American College of Physicians

Internal Medicine Meeting 2018

New Orleans, LA

Marijuana: Its Roles, Rewards, and Risks

Faculty

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Disclosure: Research Grants/Contracts: Boehringer Ingelheim, Janssen Pharma, DSI, Portola, Astra Zeneca, CSL Behring; Honoraria: BMS/Pfizer, Boehringer Ingelheim; Consultantship: Boehringer Ingelheim, Portola, BMS/Pfizer;

Clinical questions to be addressed:

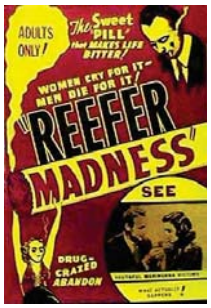
1.What are the risks of acute and chronic marijuana exposure?

2.What are the indications for medical marijuana, and how is it recommended?

3.Given rapidly changing and differing state laws, how does one handle a positive marijuana result for employment drug screening?

Posted Date: March 15, 2018

Medical Cannabis: Update on a Rapidly Advancing Clinical and Political Issue



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Historical Timeline of Medical Cannabis

2,737 BCE: First recorded use of medical cannabis in China by Emperor Shen Neng

2,000-800 BCE: Hindu sacred text *Atharvaveda* cites cannabis as one of five "sacred plants" in India

100-0 BCE: Psychotropic properties of cannabis described in *Pen Ts'ao Ching,* medicinal properties as an anesthetic advocated by Hua Tuo

***130-200*CE:** Galen prescribes medical cannabis

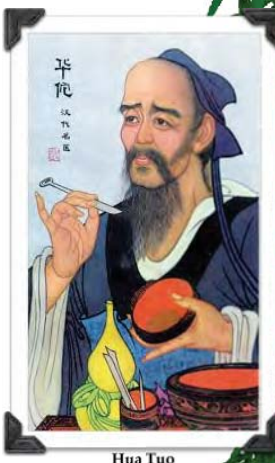
850-1272: Hemp spreads through Vikings to Arabia, Persia, Syria, Egypt, Africa

1271-1295: Marco Polo brings Europe knowledge of cannabis

1531: French physician Rabelais mentions medicinal properties of cannabis in *Gargantua and Pantagruel*

1563: Portuguese physician Garcia da Orta writes about cannabis' medical effects

1578: Li Shih-Chen from China publishes works on antibiotic and antiemetic effects



Hua Tuo

1606-1632: French and British Colonies cultivate cannabis in Port Royal (1606), Virginia (1611), and Plymouth (1632).

1621: *Anatomy of Melancholy* by Burton suggests cannabis can treat depression

1764: *The New England Dispensatory* lauds medical marijuana

1794: *The Edinburgh New Dispensary* lauds medical marijuana

1800s: Growing flourishes in Mississippi, Georgia, California, Nebraska, New York, and Kentucky

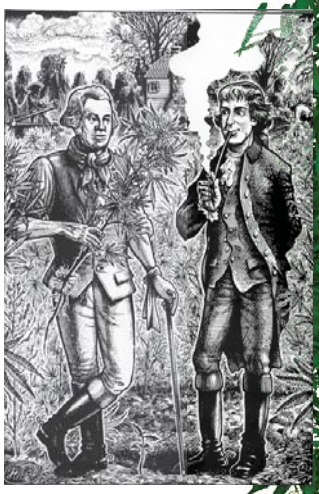
1840: Cannabis medicine is available in the US, hashish is offered in Persian pharmacies

1850: Cannabis is added to *The U.S. Pharmacopoeia*

1850-1915: Cannabis was widely used across US, available in pharmacies and general stores

1906: *Pure Food and Drug Act* was passed, regulating the labeling of products with alcohol, opiates, cocaine, cannabis, etc.

Early 1900s: Interest began to wane with broadening availability of opiates, barbiturates, chloral hydrate, aspirin, and syringes



Marijuana and hashish extracts were the first, second, or third most prescribed drugs in the US each year 1842-1892

1914: *Harrison Act* defines using marijuana, and other drugs, as a crime

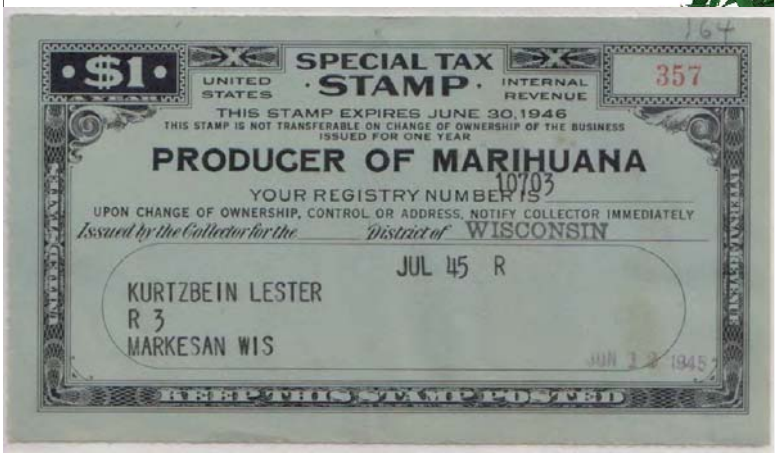
1915-1927: The U.S. prohibits cannabis use for non-medical purposes, presaging alcohol prohibition.

1915-1933: Cannabis use spreads as alcohol becomes scarce

1936: *Reefer Madness* was created as a government tactic to misinform and scare citizens from cannabis

1937: U.S. Congress passes *Marihuana Tax Act* ($1/oz for medical use, $100/oz for recreational use); the AMA stood virtually alone in opposing the Act, stating that objective data re harmful effects were lacking, and that the Act would impede research

1942: Cannabis is removed from *U.S. Pharmacopoeia*



Controlled Substances Act of 1970

	Schedule I	Schedule II
Potential for Abuse	High	High
Accepted Medical Use	No	Yes
Safety	Lack of acceptable safety for use under medical supervision	Abuse of drug may lead to psychological or physical dependence
Examples	Marijuana Heroin LSD Mescaline GHB Methaqualone	Morphine Opium Hydromorphone Oxycontin

1971: Evidence that cannabis helps glaucoma arises; University of Mississippi gains federal approval to grow marijuana for use in DEA-approved medical research

1976: FDA creates Investigational New Drug (IND) for Compassionate Use research program

1988: Howlett and Devane discover cannabinoid receptors in rat brain

Early 1990s: endogenous cannabinoids discovered

1996: California passes first medical cannabis bill

2013: Cole Memo limits US Attorneys' discretion in prosecuting MMJ

2017: Obama Administration declines to reschedule, but announces procedures for additional potential approved research grows

2018: 29 states plus District of Columbia have some form of medical cannabis program; 9 allow "adult rec" use; Cole Memo rescinded in "Sessions Memo"

Cannabis as Medicine

- Contains at least 400 identified chemical compounds
- Highest concentration of bioactive compounds is found in resin exuded from flowers of female plants
- Main psychoactive component is believed to be delta-9-tetrahydrocannnabinol
- At least 100 other 21-carbon terpenophenolic cannabinoid compounds have been identified
- Terpenoids and flavinoids may enhance cerebral blood flow, enhance cortical activity, kill respiratory pathogens, and provide ant-inflammatory activity

Cannabis (sativa, indica, ruderalis)

Plant-derived cannabinoids

- Δ^9-tetrahydrocannabinol - THC
- Δ^9-tetrahydrocannabivarin - THCV
- Cannabidiol - CBD
- Cannabigerol
- Cannabichromene
- Cannabicyclol
- Cannabielsoin
- Cannbitriol
- Cannabinol
- Miscellaneous

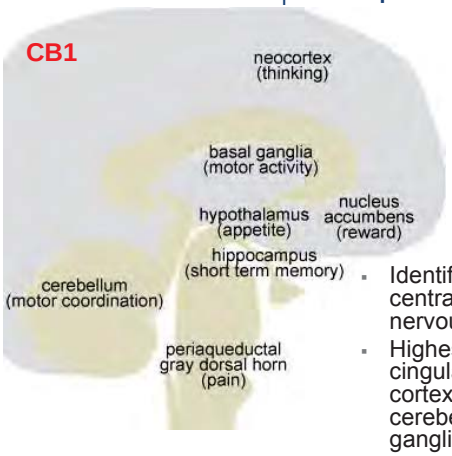
Br J Pharmacology 2006;147:S163-171

Cannabinoid Receptors

- CB_1 and CB_2 receptors have been identified
- Receptors are encoded by separate genes on separate chromosomes and share 47% amino acid identity
- G-coupled protein receptors that inhibit adenyl cyclase upon activation
  - Decreases cAMP and protein kinase A activity
  - Inhibits Ca^{++} influx through various calcium channels
  - Directly inhibits the release of multiple neurotransmitters (acetylcholine, dopamine, glutamate) and indirectly affects GABA, opioid, and serotonin receptors

Neurology 2014; 82: 1556-63

Distribution of CB_1 Receptors



- Identified throughout the central and peripheral nervous system
- Highest density in cingulate gyrus, frontal cortex, hippocampus, cerebellum, and basal ganglia
- Present in virtually all organs and tissues

Neurology 2014; 82: 1556-63

CB_2 Receptors

- Originally detected in macrophages and in the marginal zone of the spleen
- Largest concentration found in peripheral blood
  - B-cells
  - NK cells
  - immunologic cells (modulation of cell migration)
- In CNS found in the microglia (possible role in Alzheimer's?)
- Also found in bone and, to a lesser degree, in the liver

Neurology 2014; 82: 1556-63

Physiological Effects of CB Receptor Activation

- Euphoria
- Psychosis
- Impaired memory and cognition
- Reduced locomotor function
- Increased appetite
- Antiemetic effects
- Analgesic effects
- Antispasticity effects
- Sleep-promoting effects

Neurology 2014; 82: 1556-63

Medical Cannabinoids

- Currently there are two FDA-approved cannabinoids: dronabinol and nabilone
  - Both in pill form
  - Both approved for
    - nausea and vomiting associated with cancer chemotherapy
    - wasting illnesses such as HIV and cancer
- SATIVEX, a cannabinoid nasal spray, is in Phase III trials for cancer-related pain

Medicinal Marijuana: Potential Delivery Systems

- Traditionally smoked
  - Fast onset, relatively short duration of action
  - Includes tar and carbon monoxide
- Vaporized
- Edibles
- Tinctures
- Oils

Vaporization

- Progressively heats each bioactive component to its burning point without burning the plant
  - Essential oils vaporize and can be inhaled without tar, benzene, CO, etc
  - Vapor is supposedly 95% smoke and carcinogen-free
- Reduces inflammatory risk to lungs per NIDA study
- Increases yield of anti-inflammatory terpenoids that protect the lungs

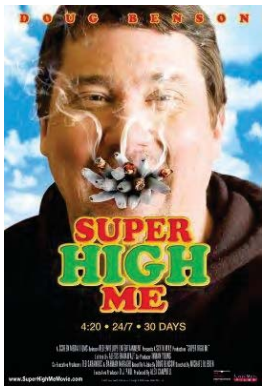
Edibles

- Typically prepared as concentrated resin cakes (hash, hashish)
- GI absorption is quite effective
- Slower onset and longer effect than smoked
- Lower peak levels of cannabinoids than smoked
- Lipophilic when bound to plasma proteins and easily crosses blood-brain barrier

Concentrates

- Available as waxes, tinctures, oils, and topical solutions
- Tinctures are consumed sublingually
- Highly concentrated with cannabinoids and terpenes
- Can control THC:CBD ratio and concentrates are typically CBD-rich
  - Charlotte's Web oil 1:35-50 ratio famous from treatment of Charlotte Figi with Dravet Syndrome
  - Haleigh's Hope oil 1:24

Psychological Effects



Psychological Effects

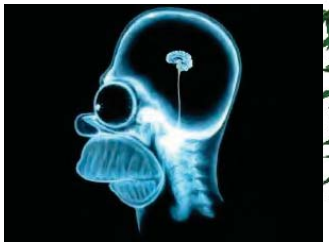
- Euphoria, relaxation, changes in perception
- Effects are dosage dependent
- Low
  - Sense of well-being
  - Enhancement of senses
  - Subtle changes in thought and expression
  - Talkativeness, giggling
  - Increased appetite

Psychological Effects

- Higher Doses
  - Visual distortion
  - Sense of time altered
  - Attention span and memory impaired
  - Thought processing altered
  - Mental perception altered

Psychological Effects

- At Any Dose
  - Reduced ability to concentrate
  - Impaired Memory
  - Tiredness
  - Confusion



Physical Effects

- Lung and throat problems with smoking
- Carcinogenic effects (controversial)
- Decreased intraocular pressure
- Allergies
- Harmful effect studies based on smoked marijuana and not on other routes or specific cannabinoids

Cannabis and Psychosis

- On an individual level, cannabis use confers an overall twofold increase in the relative risk for later schizophrenia.
  - Likely related to THC activity
- It was proposed in 2004 that at the population level, elimination of cannabis use would reduce the incidence of schizophrenia by approximately 8%, assuming a causal relationship.
  - This has subsequently been questioned
  - May be more likely a hastening of onset in predisposed patients

Causal association between cannabis and psychosis: examination of the evidence, Louise Arseneault, PhD et al, BJP 2004 184: 101

"Indications"

- Vary by individual state law
- Often advocacy-driven
- No correlate to usual FDA-driven drug development program
- Usually no specification of strain or dose
- Most common uses in US today are insomnia, pain, cancer-related symptoms, and anxiety/"PTSD"

Dosing

- There are no reliable dosing guidelines for specific illnesses, in part due to strain variability
- Unlike typical "prescription" for an FDA-approved drug, it is often the medical dispensary that selects strain and regimens
- General guidance:
  - Select product and ratio (1:1 for chronic pain, MS, ALS; 1:15-20 for childhood epilepsy, IBD)
  - Begin with a low dose
  - A few small doses/day
  - Use same dose and ratio for several days
  - Be alert for adverse effects
  - Gradually titrate up, considering euphoria vs function
  - Standard precautions (e.g. not while breastfeeding)
- There are some unexpected resources, such as

http://www.mayoclinic.org/drugs-supplements/marijuana/dosing/hrb-20059701

Dosing Advice—not like a PDR

- "Usually a few puffs prior to each meal is sufficient for most patients. Some will require about half to a whole joint prior to each meal. These are usually thinly rolled, about 0.5 grams in weight. Those who prefer non-smoked will often eat one quarter to half a brownie, or use about 0.25 grams in a vaporizer, prior to each meal."
- Canadian researchers suggest a maximum exposure of 5g/day
- Self-titration, especially with more experienced users, is often advocated

2017 NASEM Report

- Committee on the Health Effects of Marijuana: An Evidence Review and Research Agenda, a report of the Institute of Medicine aka The National Academies of Sciences, Engineering, and Medicine
- Update to 1999 IOM report
- Much more literature to review now . . . But not much would be considered authoritative

2017 NASEM Report Conclusions

- **There is conclusive or substantial evidence that cannabis or cannabinoids are effective:**
  - For the treatment of chronic pain in adults (cannabis)
  - As antiemetics in the treatment of chemotherapy-induced nausea and vomiting (oral cannabinoids)
  - For improving patient-reported multiple sclerosis spasticity symptoms (oral cannabinoids)

2017 NASEM Report Conclusions

- **There is moderate evidence that cannabis or cannabinoids are effective for:**
  - Improving short-term sleep outcomes in individuals with sleep disturbance associated with obstructive sleep apnea syndrome, fibromyalgia, chronic pain, and multiple sclerosis (cannabinoids, primarily nabiximols (1:1 THC:CBD))

2017 NASEM Report Conclusions

- **There is limited evidence that cannabis or cannabinoids are effective for:**
  - Increasing appetite and decreasing weight loss associated with HIV/AIDS (cannabis and oral cannabinoids)
  - Improving clinician-measured multiple sclerosis spasticity symptoms (oral cannabinoids)
  - Improving symptoms of Tourette syndrome (THC capsules)
  - Improving anxiety symptoms, as assessed by a public speaking test, in individuals with social anxiety disorders (cannabidiol)
  - Improving symptoms of posttraumatic stress disorder (nabilone; a single, small fair-quality trial)

2017 NASEM Report Conclusions

- **There is limited evidence that cannabis or cannabinoids are *ineffective* for:**
  - Improving symptoms associated with dementia (cannabinoids)
  - Improving intraocular pressure associated with glaucoma (cannabinoids)
  - Reducing depressive symptoms in individuals with chronic pain or multiple sclerosis (nabiximols, dronabinol, and nabilone)

2017 NASEM Report Conclusions

- **There is no or insufficient evidence to support or refute the conclusion that cannabis or cannabinoids are an effective treatment for:**
  - Cancers, including glioma (cannabinoids)
  - Cancer-associated anorexia cachexia syndrome and anorexia nervosa (cannabinoids)
  - Symptoms of irritable bowel syndrome (dronabinol)
  - Epilepsy (cannabinoids)
  - Spasticity in patients with paralysis due to spinal cord injury (cannabinoids)

2017 NASEM Report Conclusions

- **There is no or insufficient evidence to support or refute the conclusion that cannabis or cannabinoids are an effective treatment for:**
  - Symptoms associated with amyotrophic lateral sclerosis (cannabinoids)
  - Chorea and certain neuropsychiatric symptoms associated with Huntington's disease (oral cannabinoids)
  - Motor system symptoms associated with Parkinson's disease or the levodopa-induced dyskinesia (cannabinoids)

2017 NASEM Report Conclusions

- **There is no or insufficient evidence to support or refute the conclusion that cannabis or cannabinoids are an effective treatment for:**
  - Dystonia (nabilone and dronabinol)
  - Achieving abstinence in the use of addictive substances (cannabinoids)
  - Mental health outcomes in individuals with schizophrenia or schizophreniform psychosis (cannabidiol)

The Federal Regulatory Environment

- Marijuana remains a schedule 1 substance and thus is deemed to have no medical value
- The US Department of Justice (DOJ) has the authority to enforce civil and criminal federal laws related to possession and use regardless of state laws
- Growing, distributing, or possessing is a violation of federal law
- However, there is a memorandum ("Cole Memo") from August 2013 that describes the federal priorities associated with enforcement
  - BUT WAIT . . . Just rescinded by AG Sessions
- Physicians can legally prescribe THC, in the form of Marinol® or Syndros® (generic dronabinol). Dronabinol is identical to THC in marijuana.

Barriers to Research Medicinal Cannabinoids

- Regulatory
  - NIDA (or other Federally authorized source—none yet approved) must supply API
  - FDA must review to determine need for IND
  - DEA must register investigator and site (each protocol) to perform research on a Schedule 1 substance

Typical Regulatory Process for Human Study

Typical Process for Conducting Human Subject Research with Marijuana

- **Step 1:** Sponsor obtains **pre-IND number** from FDA.
- **Step 2:** Sponsor contacts NIDA or another DEA-registered source of marijuana to obtain information on the specific strains of marijuana available, so that all necessary chemistry, manufacturing, and controls (CMC) information can be included in the IND application.
- **Step 3:** Sponsor contacts DEA for registration application and Schedule 1 license.
- **Step 4:** If applicable, Sponsor obtains from NIDA as Letter of Authorization (LOA) to reference CMC information in NIDA's Drug Master File (DMF) on file with FDA.

Typical Regulatory Process for Human Study

Typical Process for Conducting Research with Marijuana

- **Step 5:** Sponsor sends copy of IND/protocol, including a LOA to reference CMC information in a **Drug Master File** (if applicable), to FDA and DEA.
- **Step 6:** FDA reviews the IND.
- **Step 7:** Sponsor contacts NIDA or another DEA-registered source to obtain the marijuana after the FDA completes its review of the IND, and the DEA registration is received.

Barriers to Research Medicinal Cannabinoids

- Supply
  - Only NIDA unless API is brought in from another country under an IND that has also been approved by DEA (the "GW Pharma route")
  - Hemp-derived cannabinoids are consider Class I substances as well (despite Farm Act of 2014 Section 7606; but see pending Industrial Hemp Act of 2018)
- Funding
  - Suffice it to say funding is limited. NIH and NIDA have limited funds for use in this space.
  - States are starting to fund observational research (very limited impact so far)

Barriers to Research Medicinal Cannabinoids

- Drug delivery
  - Smoking risk may (at least partially) offset health benefits; does "vaping" help?
  - Poor oral absorption of cannabinoids
  - First-pass effect in liver
  - Dermal, sublingual, MDI, rectal, vaginal, intra-articular
- Placebo groups
  - Active agent is widely available licitly and illicitly
- Study Design/Endpoints

Do We Know What We Know—and What We Don't Know?

- Probably not
- Perhaps no other area of contemporary medicine is driven as much by hype, advocacy, and hope, especially when considered against such an overall shallow evidence basis
- Clearly there is a role for cannabis, but in which diseases? When? And how?
- The Lambert Center is first comprehensive academic resource and networking nidus for addressing these issues
- www.Jefferson.edu/lambertcenter

Summary

- Use of cannabis and cannabinoids in medicine is a moving target
- Clinical, social, economic, and political implications
- Long on history, short on evidence
- Perhaps no better example of "patient-driven care," but don't let that discount shared decision making
- Be alert for a growing role for hemp-based medicinals