The Medicinal Use of Cannabis

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Cannabis is…

probably the most satisfactory remedy for the treatment of migraine headaches.

-- Dr. William Osler. Textbook of Medicine, 1892 - 1915

Marijuana has…

a high potential for abuse and no accepted medical value.

-- Controlled Substance Act,

1970 - 2017

Outline

1. Terminology
2. Biology
3. Medicinal Use
4. Preparations
5. Legal and Administrative

Categories of Cannabinoids

Phytocannabinoids

- Cannabis sativa plant: 104 cannabinoids; 545 total compounds

Endocannabinoids

- 4+ cannabinoids in human body (endogenous ligands)

Synthetic cannabinoids

- Multiple chemically synthesized cannabinoids: pharmaceutical and recreational

Cannabis Sativa Plant: Names

Hemp

- Refers to the plant and its products
- Oldest term

Marijuana

- Refers to both plant and drug
- Relatively new slang term

Cannabis

- Refers to both plant and drug
- DSM-5: “most appropriate scientific term”

Cannabis Sativa: A Unique Plant

- Source of 3 important types of products
  1. Fiber (fabric, rope)
  2. Food (seed, oil)
  3. Psychoactive substances
     - Used for religious rituals, medicine, recreation
- Controversy about whether Cannabis Indica exists as a separate subspecies

Cannabis Sativa: Ingredients

- Tetrahydrocannabinol (THC)
  - Primary, but not only, psychoactive ingredient of plant
- Cannabidiol (CBD)
  - No rewarding, euphorigenic effect
    - Counteracts psychoactive effect of THC
- THC and CBD are inversely proportional in cannabis plant
  - Strains developed based on goal of use

2. BIOLOGY

Modern Timeline

- 1940. Cannabidiol (CBD) isolated from plant
- 1964. THC isolated from plant
- 1981. CBD anticonvulsant effect demonstrated
- 1985. Synthetic THC approved by FDA
- 1988. CB1 receptor identified
- 1992. Endogenous anandamide (AEA)
- 1993. CB2 receptor identified
- 1995. Endogenous 2-arachidonoyl glycerol

Raphael Mechoulam

- 86 y.o. Israeli chemist, still professionally active
- Identified THC as the primary psychoactive ingredient in cannabis
- Discovered the endocannabinoid system
- "The Scientist": YouTube documentary about his discoveries
  - https://www.youtube.com/watch?v=csbJnBKqwlw

Endocannabinoid System: Helps Regulate Multiple Systems

- Pain
- Immunity
- Inflammation
- Movement
- Bone density
- Tumor surveillance
- Appetite
- Stress
- Mood

Endocannabinoid Receptors

- CB1
  - Most common receptor in CNS
    - Responsible for psychoactive effects
    - Absent in brain stem → no respiratory depression
  - Also in peripheral nerves and non-neuronal tissues
- CB2
  - Located in macrophages
  - Involved in immune system and anti-inflammatory activity
    - Exact functions unknown due to absence of good probes
- Both inhibit synaptic transmission
- Other receptors not as well characterized

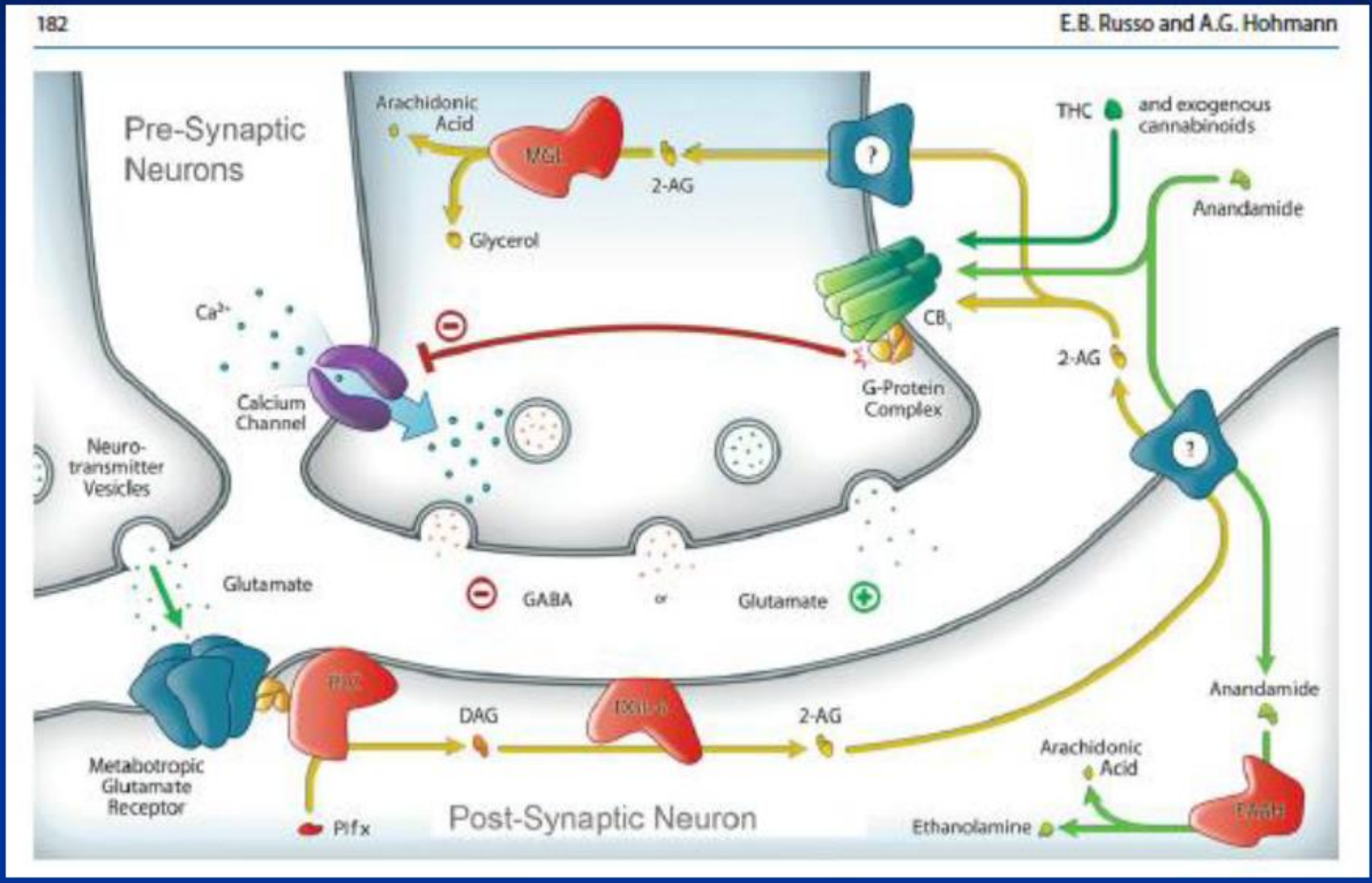
Endocannabinoid Ligands

- Anandamide (AEA)
  - Partial agonist
  - CNS: Stress response. Periphery: pain
  - Metabolized by fatty acid amide hydrolase (FAAH)
- 2-arachidonoyl gylcerol (2-AG)
  - Full agonist
  - Broadly expressed. “Workhorse”
  - Metabolized by mono-acyl-glycerol (MAGL)
- Ligand diversification: Both act on CB1 receptor but act differentially to modulate systems

Cellular Neurobiology

- Neuromodulator (vs. neurotransmitter)
  - Synthesized on demand rather than stored
  - Lipids derived from cell membranes, not proteins
- Retrograde signaling
  - Synthesized in post-synaptic cell and released into synaptic cleft
  - Binds to pre-synaptic CB1 receptor
  - Acts on pre-synaptic cell to inhibit release of both excitatory and inhibitory neurotransmitters
- Interacts with opioid system

Endocannabinoid System



3. MEDICINAL USE

Efficacy

- High quality evidence
  - Chemotherapy-induced nausea and vomiting
  - Appetite stimulation
  - Chronic pain, neuropathic (especially HIV/AIDS)
  - Spasticity of multiple sclerosis, spinal cord injury
  - Anticonvulsant (CBD for Dravet Syndrome)
- Low quality evidence
  - Anxiety, sleep disorders, PTSD
- Possible role in addiction treatment
  - Reduce cannabis withdrawal
  - CBD counteracts psychoactive effect of THC
  - CB1 blocker rimonabant withdrawn 2008

Cannabinoids and Pain

- Analgesic properties extensively documented and widely accepted in Western medical practice in 19th and early 20th Centuries
  - "Used for pain since beginning of recorded time."
  - Prescribed to Queen Victoria for pain
  - Especially for neuropathic and inflammatory pain
- Do not induce tolerance
- Interact with opioid system and may allow reduced doses of opioids
  - CB1 receptors : 10 x more in CNS than mu-opioid receptors, especially in pain areas

Cannabinoids and Pain: Review of RCTs (Aggarwal)

- 38 studies, mostly outside of U.S.
- Preparations: synthetic, extracted, herbal
- Routes: oral, oro-mucosal, smoked, topical
- Results: 71% found statistically significant pain relief
  - Modestly effective
  - Safe and well tolerated

Cannabinoids and Pain: Review of RCTs

Indications

- Neuropathic pain
- Fibromyalgia
- Rheumatoid arthritis
- HIV neuropathy
  - No reduction in viral load or CD4 cell count

Advantages

- Minimal tolerance
- No toxic overdoses or end organ failure
- Enhances analgesic effect of opioids

Cannabinoids and Pain: Review of RCTs

Adverse Effects

- Vast majority are not serious
  - No withdrawals from study versus 33% for opioids
- Cognitive impairment
- Intoxication
  - Reduced by co-administration of CBD
- Addiction and withdrawal

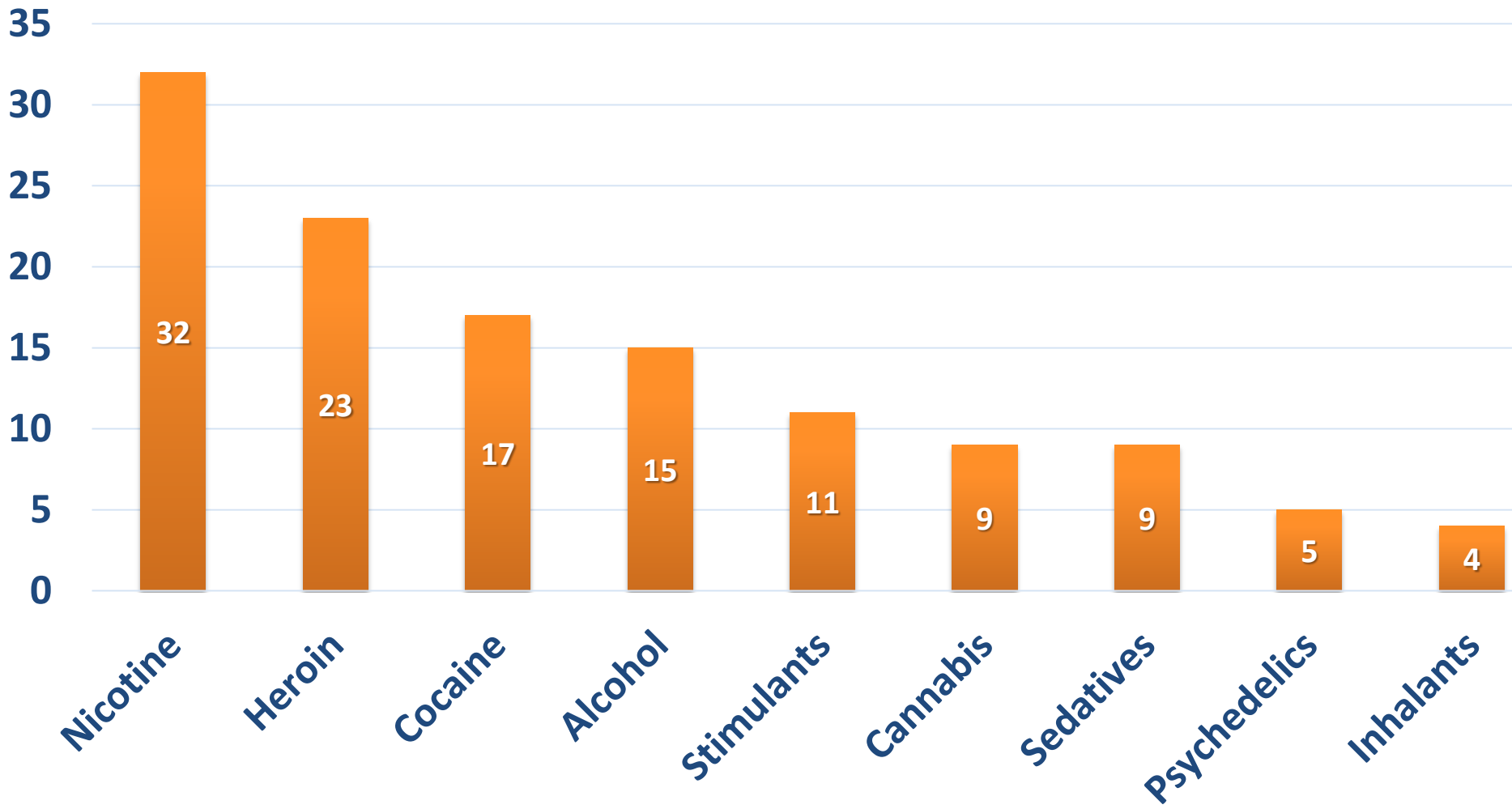
Contraindications

- History of Cannabis Use Disorder
- Use cautiously if history of psychosis

Safety

- No overdose deaths
  - Absence of CB receptors in brainstem
- Intoxication
  - Impaired driving
    - Especially if mixed with alcohol
  - Delayed effect
- Addictive potential
  - "Gateway hypothesis"
- Cognitive deficits resulting from heavy use before age 18
- Fetal development
  - Negative effect on cognitive functioning in children
- Association with psychosis
  - Causation possible

Percentage of People Addicted After Using A Substance



4. PREPARATIONS

Pharmaceutical: Synthetic, Oral

- Dronabinol (Marinol, Syndros)
  - Synthetic THC isomer
  - Schedule III
  - Indications
    - Anti-emetic for cancer chemotherapy when other medications have failed
    - Anorexia from AIDS
- Nabilone (Cesamet)
  - Analogue of dronabinol
  - Schedule II
  - Indication
    - Anti-emetic for cancer chemotherapy when other medications have failed

Pharmaceutical: Plant Extract

- "Entourage Effect"
- FDA has approval path for botanical medication
- Sativex (1:1 ratio of THC/CBD)
  - Oro-mucosal spray (2.7 mg THC/2.5 mg CBD)
  - Approved in 28 countries for spasticity from multiple sclerosis, neuropathic pain, cancer pain
  - U.S.: Phase III clinical trials, fast tracked by FDA in April, 2014
- Epidiolex (cannabidiol)
  - Purified liquid extract
  - Anticonvulsant for Dravet syndrome
  - Orphan Drug Status from FDA, pre-IND

Development of Parallel Systems

	"Medical Marijuana"	Pharmaceutical Cannabinoids
Form	Raw plant or extracts	Synthesized or extracted by government standards
Route	Smoked, oral, topical	Oral (capsule or spray)
DEA Class	Schedule I	Schedule II, III
Physician Role	Recommend	Prescribe
Source	"Artisanal" growers and dispensaries	Pharmaceutical companies and pharmacies

Non-Pharmaceutical Preparations

- Quality and standardization issues
  - Artisanal vs. scientific
  - Pesticides, contaminants
  - New emphasis on “product safety protocols”
    - Maryland has adopted American Herbal Products Association standards
- Production is evolving from home grown and co-ops to regulated businesses
  - Outdoor versus indoor (artificial vs. natural light)

Non-Pharmaceutical Preparations: European Example

- Whole-flower
- Varieties with standardized THC/CBD ratios
  - 22%/<1%
  - 14%/<1%
  - 7%/9%
  - <1%/9%

5. LEGAL AND ADMINISTRATIVE

Many Puzzles

1. Why was cannabis removed from clinical medicine without having the problems of over-prescription and overdoses experienced with opioid medications?
2. Why is the endocannabinoid system not taught in medical schools?
3. Why is cannabis the most difficult of the Schedule 1 substances to research?

Repetitious Process

1. Concern about widespread illegal use and uncertainty about facts
2. Appointment of high level government commission or scientific committee
   - Conclusion: "Cannabis is not without dangers, but penalties for use are disproportionate to the threat"
   - Recommend decriminalization
3. Opposition from law enforcement, politicians, some physicians
4. Sweeping, confident, disrespectful assertions by extremes on both sides
5. Stalemate with minimal or no legal changes

Commissions and Committees

- 1893-4, UK: Indian Hemp Drugs Commission
- 1929, U.S.: Panama Canal Zone Military Investigation
- 1939-44, U.S.: LaGuardia Report. NY Academy of Science
- 1968, UK: Baroness Wootton
- 1970, Canada: Le Dain Commission
- 1970-2, U.S.: Schafer Commission (Nixon)
- 1999, U.S.: Institute of Medicine

Long History of Medicinal Use

- 2700 BC. First documented use (China)
- Used for millennia in India, China, Egypt, Middle East
- Western medicine: mainstream use in 19th and early 20th Centuries
  - 1850 to 1942. Listed in U.S. Pharmacopoeia
    - Fluid extracts (not raw plant for inhalation)
    - Manufactured by major pharmaceutical companies
  - Included in major medical publications
    - William Osler's textbook and others

De-Medicalization of Cannabis
(Harry Anslinger)

1937

Marijuana Tax Act

- Allowed medical use but imposed heavy administrative burdens
- Adopted despite AMA opposition
- Declared unconstitutional in 1969

1942

Removed from U.S. Pharmacopeia

1961

Included in UN Single Narcotics Convention

1970

Classified as Schedule 1 Substance in Controlled Drug Substances Act

DEA Schedule I Criteria

1. High potential for abuse
2. No currently accepted use for treatment in the United States
3. Lack of accepted safety for use under medical supervision

Context of Classification as Schedule I

"Since there is still a considerable void in our knowledge of the plant and effects of the active drug contained in it, our recommendation is that marijuana be retained within Schedule I **at least until the completion of certain studies now underway to resolve the issue**."

Dr. Roger O. Egeberg
Assistant Secretary of Health
August 14, 1970

Simplified Legal Alternatives

1. Decriminalize
   - Treat possession of small amounts as a civil offence or misdemeanor instead of a felony
     - Manage offenses with fines instead of incarceration
   - Intent: discourage use, prohibit distribution
2. Legalize for recreational use
   - Regulate and tax like alcohol and tobacco
   - Intent: eliminate black market, collect taxes
   - Opens door for commercial marketing
3. Legalize for medical use

Current Conflicted Legal Status

- Federal law: Use is illegal for any purpose
- Many state laws allow medical or recreational use
- The Supremacy Clause of U.S. Constitution:
  - State laws that actively impede or conflict with federal law are invalid

Medical Legalization History

- 1981. First bill introduced in US Congress (AIDS)
- 1996. California became first state to legalize
  - System flourished despite Federal raids
  - Drug czar threatened physicians with loss of DEA license if they recommended cannabis
    - 2002. Blocked by 9th Circuit. Supreme Court refused to hear appeal thus allowing ruling to stand
- 2005. Supreme Court allowed Federal government to intervene on users, growers, enterprises despite state law (*Gonzales v. Raich*)
  - Perpetuates gray area

Medical Legalization History (cont.)

- 2009. DOJ "Ogden Memo": deprioritize CSA enforcement in states where medical cannabis is well regulated
- 2014. Rohrbacher-Farr Amendment (US House of Rep). Blocks DOJ from intervening
  - 2015. Court decision ordered DOJ to comply
- 2015. CARERS Act would eliminate gray zone
  - 2017. Passage is uncertain
- 2016. DEA reiterated refusal to reschedule
  - Will permit growers other than Univ of Mississippi

Summary of 2017 Status

- Medically legal in 28 states
  - 14 additional states permit cannabidiol oils
- Patchwork of state programs – no set of best practices
- Quality of substance from non-pharmaceutical sources is evolving
- For physicians
  - Legal gray zone has narrowed but persists
    - Physicians are protected from prosecution or loss of DEA license
  - Few clinical guidelines

Resulting Obstacles in U.S.

- Access
  - Single source for research grade
    - University of Mississippi farm, contracted by NIDA
    - Low THC concentration of research grade
    - Fall, 2016: DEA willing to allow other sources
  - 5 levels of approval (more than any other drug)
    - ❖ DEA – not FDA – has final authority
- Organizational issues
  - No government agency focused on beneficial uses
- Discourages development of new pharmaceutical products

Medical Cannabis in Maryland

- Law enacted 2013 and 2014, amended 2015
- Regulated by Maryland Medical Cannabis Commission
  - Final regulations issued October, 2015
- Process
  - Physicians must register
  - Producers and dispensaries must be licensed
  - Physician writes recommendation for patient
    - Any condition that is severe, for which other medical treatments have been ineffective, and if the symptoms "reasonably can be expected to be relieved" by the medical use of cannabis.
  - Patient obtains medication from dispensary

Current Status of Maryland Program

- Patients are not yet being registered
- 214 physicians registered as of February 2017
- Growers and processors licensees announced August, 2016
  - Challenges pending
- Updates and answers to FAQs at: mmcc.maryland.gov

What Are We Learning?

- Market forces join political forces to obscure scientific issues
  - Expansion or elimination of qualifying conditions
  - Importance of pricing to avoid gray market
- Most recommendations are made by a small subset of physicians
- Some de facto recreational use occurs
  - See increase in heavy use more than general use
  - No significant increase in use by youth so far
- Thorny issues remain to be resolved
  - Impaired driving
  - Positive urine screens at work

Summary

- Cannabis has medicinal value
  - Benefits and risks tend to be exaggerated
- Influence of law enforcement agencies has outweighed health agencies
- Political considerations have interfered with scientific evaluation and left physicians in a disadvantaged position
  - Beware of selective use of data to support particular positions
- Barriers to research and pharmaceutical development should be lowered

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Thank You

Questions and Comments

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