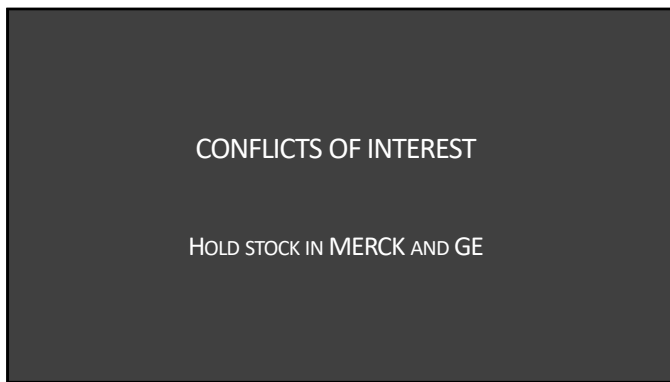
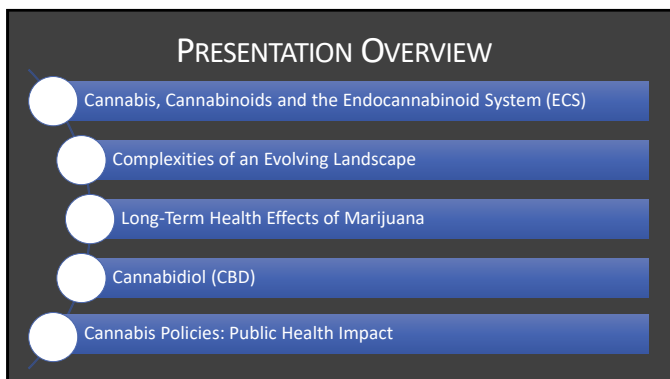


1

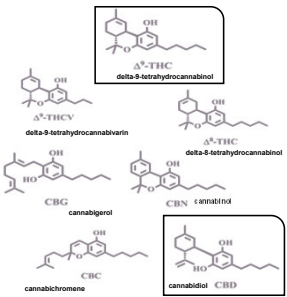


2




3

CANNABIS CONTAINS >120 CANNABINOIDS
PLUS OTHER CHEMICALS IN VARYING CONCENTRATIONS




- Plant with *long history of use* worldwide
- Illegal* under US Federal law (Schedule I substance)
- Legal for medical use* in 36 States + D.C.
- Legal for adult use* in 18 States + D.C.
- Low THC products *legal for medical use* in 11 States
- CBD from Hemp* (defined as cannabis sativa <0.3% THC) no longer falls under the Controlled Substances Act (CSA)
- Versions of *active ingredients* approved (or in clinical trials) for medical indications in U.S. and other countries
 - Synthetic - Marinol, Syndros, Cesamet
 - Plant Derived - Sativex (THC/CBD)
 - Plant Derived-Epidiolex (CBD: FDA approved; not scheduled)



4

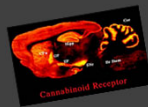
MARIJUANA'S ACUTE EFFECTS: INTOXICATION PHASE

- Euphoria
- Appetite stimulation
- Altered perception of time
- Heightened sensation
- Impaired coordination and balance
- Increased heart rate: 20 - 100%
 - Some evidence for increased risk of heart attack, strokes
- Increased risk of accidents (~2 fold), higher when combined with alcohol
- Cognition
 - Impaired short-term memory
 - Difficulty with complex tasks
 - Difficulty learning
- Executive Function
 - Impaired decision-making
 - Increased risky behavior
- Mood (especially after high doses or edibles)
 - Anxiety – panic attacks
 - Psychosis – paranoia



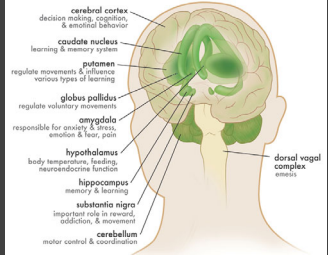
5

CANNABINOID RECEPTORS ARE LOCATED THROUGHOUT THE BRAIN



Regulation of:

- Brain Development
- Memory & Cognition
- Movement Coordination
- Pain Regulation & Analgesia
- Immune Function
- Appetite
- Motivational Systems & Reward

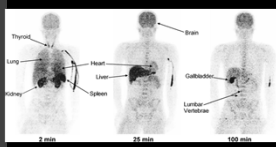


Source: Canadian Consortium for the Investigation of Cannabinoids, <http://www.cciic.net/>

6

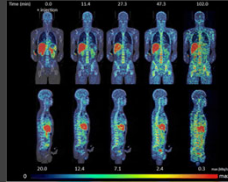
CANNABINOID RECEPTORS ARE ALSO LOCATED THROUGHOUT THE BODY

Whole Body Distribution of CB1 Receptors (2, 25, and 100 min after injection of ^{11}C -MePPEP)



Terry et al., Eur J Nucl Med Mol Imaging, 2010

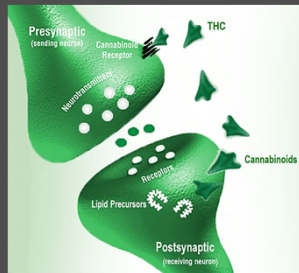
PET images of ^{11}C -NE40 (CB2R radioligand)



Ahmad et al., Mol Imaging Biol, 2013 A

7

ENDOCANNABINOID SYSTEM

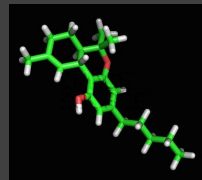


Endocannabinoids are produced *on demand*. They travel back to the transmitting neuron to dampen further activity.

8

MARIJUANA: MOST COMMONLY USED "FEDERALLY" ILLICIT DRUG IN THE U.S.

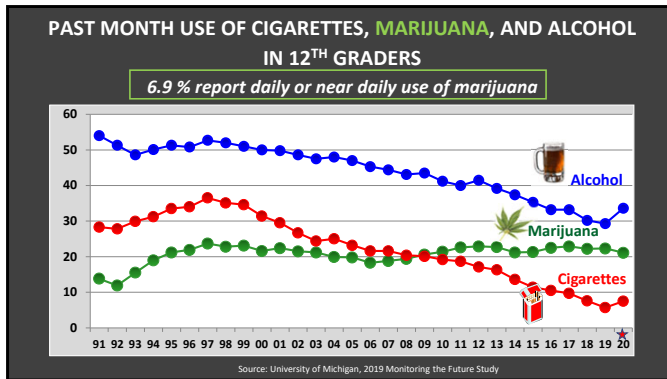
- Almost **32 million** Americans 12 and older report past month use.
- Approximately **4.8 million** Americans met criteria for cannabis use disorders in 2019.
- An estimated **3.5 million** Americans used cannabis for the first time; **1.4 million** were between the ages of 12 and 17.



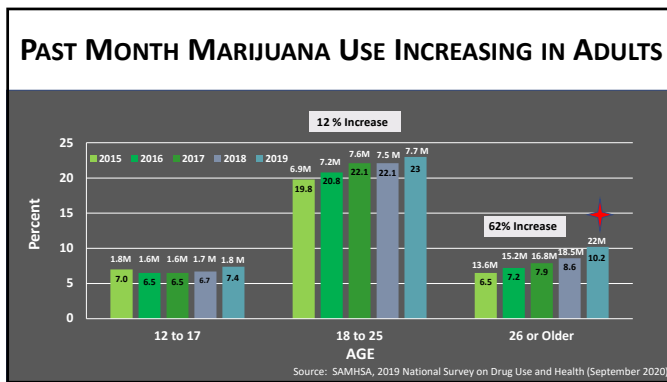
Tetrahydrocannabinol (THC)
Psychoactive Ingredient in Marijuana

Source: 2019 National Survey on Drug Use and Health, SAMHSA

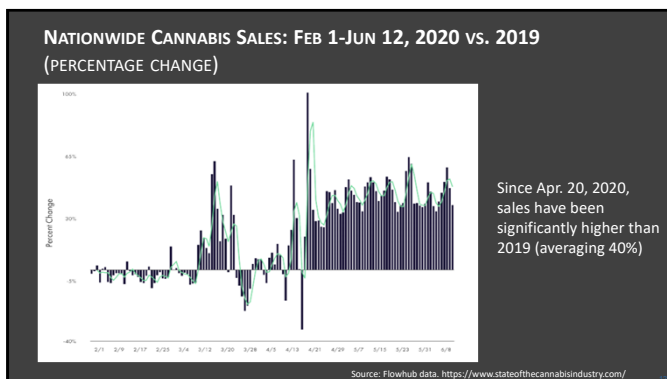
9



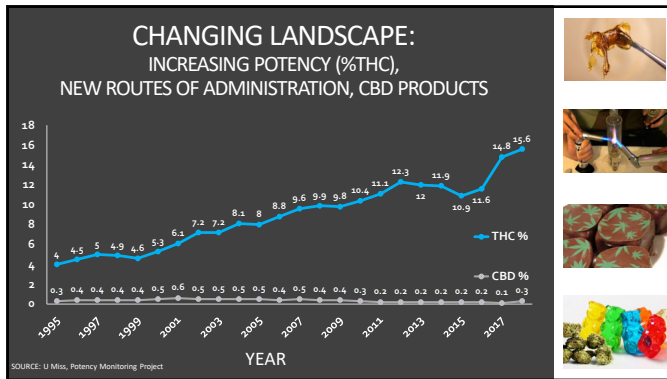
10



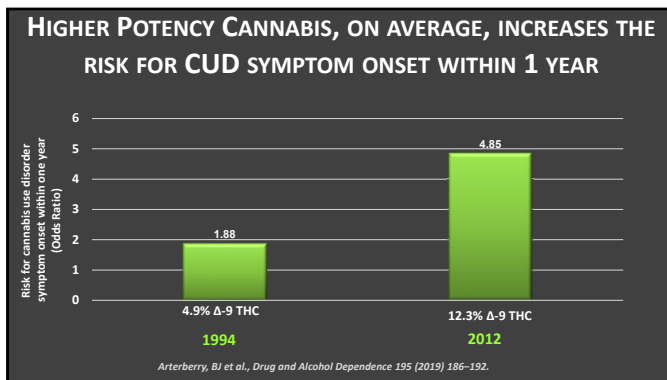
11



12



13

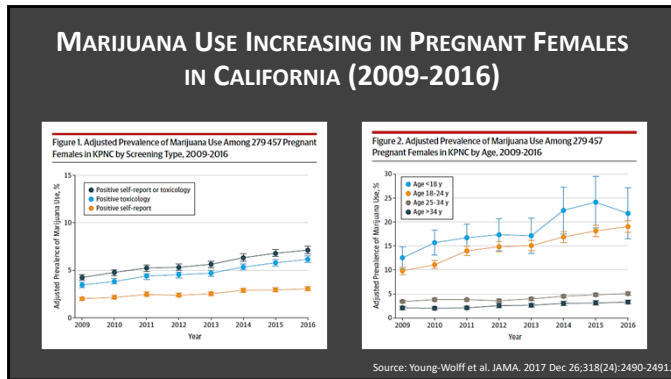


14

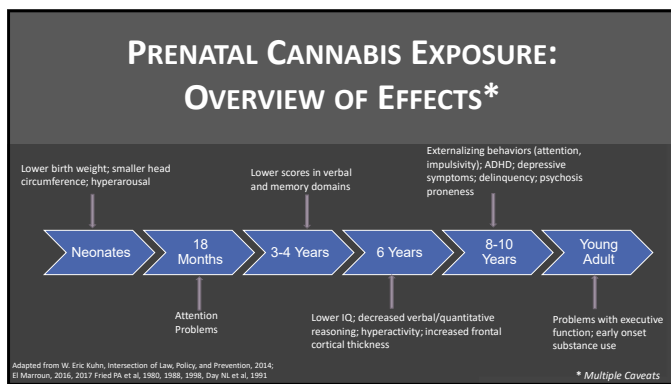
LONG TERM HEALTH CONSEQUENCES:
MENTAL HEALTH, COGNITION, PRE/POST NATAL EXPOSURE EFFECTS, SUBSTANCE DISORDERS

WE NEED MORE INFORMATION ON LONG TERM HEALTH IMPACT, PARTICULARLY WITH RESPECT TO **CAUSALITY**.

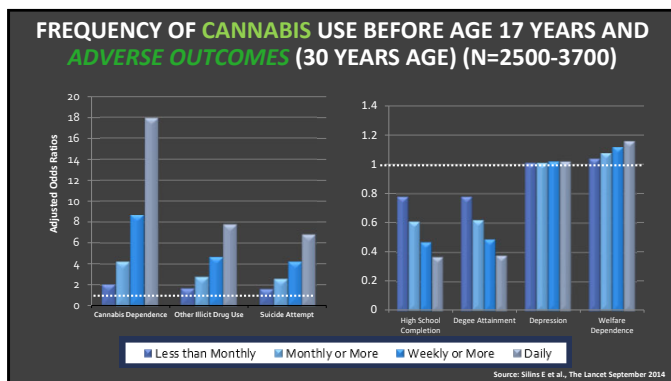
15



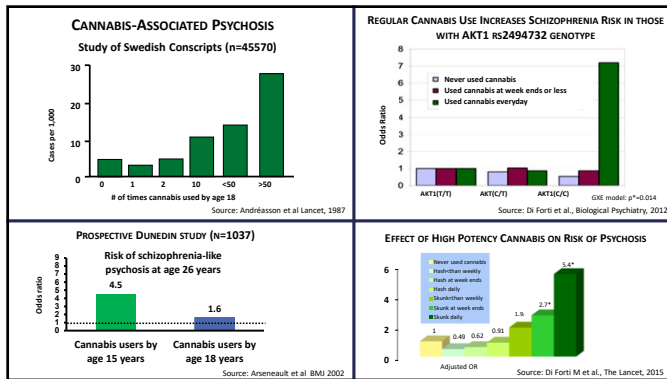
16



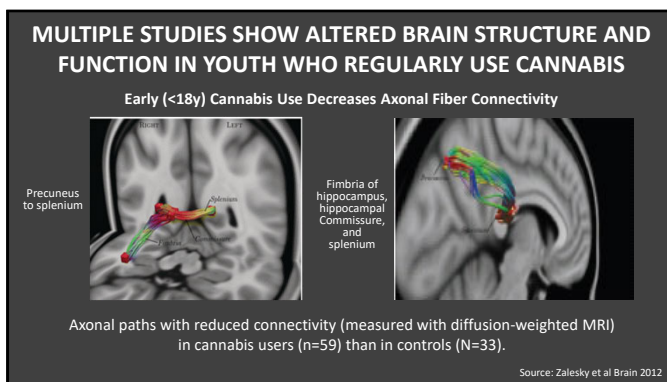
17



18



19




20

CANNABIS: RISKS FOR ADVERSE NEURODEVELOPMENTAL OUTCOMES

- Some populations more vulnerable than others: those exposed pre- or postnatally, adolescents, individuals with mental disorders
- Several cohort studies have documented modest neurodevelopmental deficits in children, adolescents, and young adults who were prenatally exposed to cannabis (multiple caveats)
- In adolescents: effects on learning, IQ, motivation, long term academic and career outcomes
 - But.....heavy using adolescents often use multiple substances
 - And....we don't know whether effects persist if cannabis use is stopped

21



CANNABIS: RISKS FOR ADVERSE NEURODEVELOPMENTAL OUTCOMES

Biological plausibility:

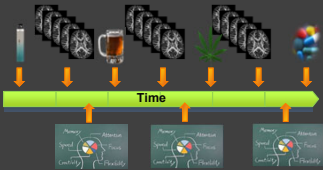
- Cannabinoids cross the placenta and accumulate in fetal tissues, especially brain
- Also found in breast milk
- Endocannabinoid system (ECS) is important for neural development, glial differentiation, axonal migration, myelination, etc.
- Human imaging studies report alterations in CB1 receptor-rich brain areas following cannabis exposure
- Human fetal imaging studies find alterations in dopamine D2 receptors
- Preclinical studies of prenatal/adolescent exposure show lasting effects of THC on adult drug seeking, stress responses, brain reward systems, which may involve epigenetic mechanisms, and are exacerbated by stress exposure.

22

ADOLESCENT BRAIN COGNITIVE DEVELOPMENT (ABCD) STUDY

A Federal Collaboration: NIDA, NIAAA, NCI, NIMH, NIMHD, NICHD, NINDS, OBSSR, ORWH, CDC-DASH, CDC-DVP, DOJ, NEA

Ten year longitudinal study of ~12,000 children from age 10 to 20 years to assess effects of childhood experiences, including use of *cannabis* and other substances on individual brain development trajectories



Time

23

WHAT DO WE KNOW NOW?

- Risks during intoxication:
 - Psychosis/paranoia
 - Cardiovascular events/Postural hypotension
 - Driving Accidents: slowed reaction time/attention deficits (worse combined with alcohol)
- High Potency Products:
 - Risk of adverse reactions, especially in naïve users; or those exposed accidentally
- Risks of Chronic Use (especially in those exposed prenatally or in adolescence)
 - Cannabis Use Disorder
 - Other Substance Use Disorders
 - Mental Illness, especially psychotic disorders; suicidal ideation
 - Poorer academic achievement, financial success, and life satisfaction
 - Hyperemesis Syndrome
- Prenatal exposure: low birthweight, modest effects on brain development and behavioral outcomes through early adulthood.

24

What is Cannabidiol (CBD)?

- Constituent of the cannabis plant (hemp or marijuana)
- Does not have intoxicating effects
- May counteract some adverse effects of THC
 - Bred out of "high potency" cannabis
- Multiple mechanisms of action
- May have a wide range of medical and other health uses
 - Few clinical trials (except epilepsy)
- FDA-approved medication (Epidiolex) for severe childhood epilepsies.
- Widely available in dietary supplement, foods, cosmetics, veterinary products—*not FDA regulated*



25

HEALTH BENEFITS CBD OIL



Cannabidiol:
Potential
Medical Uses

26

CANNABIDIOL RESEARCH: CURRENT INVESTMENTS AND FUTURE NEEDS


NIH: 105 active studies

CLINICAL TRIALS.gov: 8/2021: 148 active studies (10 Federally funded)



- **BASIC SCIENCE:** Mechanisms of action; pharmacokinetics; pharmacodynamics
- **THERAPEUTIC POTENTIAL:** Addiction: OUD, Alcohol, Nicotine; Social Anxiety, PTSD, Digestive Disorders, Cancer, Pain, Epilepsy, Sleep
- **SAFETY CONCERNS/RISKS:** Neurodevelopment, drug/drug interactions, long-term and cumulative exposure to multiple products, liver toxicity, vulnerable populations (e.g., pregnant women)


27



CBD LEGAL STATUS: AGRICULTURE IMPROVEMENT ACT 2018 (FARM BILL)

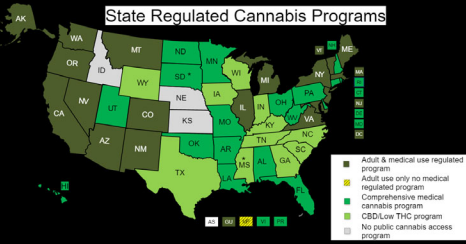
- Removed Industrial Hemp (defined as cannabis sativa plant containing less than 0.3% THC) from Controlled Substances Act
- Re-affirms the regulatory role of the FDA for hemp – derived products
 - Medications (to treat illnesses or symptoms)
 - Dietary Supplements (wellness)
 - Food Additives
- Public Hearing: May 31, 2019 >120 speakers provided input as FDA considers how to go about regulating CBD; public comments still being solicited to assist FDA in regulating CBD.
- CBD: A multibillion \$ industry
- Concerns re: current market: Unregulated Products; Unverified Claims; Uninformed Users (e.g., side effects, drug interactions).

FDA seeking "real world data" to establish safety, including long term studies



28

U.S. STATE CANNABIS LAWS



National Conference of State Legislators (NCSL), 2021

States with MML vary on:

- Allowable conditions and routes of administration
- Dispensaries/home growth and registries
- Testing, regulatory requirements

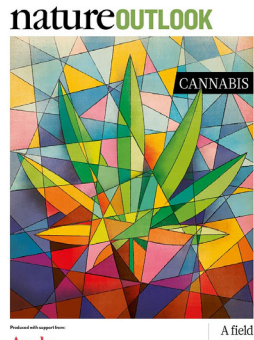
States with Adult Use Laws vary on:

- Marketing, product labeling, distribution (home growth, delivery)
- Public consumption
- Taxation
- Licensing
- Expungement and Equity

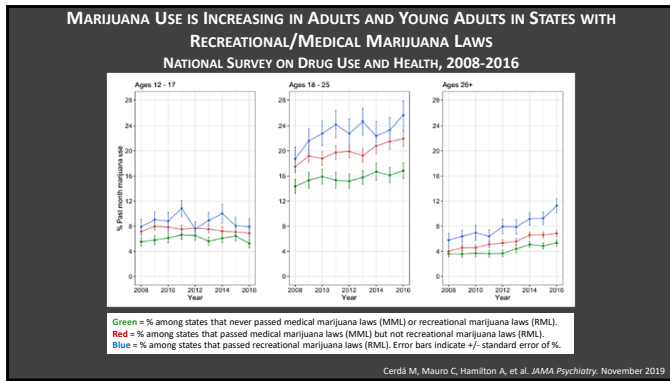
29

WHAT IS THE IMPACT OF LEGALIZATION?

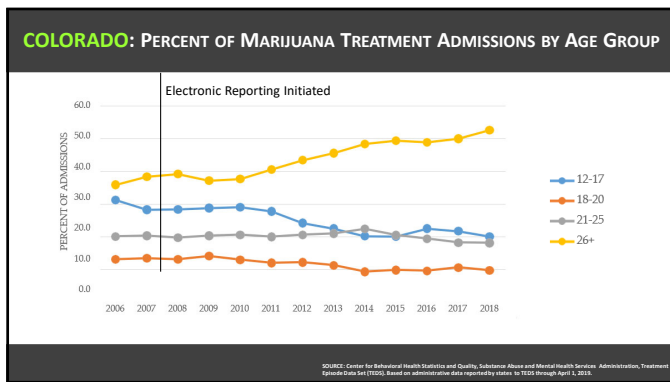
- Use, Harmful Use, Use Disorders
- Mental Health**
- Other Substance Use
- Academic Achievement
- Child/Adolescent Development**
- Accidents, ER Visits
- Other Health Effects (e.g., lung)
- Secondhand Smoke
- Pregnancy Outcomes**
- Productivity
- Economics (Revenue vs. Costs)
- Criminal Justice Disparities
- Benefits



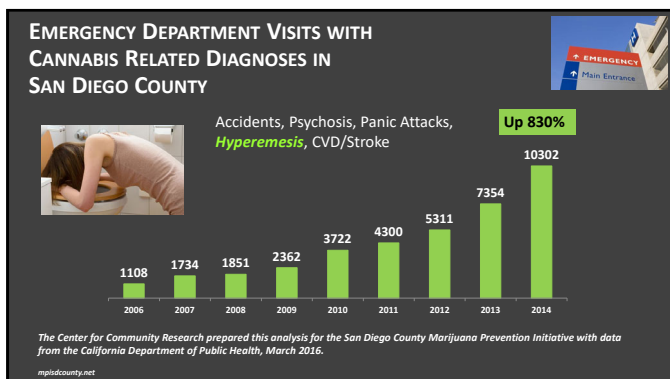
30



31



32



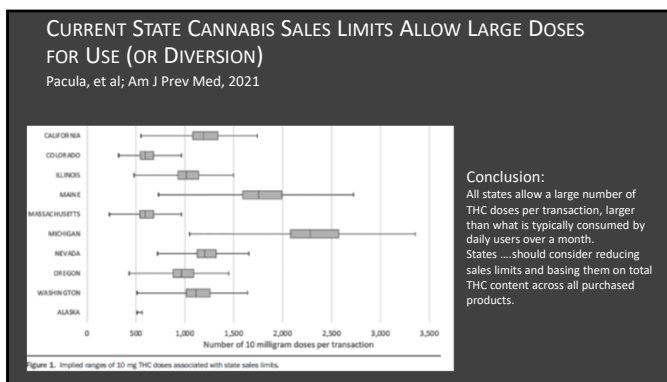
33

*Secondhand Cannabis Smoke
San Francisco, 2017...*



"NOW SERVING CANNABIS FOR BRUNCH"
In S.F., gourmet fare infused with artisanal weed offers medicated spreads to new connoisseurs" –
SF Chronicle 1/22/17
(slide courtesy of Matt Springer, UCSF)

34



35

REGULATIONS MATTER



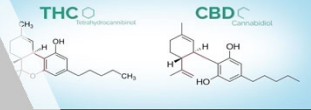
- Regulatory Scheme (full commercialization in most states)
- Product Availability
- Serving Sizes/Potency Limits
- Marketing Restrictions
- Labeling Requirements (health warnings)
- Product Testing/Allowable Ingredients
- Smoke – free laws
- Consumption sites
- Licensing requirements
- Taxes (how much and where does the money go?)
- Social Equity
- WHO IS MAKING THESE DECISIONS?

36

CANNABIS RESEARCH BARRIERS

SCIENTIFIC

- Complexity of plant (120 + cannabinoids + other components), entourage effect?
- Dosing/Route of administration
- Need proper controls, sufficient study duration (blinding, driving...)
- Should be learning from what is already happening in the states and in other countries (e.g., patient registries; adverse outcomes; medical benefits).
- Should be studying products that people are using to understand full range of health consequences.
- Need better measures of use/harmful use, including products, potency, and frequency of use.
- Standardized unit (THC) for research.



37

HOW CAN *SCIENCE* INFORM *POLICY*?

- Need to acknowledge the polarized nature of the issue and encourage reasonable (unbiased) discourse.
- Need to be explicit and clear about what we know, what we think we know, and what we don't know.
- Research needs to answer real world questions: E.g., does cannabis legalization impact the opioid epidemic? Is there a potency limit that should be imposed? Should certain products be prohibited? How dangerous is prenatal exposure to cannabis?
- Need to be precise in our terminology: distinguish cannabis (the plant) from cannabinoids (plant derived or synthetic); cannabidiol (CBD) vs. other medicinal preparations.
- Help ensure that the public health interests are front and center when regulations are developed.
- Need to better disseminate the knowledge that we have.

38



39
