Medical Cannabis and Cannabis Use Disorders

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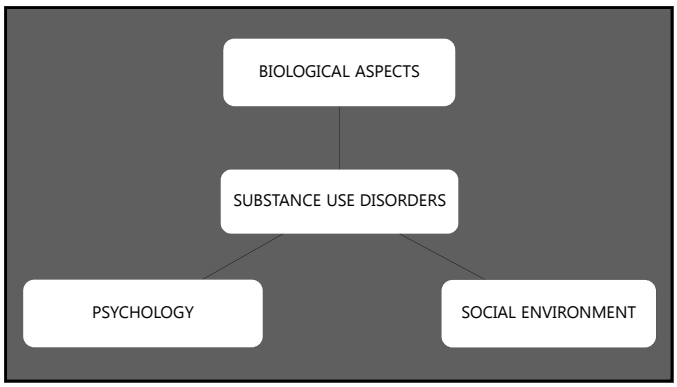
SUBSTANCE USE DISORDERS

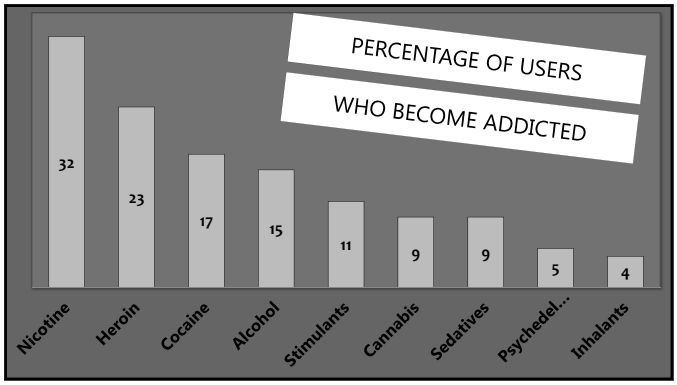


- Psychosocial interventions are the foundation of the treatment of substance use disorders
- Medications, when available, provide an important secondary and supportive role

TREATMENT

- Physical withdrawal: physiologic onset of symptoms following abrupt discontinuation
  - Occur with opioid, caffeine, and SSRI use in normal people
- Substance use disorder ("addiction"): continued use despite adverse consequences
  - Insignificant withdrawal syndrome in stimulant use disorders

IMPORTANT DISTINCTION



- Withdrawal management
  - Two goals

    Short term: safety and comfort
    Long term: transition into ongoing treatment and recovery
- Stabilization and relapse prevention

USE OF MEDICATION FOR SUD

OUTLINE

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- Historical Background
- Basic Science
- Negative Effects

OUTLINE

- Potential therapeutic uses
- Medical cannabis in Maryland

OUTLINE

HISTORICAL BACKGROUND

How did a medication – that had been used for millennia and was a mainstream commercial pharmaceutical during the 19th and early 20th centuries – disappear from medical use and return as a controversial treatment operating parallel to current conventional medical practice?

CAUGHT UP BETWEEN SCIENCE, EMOTION AND POLITICS

- 2700 BC -First documented use (China)
- Used for millennia in India, China, Egypt, Middle East

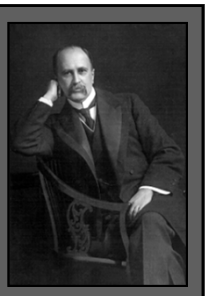
LONG HISTORY OF MEDICINAL USE

- 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

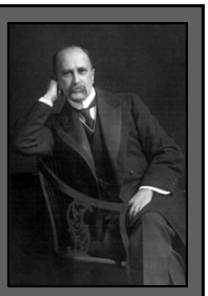
LONG HISTORY OF MEDICINAL USE

- Regarding medication in general
  - "One of the first duties of the physician is to educate the masses not to take medication"
  - "You cannot have a drug for every malady"



DR. WILLIAM OSLER'S OPINIONS

- Regarding cannabis
  - "Probably the most satisfactory remedy for the treatment of migraine headaches"
    Textbook of Medicine, 1892 - 1915



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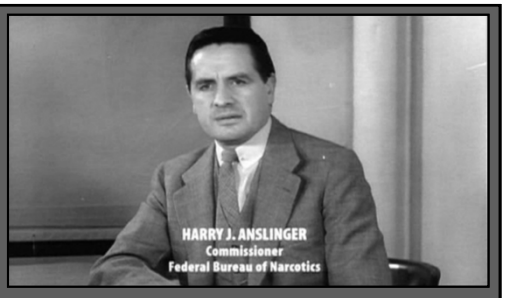


DE-MEDICALIZATION OF CANNABIS

- 1937- Marijuana Tax Act
  - Allowed medical use but imposed heavy administrative burdens
  - Adopted despite AMA opposition
  - Declared unconstitutional in 1969

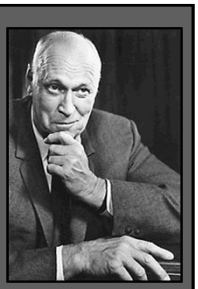
DE-MEDICALIZATION OF CANNABIS

- 1942- Removed from the US Pharmacopeia
- 1961- Included in the UN Single Narcotics Convention
- 1970- Classified as a Scheduled I substance in Controlled Drug Substances Act

DE-MEDICALIZATION OF CANNABIS

"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



CONTEXT OF CLASSIFICATION AS SCHEDULE I

- Schedule I status limits research
  - Cannabis more restricted than any other Schedule I substance
  - DEA has agreed to permit production by more than one source

    Higher levels of DOJ have not acted on this recommendation

CANNABIS: RESEARCH BARRIERS

- Limits knowledge about medical benefits as well as treatment of addiction
- Limits development of pharmaceutical preparations

CANNABIS: RESEARCH BARRIERS

CANNABIS: BASIC SCIENCE

- Tetrahydrocannabinol (THC)
  - Primary, but not only, psychoactive agent
  - Concentrations in plant:

    Leaves (1972):<1%
    Hashish: Dried resin and flowers- 2-8%
    Sinsemilla: Flowering plants of unfertilized female plants- 14-20%

CANNABIS PLANT: 60+ CANNABINOIDS

- Cannabidiol (CBD)
  - Not euphorigenic
  - Counters psychogenic effects of THC
- THC/CBD: Inversely proportional in different strains

CANNABIS PLANT: 60+ CANNABINOIDS

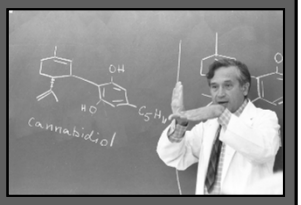
- 1940: Cannabidiol (CBD) isolated from plant
- 1964: Tetrahydrocannabinol(THC) isolated from plant
- 1981: CBD anticonvulsant effect demonstrated
- 1985: Synthetic THC approved by FDA

CANNABIS: RESEARCH TIMELINE

- 1988: CB1 receptor identified
- 1992: First endogenous ligand identified
- 1993: CB2 receptor identified
- 1995: Second endogenous ligand identified

CANNABIS: RESEARCH TIMELINE

- 86 y/o Israeli chemist, still professionally active
- Identified THC as the primary psychoactive ingredient in cannabis



RAPHAEL MECHOULAM

- Discovered the endocannabinoid system
- "The Scientist": YouTube documentary about his discoveries

RAPHAEL MECHOULAM

- CB1
  - Most common receptor in CNS
    - Responsible for psychoactive effects
    - Absent in brain stem - no respiratory depression, no overdose deaths
  - Also in peripheral nerves and non-neuronal tissues

ENDOCANNABINOID RECEPTORS

- CB2
  - Located in macrophages
  - Involved in immune system and anti-inflammatory activity
    - Exact functions unknown due to absence of good probes

ENDOCANNABINOID RECEPTORS

- Both inhibit synaptic transmission
- Other receptors are not as well characterized

ENDOCANNABINOID RECEPTORS

- Anandamide (AEA)
  - Partial agonist
  - CNS: Stress response. Periphery: pain
  - Metabolized by fatty acid amide hydrolase (FAAH)

ENDOCANNABINOID LIGANDS

- 2-arachidonoyl glycerol (2-AG)
  - Full agonist
  - Broadly expressed. "Workhorse"
  - Metabolized by mono-acyl-glycerol (MAGL)
- Ligand diversification: Both act on CB1 receptors but act differentially to modulate systems

ENDOCANNABINOID LIGANDS

- Helps regulate multiple systems
  - Pain
  - Immunity
  - Inflammation
  - Movement

ENDOCANNABINOID SYSTEM

- Helps regulate multiple systems
  - Bone Density
  - Tumor Surveillance
  - Appetite
  - Stress
  - Mood

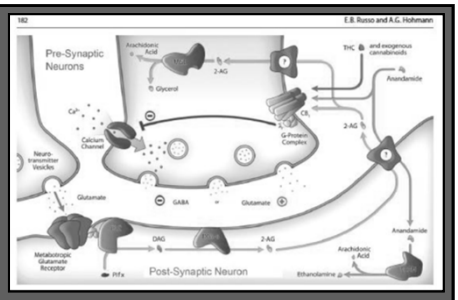
CANNABIS: RESEARCH TIMELINE

- Neuromodulator (vs. neurotransmitter)
  - Synthesized on demand rather than stored
  - Lipids derived from cell membranes, not proteins
- Interacts with opioid system

CANNABIS: CELLULAR NEUROBIOLOGY

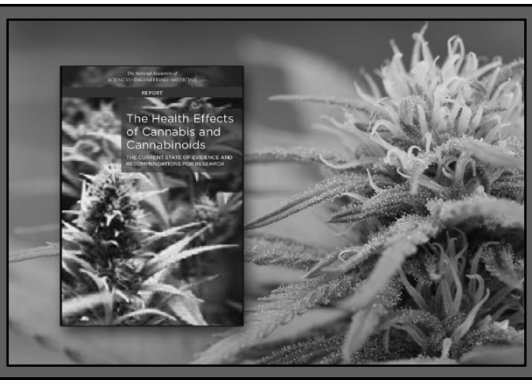
- Retrograde signaling
  - Synthesized in and released from post-synaptic cell
    - Diffuses into synaptic cleft
  - Acts on pre-synaptic cell to inhibit release of both excitatory and inhibitory neurotransmitters
    - Analogous to the oil in an engine
  - Returns to post-synaptic cell and is hydrolyzed

CANNABIS: CELLULAR NEUROBIOLOGY



ENDOCANNABINOID SYSTEM

CANNABIS: NEGATIVE EFFECTS



SUMMARY REPORT DETAILS

- Third review by IOM and National Academy of Sciences
  - Previous reviews: 1982, 1999
- 487 pages
- Download at http://www.nap.edu/24625

MAJOR FINDINGS: DANGERS

- Substantial evidence of association
  - Lower birth weights
  - Worse respiratory symptoms
  - Development of schizophrenia and other psychoses
    - Association rather than causal
  - Increased motor vehicle crashes

OTHER SOURCES: DANGERS

- Addictive potential equal to benzodiazepines (9%)
  - Less than alcohol (15%)
- Cognitive deficits resulting from heavy use before age 18
- Fetal development
  - Negative effect on cognitive functioning in children

CANNABIS AND DRIVING: CONFOUNDS

- THC: most common detected intoxicant in US drivers (13% vs. 8% for alcohol, 3% >0.08)
  - THC detected longer than is alcohol
- Plurality of users do not believe that use increases risk of auto accidents

CANNABIS AND DRIVING: CONFOUNDS

- THC impairs reaction time and visual-spatial judgment
  - No rapid, accurate test for detection
    Must distinguish between active and inactive THC metabolites
  - No correlation between THC levels and impairment
    Dose-effect curve for fatality risk is very controversial
    States: 5 nanograms or zero tolerance

CANNABIS, ALCOHOL AND DRIVING

- Cannabis effects are greater with automatic driving functions
- Alcohol effects are greater with complex tasks that require conscious control

CANNABIS, ALCOHOL AND DRIVING

- Cannabis users are more aware of being impaired and tend to use various behavioral strategies to compensate for impairments
  - Adding alcohol eliminates the ability to use these strategies effectively, resulting in impairments at doses that would be insignificant if either substances were used alone

CANNABIS AND DRIVING: FUTURE?

- Development of simple, accurate test
- Educating users about dangers
- Criminalizing combining cannabis use with alcohol use

CANNABIS AND DRIVING: DELAYED EFFECTS

- 10 experienced licensed pilots trained on a flight simulator landing task
- Smoked single cannabis cigarette (19 mg)
- 24 hours later
  - Impairment of performance in simulator
  - No awareness of impairment

(*Am J Psychiatry* 142: 1325-1329. **1985)**

CANNABIS : NEGATIVE EFFECTS ON TEENAGERS

- Prospective study of 1,000 from birth to age 38 found cognitive deficits if heavy use began before age 18 in:
  - IQ (8 points, no recovery)
  - Attention (poor recovery)
  - Memory
  - Processing speed
  - Reasoning skill

CANNABIS WITHDRAWAL

- Diagnosis added to DSM 5
- Higher THC concentration in cannabis has made cannabis withdrawal more clinically significant
- Anxiety, insomnia, persistent craving

POTENTIAL THERAPEUTIC USES

	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

DEVELOPMENT OF PARALLEL SYSTEMS

- Quality and standardization issues
  - Artisanal vs. scientific
  - Pesticides, contaminants
  - New emphasis on "product safety protocols"

    Maryland has adopted American Herbal Products Association standards

NON-PHARMACEUTICAL PREPERATIONS

- Production is evolving from home grown and co-ops to regulated businesses
  - Outdoor versus indoor (Natural vs. artificial light)

NON-PHARMACEUTICAL PREPERATIONS

- Dronabinol (Marinol, Syndros)
  - Synthetic THC isomer
  - Schedule III
  - Indications
    - Anti-emetic for cancer chemotherapy when other medications have failed
    - Anorexia from AIDS

PHARMACEUTICAL:SYNTHETIC, ORAL

- Nabilone (Cesamet)
  - Analogue of dronabinol
  - Schedule II
  - Indications
    - Anti-emetic for cancer chemotherapy when other medications have failed

PHARMACEUTICAL:SYNTHETIC, ORAL

- "Entourage effect"
- FDA has approved path for botanical medication

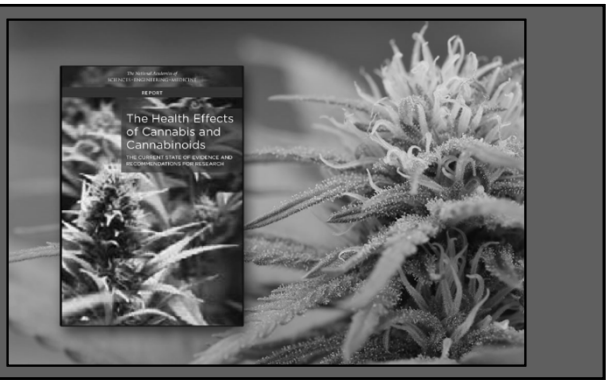
PHARMACEUTICAL:PLANT EXTRACT

- 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 trials, fast tracked by FDA in April, 2014

PHARMACEUTICAL:PLANT EXTRACT

- Epidiolex (cannabidiol)
  - Purified liquid extract
  - Anticonvulsant for Dravet syndrome of childhood
  - Recently approved by FDA

PHARMACEUTICAL:PLANT EXTRACT



- Conclusive or substantial evidence
  - Chronic pain
  - Anti-emetic in chemotherapy
  - Spasticity in multiple sclerosis

FINDINGS:THERAPEUTIC EFFECTIVENESS

- Moderate evidence
  - Short-term sleep outcomes associated with sleep apnea, fibromyalgia, chronic pain, MS (nabiximols)

FINDINGS:THERAPEUTIC EFFECTIVENESS

- Limited evidence
  - Increased appetite, HIV/AIDS
  - Tourette Syndrome
  - Public speaking anxiety with social anxiety disorder
  - PTSD (1 small fair-quality study)

FINDINGS:THERAPEUTIC EFFECTIVENESS

- Insufficient evidence
  - Epilepsy
  - Spasticity from spinal cord injury
  - PTSD
  - Anxiety
  - Sleep

FINDINGS:THERAPEUTIC EFFECTIVENESS

- Dronabinol (Marinol)
  - Synthetic pharmaceutical THC
  - Reduction in withdrawal symptoms using 20 mg twice daily
  - Extended use: no improvement in long-term outcomes

MEDICATIONS FOR WITHDRAWAL

- Nabiximols (Sativex)
  - Botanical pharmaceutical, 1 to 1 mix of THC and CBD
  - Same result as dronabinol

MEDICATIONS FOR WITHDRAWAL

MEDICAL CANNABIS IN MARYLAND

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LAWS AND REGULATIONS

- Law enacted 2013 and 2014, amended 2015
  - 2015- Comments submitted by Med Chi
- Regulated by Maryland Medical Cannabis Commission
  - Updates and answers to FAQs at: mmcc.maryland.gov

LAWS AND REGULATIONS

- Process
  - Provider must register
  - Producers and dispensaries must be licensed
  - Patients must register
  - Provider writes recommendation for patient
  - Patient obtains medication from dispensary

- Cachexia
- Anorexia
- Wasting syndrome
- Severe or chronic pain
- Severe nausea

QUALIFYING CONDITIONS

- Seizures
- Severe or persistent muscle spasms
- Glaucoma
- Post-traumatic stress disorder
- Another chronic medical condition which is severe and for which other treatments have been ineffective

QUALIFYING CONDITIONS

Provider Type	Number (Total: 1075)
Physician	**684**
Nurse	**320**
Dentist	**68**
Podiatrist	**11**

BY PROVIDER (OCTOBER 2018)

County	# of Patients	% State Population	% State Patients	% State Providers	# of Providers
Montgomery	4446	16	16	21	149
Baltimore	3892	14	14	17	
Anne Arundel	2635	9	9	10	
Frederick	2351	4	8	2	
Baltimore City	2211	11	8	11	
Prince George's	2057	15	7	13	

BY LOCATION (OCTOBER 2018)

Condition	# of Patients
Chronic pain	19,083
Other	12,543
Severe pain	5,031
PTSD	2,154
Muscle spasms	1,962
Severe nausea	1,393

BY CONDITIONS (OCTOBER 2018)

- Cannabis has medicinal value
  - Benefits and risks tend to be exaggerated
- Influence of law enforcement agencies has outweighed health agencies

SUMMARY

SUMMARY

- 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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HEALTH SYSTEM

KOLMAC
Outpatient Recovery Centers
Leaders in addiction treatment since 1973