The Return of Medical Cannabis

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Cannabis Outline

- Historical Background
- Basic Science
- Negative Effects
- Potential Therapeutic Uses
- Medical Cannabis in Maryland

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Historical Background

Caught Up Between Science, Emotion, and Politics

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?

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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

Dr. William Osler's Opinions

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

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

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

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Cannabis: Research Barriers

- Schedule 1 status limits research
  - Cannabis more restricted than any other Schedule 1 substance
  - DEA has agreed to permit production by more than one source
    - Higher levels of DOJ have not acted on this recommendation
- Limits knowledge about medical benefits as well as treatment of addiction
- Limits development of pharmaceutical preparations

Basic Science

Cannabis Plant: 60+ Cannabinoids

- THC
  - Primary, but not only, psychoactive agent
  - Concentrations in plant:
    - Leaves (1972): < 1%
    - Hashish (dried resin and flowers): 2% to 8%
    - **Sinsemilla** (flowering tops of unfertilized female plants): 14 – 20%
- Cannabidiol (CBD)
  - Not euphorigenic
  - Counters psychoactive effect of THC
- THC/CBD: Inversely proportional in different strains

Research 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. First endogenous ligand identified
- 1993. CB2 receptor identified
- 1995. Second endogenous ligand identified

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 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

Endocannabinoid System: Helps Regulate Multiple Systems

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

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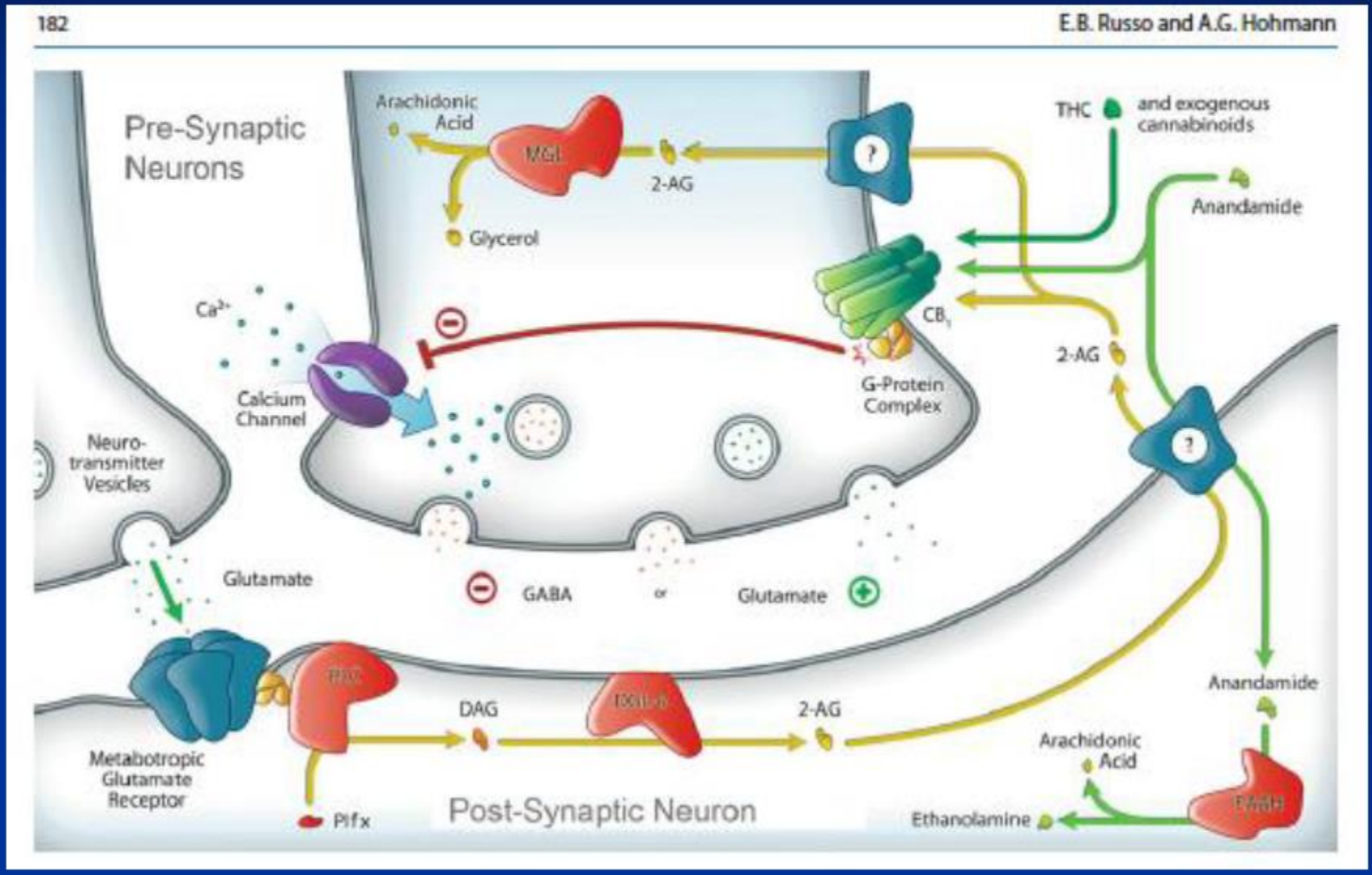
Cellular Neurobiology

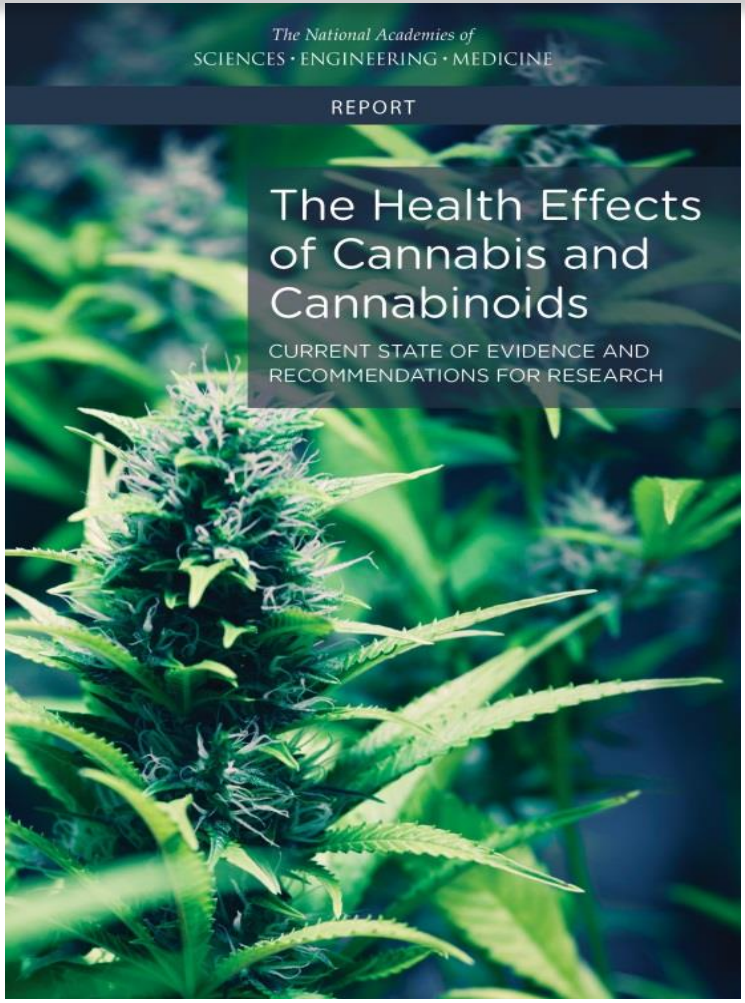
- Neuromodulator (vs. neurotransmitter)
  - Synthesized on demand rather than stored
  - Lipids derived from cell membranes, not proteins
- Retrograde signaling
  - Synthesized in and released from post-synaptic cell
    - Diffuses into synaptic cleft
  - Acts on pre-synaptic cell to inhibit release of both excitatory and inhibitory neurotransmitters
    - Analogous to the oil in an engine
  - Returns to post-synaptic cell and is hydrolyzed
- Interacts with opioid system

Endocannabinoid System



Negative Effects of Cannabis

2017 Comprehensive Summary



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Details

- Third review by IOM and National Academy of Sciences
  - Previous: 1982, 1999
- 487 pages
- Summary, pages 13 to 22
- Download at http://www.nap.edu/24625

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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

- No overdose deaths
  - Absence of CB receptors in brainstem
- Intoxication a problem
  - Impaired driving
    - Especially if mixed with alcohol
  - Delayed effect
- 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 Impaired Driving: Confounds

- THC: most common detected intoxicant in US drivers (13% vs. 8% for alcohol, 3% > .08)
  - THC detected longer than is alcohol
- 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
- Plurality of users do not believe that use increases risk of auto accidents

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Cannabis Impaired Driving: Alcohol

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

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Cannabis Impaired Driving: Future?

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

Delayed Effects of Acute Use

- 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**

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Negative Effects on Teenaged Users

- Prospective study of 1,000 from birth to 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

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)

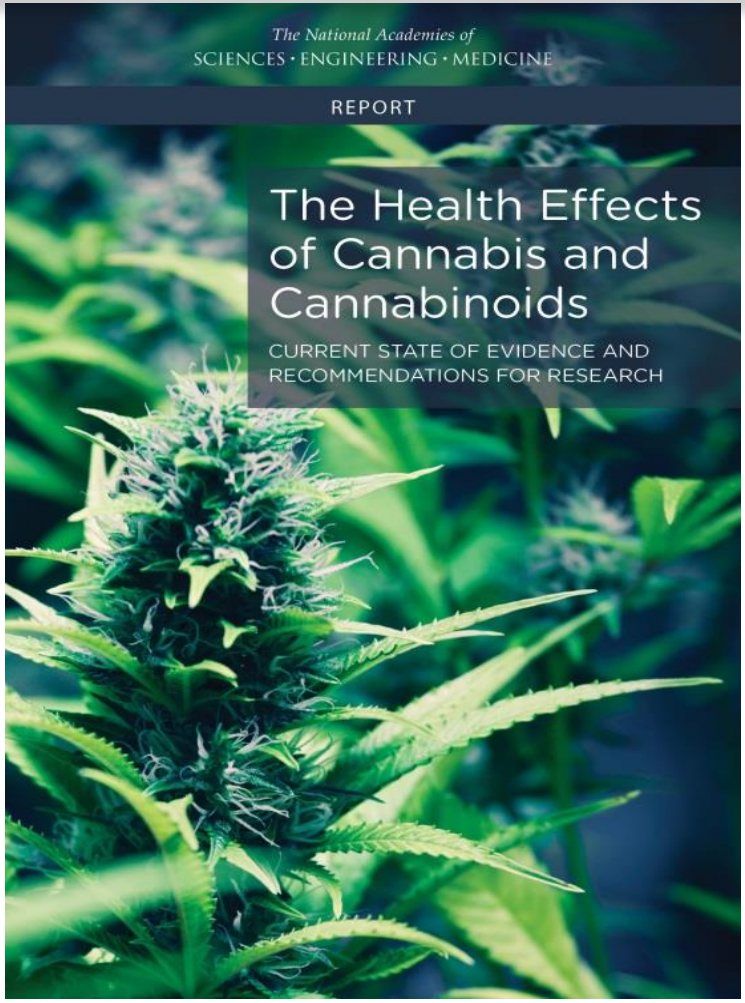
Pharmaceutical: Synthetic, Oral

- 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 trials, fast tracked by FDA in April, 2014
- Epidiolex (cannabidiol)
  - Purified liquid extract
  - Anticonvulsant for Dravet syndrome of childhood
  - Recently approved by FDA
    - DEA placed in Schedule IV

2017 Comprehensive Summary



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Findings: Therapeutic Effectiveness

- Conclusive or substantial evidence
  - Chronic pain
  - Anti-emetics in chemotherapy
  - Spasticity of multiple sclerosis
- Moderate evidence
  - Short-term sleep outcomes associated with sleep apnea, fibromyalgia, chronic pain, MS (nabiximols)
- 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

Medications for Withdrawal

- Dronabinol (Marinol)
  - Synthetic pharmaceutical THC
  - Reduction in withdrawal symptoms using 20 mg twice daily
  - Extended use: no improvement in long-term outcomes
- Nabiximols (Sativex)
  - Botanical pharmaceutical, 1 to 1 mix of THC and CBD
  - Same result as dronabinol

Medical Cannabis in Maryland

Laws and Regulations

- Law enacted 2013 and 2014, amended 2015
  - 2015. Comments submitted by MedChi
- Regulated by Maryland Medical Cannabis Commission
  - Updates and answers to FAQs at: mmcc.maryland.gov
- Process
  - Provider must register
  - Producers and dispensaries must be licensed
  - Patients must register
  - Provider 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

Qualifying Conditions

- Cachexia
- Anorexia
- Wasting syndrome
- Severe or chronic pain
- Severe nausea
- Seizures
- Severe or persistent muscle spasms
- Glaucoma

❖ Post-traumatic stress disorder (PTSD)

❖ Another chronic medical condition which is severe and for which other treatments have been ineffective

By Provider (October 2018)

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

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By Location (Patients: 64K , 300/Day)

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 Georges	2057	15	**7**	13	

By Conditions (May 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

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Some Early Concerns

- Dispensary staff
  - Not following physician recommendations
  - Onsite professional consultation variable
- Amount of cannabis dispensed
  - Default amount may be excessive
    - 120 grams of dried plant or 36 grams of extract

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Summary

- Cannabis has medicinal value, especially for chronic pain and muscle spasms
  - 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

Thank You

Questions?

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