetrahydrocannabinolic acid (THCA)
- Tetrahydrocannabinol (THC)
- Cannabidiolic Acid (CBDA)
- Cannabidiol (CBD)
- Cannabigerol (CBG)
- Cannabichromene (CBC)
- Tetrahydrocannabinicarin (THCV)
The Entourage Effect: Phytocannabinoids and Terpenes

- Naturally occurring aromatic oils that produce different sensations and effects on the body.

- Terpenes share precursor molecule with Phytocannabinoids, flavors and fragrances.

- Cannabis-derived terpenes include:
  - Limonene, Myrcene, α-pinene, linalool, B-caryophyllene, caryophyllene oxide, nerolidol and phytol
The eCB system represents a microcosm of psycho-neuroimmunology or “mind–body” medicine.
## Cannabinoids and Health Conditions

<table>
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<tr>
<th>ADD/ADHD</th>
<th>Diabetes</th>
<th>Neuralgia</th>
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<tr>
<td>ALS</td>
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<td>HIV/AIDS</td>
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<td>Insomnia</td>
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<td>Migraine</td>
<td>Stroke</td>
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<td>Chronic pain</td>
<td>MRSA</td>
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<td>Cramps</td>
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<td>Vomiting</td>
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<td>Crohn’s</td>
<td>Nausea</td>
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</table>
• Why is one plant involved in so many disease processes?
• The eCB system represents a microcosm of psycho-neuroimmunology or “mind–body” medicine.
Anandamide and 2-AG are produced by the nervous system upon both chemical and mechanical trauma (Mechoulam, 2002).

- Delta-9-THC, CBD, AEA, 2-AG, HU-220 all decrease glutamate excitotoxicity (Baker, 2003)
  - Reduce seizure activity
  - Limit infarct size post-stroke

- Cannabinoids effective at reducing and preventing perinatal brain injury

Neural Protection: Federal Patent
Endocannabinoid System (ECS)

ECS: internal homeostatic regulatory systems with 3 components:
1. Endocannabinoids
2. CB1, CB2, TRPV1 receptors
3. Regulatory enzymes (Fatty Acid Amide Hydrolase, Monacyl glycerol)

Endocannabinoids are produced on demand, retrograde travel to presynaptic neurons, inhibiting neurotransmitter release.
CB1 Receptor

- CB1: most abundant G-protein-couple receptor in the brain with major neuromodulatory function
- CB1 receptors are present in areas of nociception (pain modulation)
- Cerebellum, limbic system, basal ganglia and reward pathways, substantia nigra and periaqueductal grey matter
  - Movement, addiction, sex and food
- Limited distribution in brainstem and not found in the Medullary respiratory centers
  - Inherent safety mechanisms
- CB1 also found in testis, presynaptically on sympathetic nerve terminals, adrenal glands, heart, lungs, prostate, bone marrow, thymus and tonsils
CB2 Receptors

- CB2 impacts pain modulations and plays an important role in immune function and inflammation.
- CB2 activation reduces nociception in a variety of models
  - Tactile, thermal, allodynia, mechanical and thermal hyperalgias and writhing
- Neuropathic modulation in pain thought to be related to CB2 receptors on microglia and reducing cytokine-mediated neuroinflammation
Endocannabinoid System Function

- Endocannabinoid System: 500 millions years old
  - Very primitive system just like endogenous opioid system
- Mood, stress response, pain, embryology, memory, sleep, immune response, reproductive function, energy metabolism
- Preserved across all vertebrate
- Homeostasis: maintenance of dynamic balance
SAFETY AND ADVERSE EFFECTS OF CANNABIS
Cannabinoids have a high therapeutic index.

No fatalities reported directly related to the toxicity of any cannabinoid, even at extremely high doses.

Potential severe cognitive, psychomotoromimetic and substance abuse-related adverse effects due to THC in the young or cannabis-naïve.
Side Effects of Cannabis

- Dizziness
- Dry mouth
- Nausea
- Fatigue
- Sleepiness
- Euphoria
- Depression
- Vomiting

- Impaired balance
- Paranoia
- Confusion
- Anxiety
- Disorientation

Risk of Dependency with Use of Illicit Drugs

Lifetime risk of dependency

- Cannabis 5%
- Stimulants 11%
- Alcohol 15%
- Nicotine 32%
- Heroin 23%
- Cocaine 17%

Highest risk of dependency

- Poor academic achievement
- Deviant behavior in childhood
- Poor parental relationship
- Parental history of drug abuse

IMPAIEMENTS FROM CANNABIS
Impairment is Real with Cannabis

• Can cannabis cause temporary changes in performance?

  • Short term changes in psychomotor performance are exacerbated when cannabis is consumed in combination with alcohol.
  • Route of administration will also impact drug effects.
    • Oral THC is associated with delayed onset and prolong duration of drug effect, greater drug bioavailability and greater THC to 11 hydroxy THC conversion.
  • Habitual consumers may become tolerant to drug effect over time (Marinol, Sativex).
Drug Testing and Impairment

• Standard drug detection methods do not identify impairment of performance
  • (presence of THC, 11 hydroxy THC, and or carboxy THC)
• Residual traces of THC may be present in blood, particular in habitual users, well beyond any expected period of drug induce impairment
• Blood levels THC does not correct with IMPAIRMENTS
  • Influence on behavior diminishes relatively rapidly some 60 minutes (*National Highway Traffic Safety Administration, 2003*) to 2.5 hours (Sewell et al., 2009) after inhalation.
Cannabis and Driving

- Cannabis is generally associated with less elevated risk of accidents compared to other drugs.
  - THC positive drivers OR 1.3 following adjustment
Cannabis As an Exit Drug

• 350 individuals surveyed at medical cannabis dispensary
  • 40% use as substitute for alcohol
  • 26% use as substitute for illicit drugs
  • 66% use as substitute for prescription drugs

• Most common reasons for substituting
  • Less adverse side effects (65%), better symptom management (57%), decreased withdrawal potential with cannabis (34%)

FUTURE OF CANNABIS IN MEDICINE
Future of Cannabinoid Medicine

- Endocannabinoid signaling involved in multiple disease process
- Clinical Endocannabinoid Deficiency
- Opioid Sparing Properties
- CB2 Mediated Pharmacology
- Phyto-combination Drugs Developed
- Recreational Use
- Public Health Implications
- Schedule 1 Status
THANKS FOR YOUR ATTENTION

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