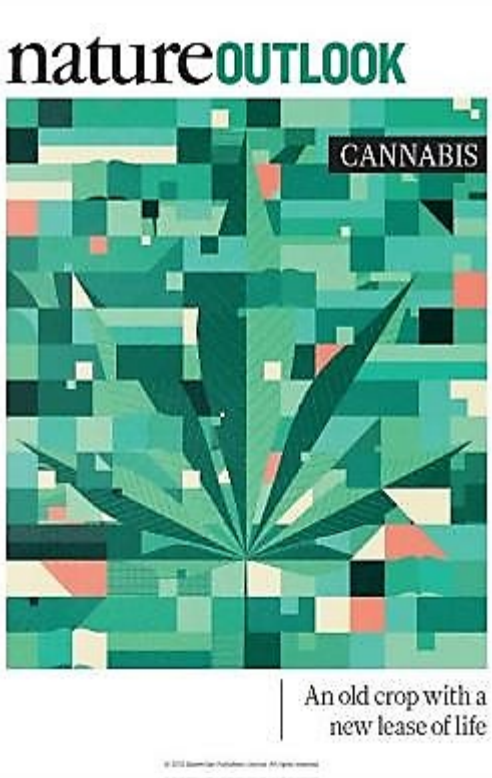
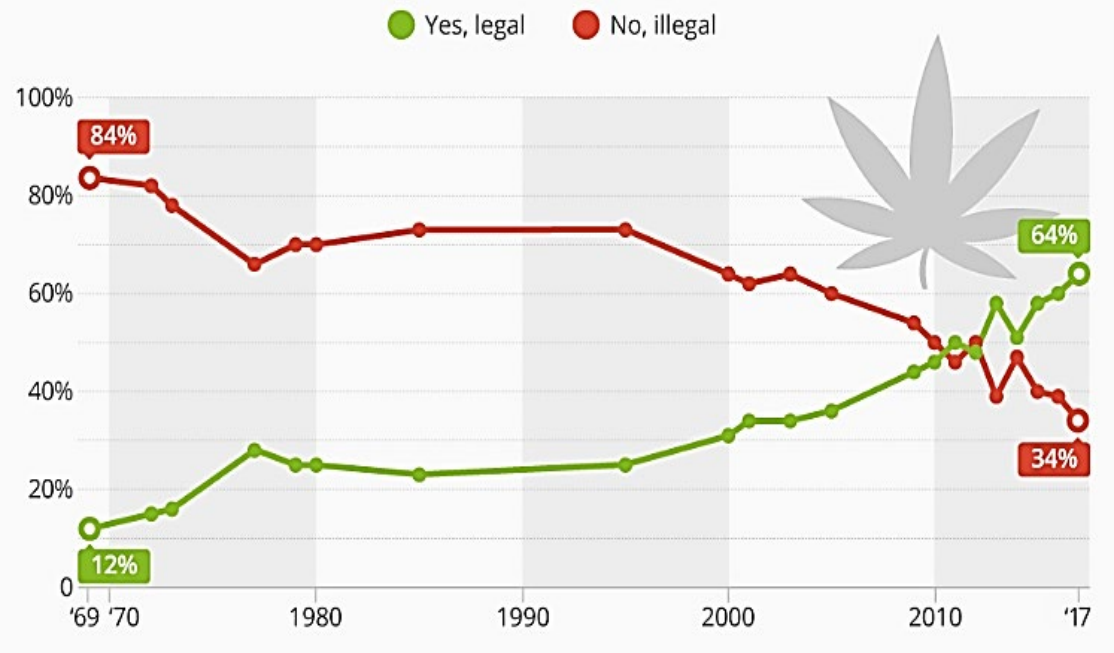


NIH RESEARCH ON CANNABIS AND ITS CONSTITUENTS

Steven Gust, Ph.D.
Office of the Director
National Institute on Drug Abuse

NIH National Institute on Drug Abuse

PUBLIC OPINION ON CANNABIS IS CHANGING



- Public Opinion
- Economic Considerations
- Interest Groups:
  - *Pro* and *Con* Legalization
- Lobbying and Other Political Activity
- Media
- Federal Agencies
- *Science* (*we hope*)

Source: The Pew Research Center/Gallup

STATE CANNABIS LAWS

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).
- Taxation.

FEDERAL POLICY

- Cannabis: Schedule I Substance → Controlled Substances Act (1970): high risk for abuse/dependence; <u>no accepted medical use</u>.
  - Cannabis is illegal to grow, possess, or distribute except under strict government control (DEA licensure) and only for research purposes
  - Currently, international treaties as interpreted by the Dept of Justice limit each nation to a single source of marijuana for research purposes
  - The DEA has designated *NIDA* to be that source using a contract with the University of Mississippi

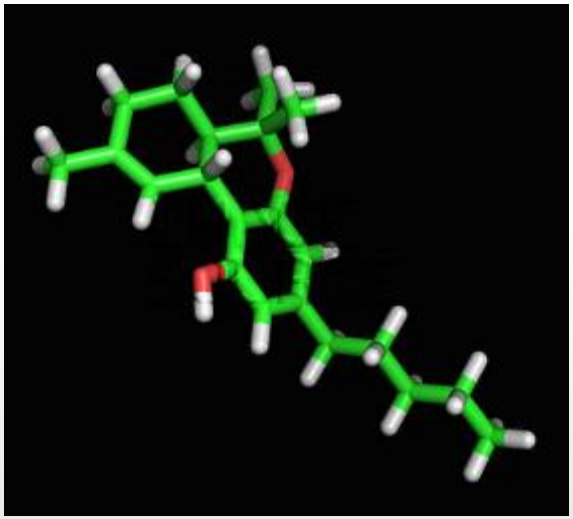
NIDA's Marijuana Farm

CONSEQUENCES OF CONFLICTING FEDERAL AND STATE POLICIES

- INCREASED USE OF NEW AND POTENTIALLY RISKY PRODUCTS
- STATES are developing DIFFERENT APPROACHES to TESTING and LABELING of PRODUCTS
  - What are ALLOWABLE products?
- UNEVEN QUALITY CONTROL, especially for home grown Cannabis
- No NATIONAL Guidance, Oversight, or Monitoring of what States are providing to Patients/Recreational Users
- Proliferation of 'medical' uses without Federal approval and with little research justification
- BARRIERS to RESEARCH
  - SCHEDULE I STATUS
  - SINGLE SOURCE FOR MARIJUANA

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

- Over 26 million Americans 12 and older report past month cannabis use.
- Approximately 4.0 million Americans met criteria for cannabis use disorders in 2017.
- An estimated 3.0 million Americans used cannabis for the first time; 1.2 million were between the ages of 12 and 17.

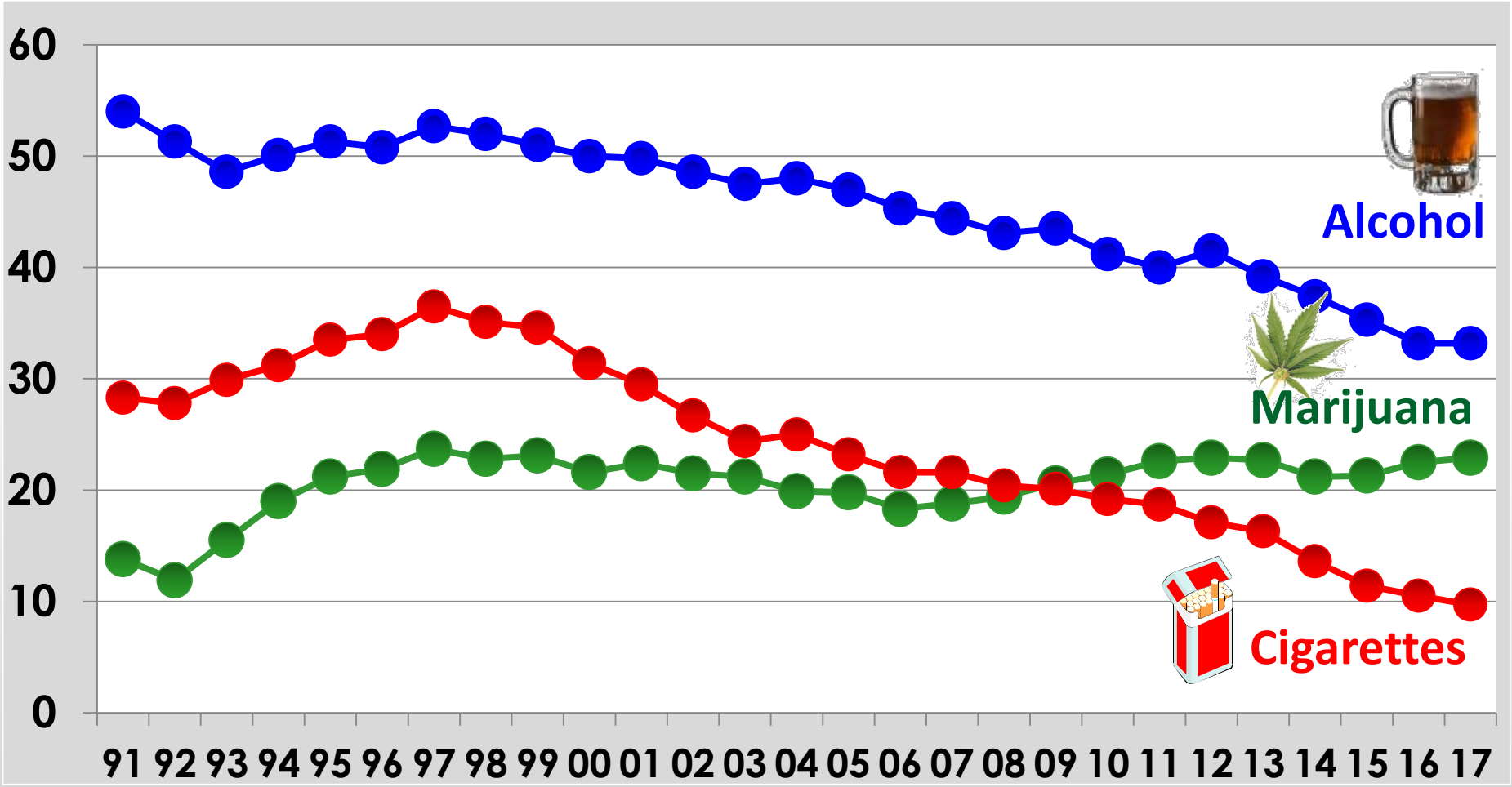


Tetrahydrocannabinol (THC)
Psychoactive Ingredient in Marijuana

Source: 2017 National Survey on Drug Use and Health, SAMHSA

PAST MONTH USE OF CIGARETTES, MARIJUANA, AND ALCOHOL IN 12TH GRADERS

nearly 6% report daily use of marijuana



Source: University of Michigan, 2017 Monitoring the Future Study

CANNABIS' EFFECTS

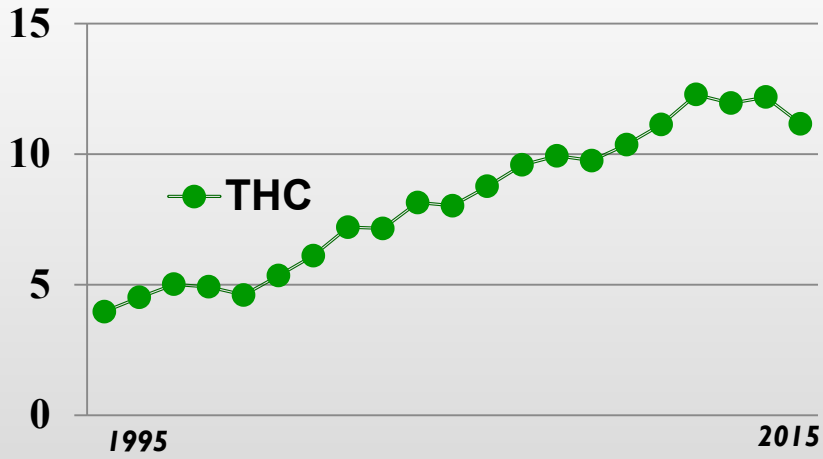
- Intoxication (euphoria)
- Reduced reaction time
- Appetite stimulation
- Altered perception of time
- Impairs coordination and balance
- Increased heart rate: 20 - 100%
  - Some evidence for increased risk of heart attack, may be exacerbated in vulnerable individuals (e.g., baby boomers?)
- Orthostatic (postural) hypotension
- Increased risk of accidents (~2 fold), higher when combined with alcohol
- Hyperemesis (abdominal pain and vomiting)
- Risk of psychosis
- Effects on brain development

CANNABIS' *ACUTE* EFFECTS

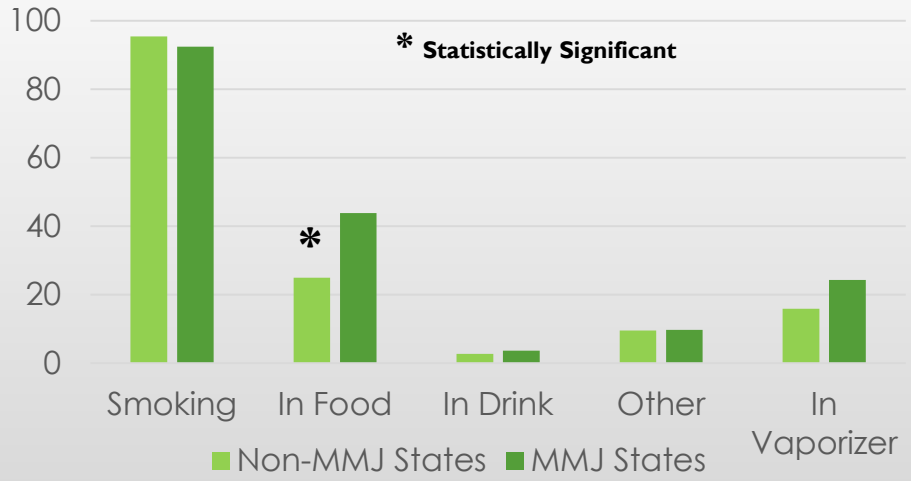
- **Cognition**
  - Impaired short-term memory
    - Difficulty with complex tasks
    - Difficulty learning
- **Executive Function**
  - Impaired decision-making
  - Increased risky behavior – STDs, HIV?
- **Mood** (especially after high doses or edibles)
  - Anxiety – panic attacks
  - Psychosis – paranoia

CHANGING LANDSCAPE:
INCREASING POTENCY & NEW ROUTES OF ADMINISTRATION

THC Potency



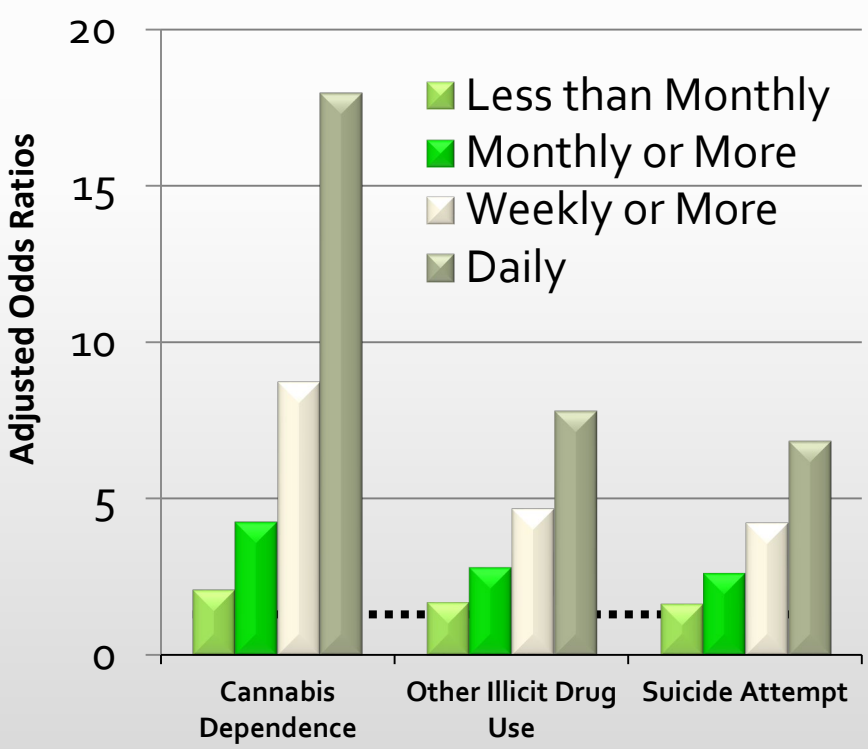
12th Grade Past Year Users

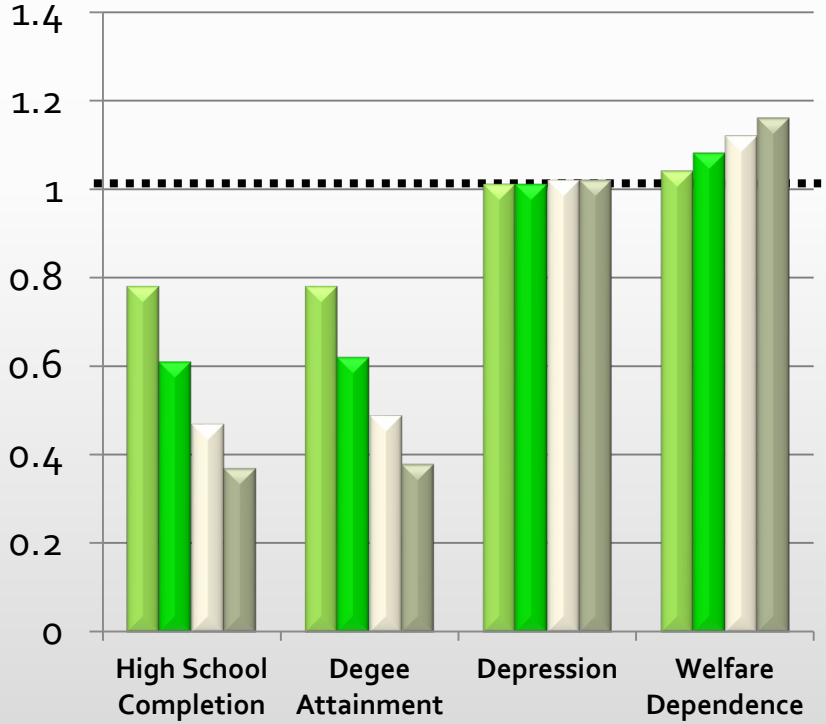


SOURCE: University of Michigan, 2017 Monitoring the Future Study; U Miss, Potency Monitoring Project

FREQUENCY OF CANNABIS USE BEFORE AGE 17 YEARS AND *ADVERSE OUTCOMES* (30 YEARS AGE) (N=2500-3700)

Consistent and dose-response associations were found between frequency of adolescent cannabis use and adverse outcomes

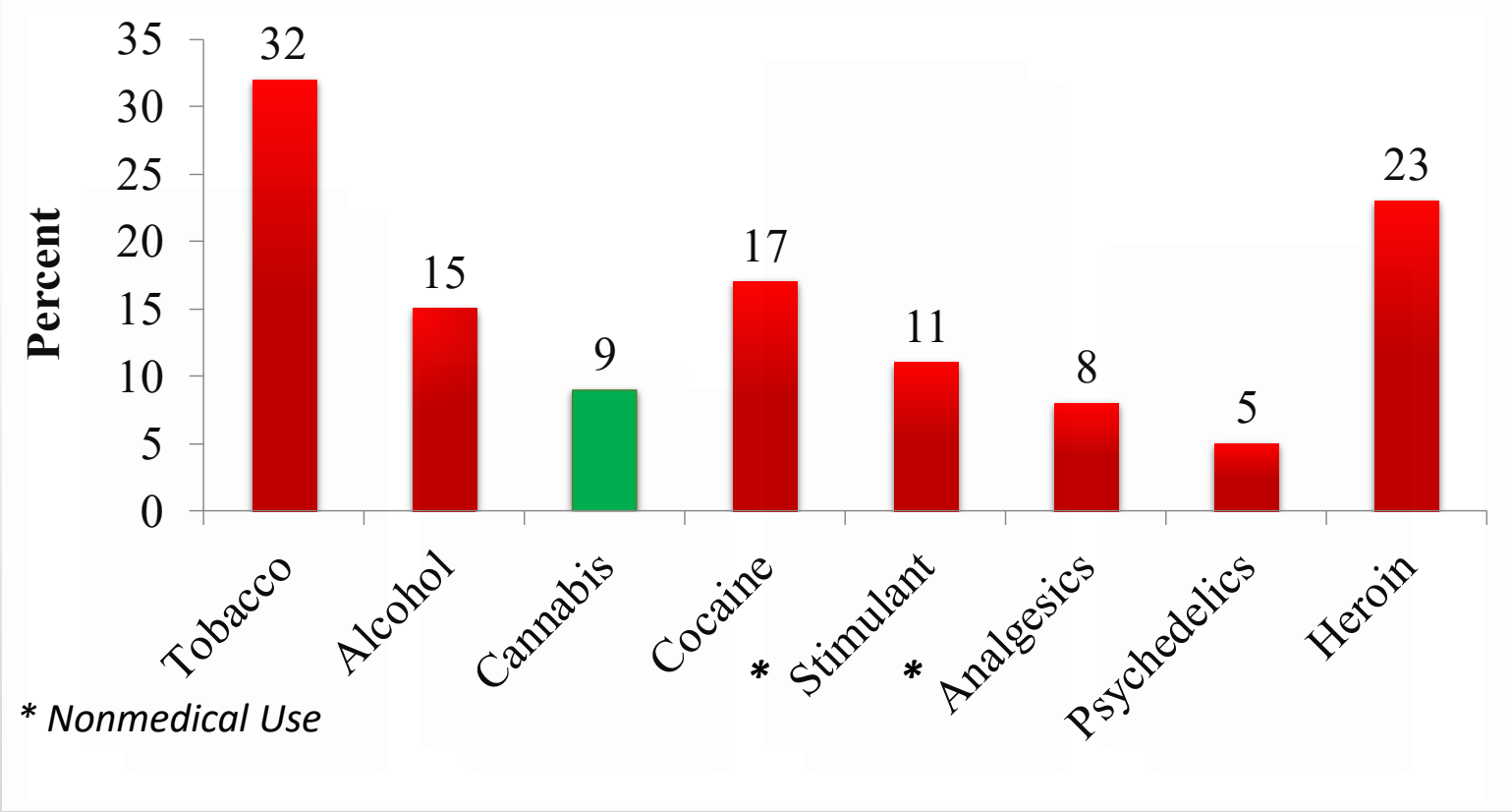




Source: Silins E et al., The Lancet, 2014

ADDICTION: ABOUT 9% OF USERS BECOME DEPENDENT, 1 IN 6 WHO START USE IN ADOLESCENCE, 25-50% OF DAILY USERS

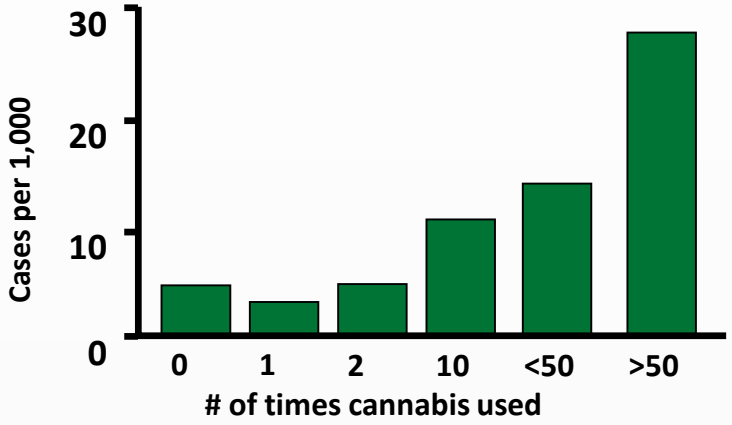
Estimated Prevalence of Dependence Among Users



Source: Anthony JC et al., 1994

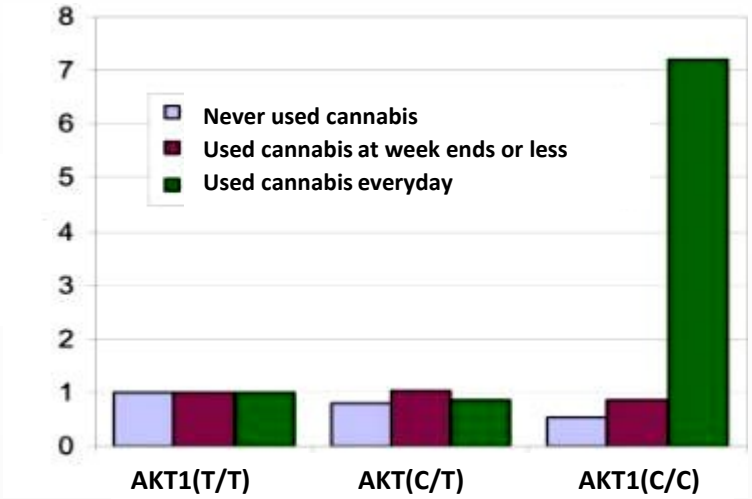
Cannabis-Associated Psychosis

Study of Swedish Conscripts (n=45570)



Source: Andréasson et al Lancet, 1987

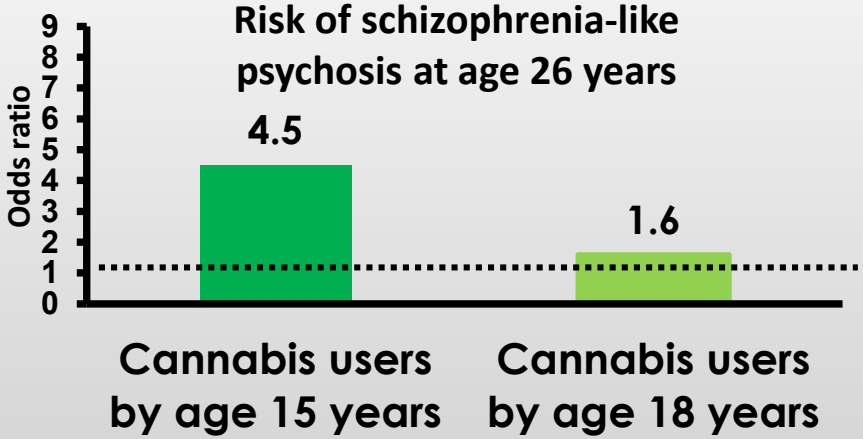
Regular Cannabis Use Increases Schizophrenia Risk in those with AKT1 rs2494732 genotype



GXE model: p*=0.014

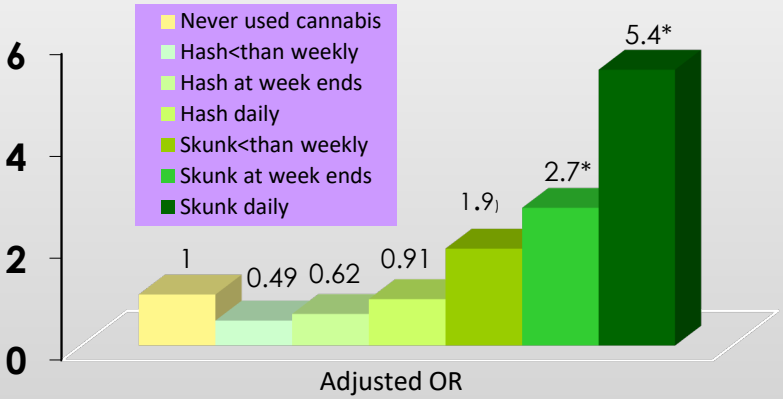
Source: Di Forti et al., Biological Psychiatry, 2012

Prospective Dunedin study (n=1037)



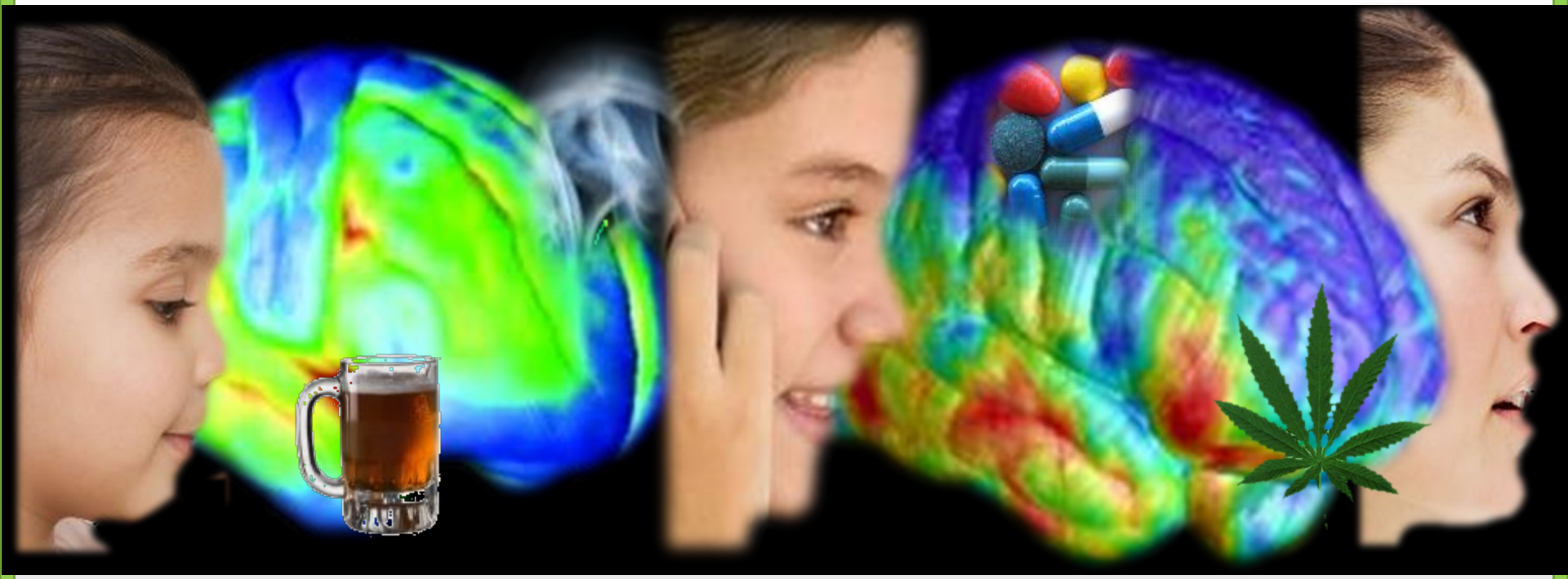
Source: Arseneault et al BMJ 2002

Effect of High Potency Cannabis on Risk of Psychosis



Source: Di Forti M et al., The Lancet, 2015

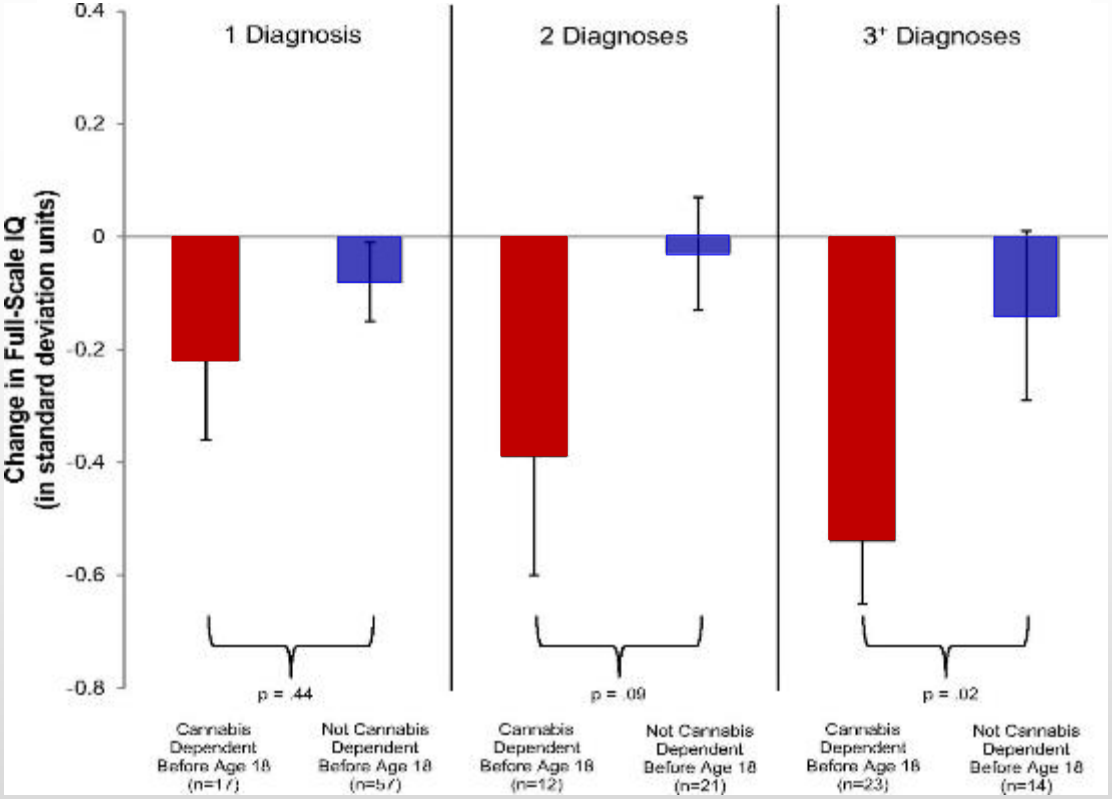
THE BRAIN CONTINUES TO MATURE INTO EARLY ADULTHOOD



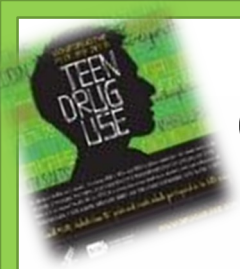
Does **Cannabis** (and other substances) affect the developing brain and an individual's trajectory into adulthood?

COGNITION: PERSISTENT CANNABIS USE DISORDER LINKED TO SIGNIFICANT IQ DROP BETWEEN CHILDHOOD AND MIDLIFE

- Followed 1,037 individuals from birth to age 38
- Tested marijuana use and disorders at 18, 21, 26, 32 and 38
- Tested for IQ at ages 13 and 38



Source: Meier MH et al., PNAS Early Edition 2012.



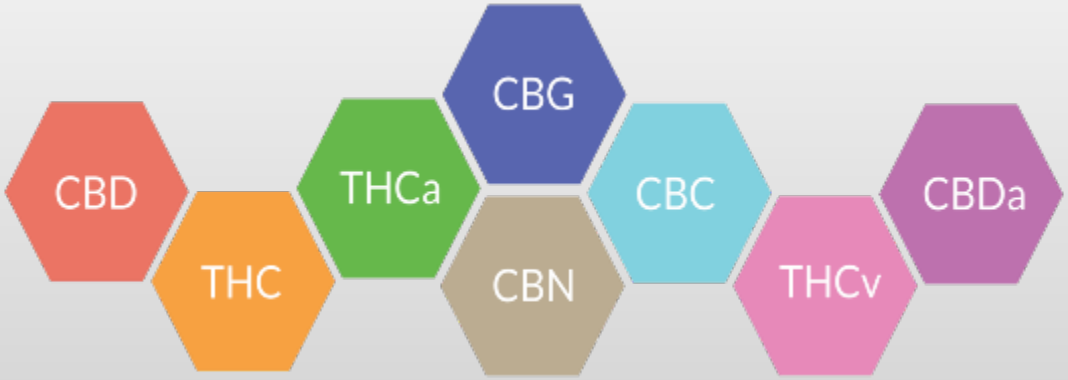
CANNABIS USE AND DEVELOPMENT: PROBABLE FACTS

- Some populations more vulnerable to adverse consequences than others: those exposed pre- or postnatally, adolescents, older adults (?), 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

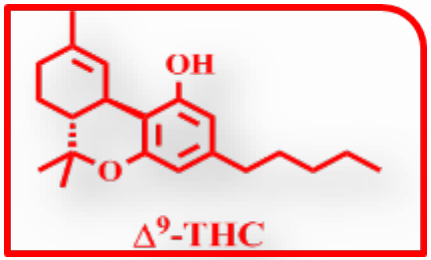
Biological plausibility:

- Cannabinoids are lipid soluble, 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.
- Preclinical studies of prenatal or adolescent exposure show lasting effects of THC exposure on adult drug seeking behavior, stress responses, brain reward systems, which may involve epigenetic mechanisms

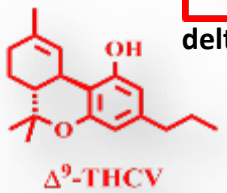
THERAPEUTICS:
PROMISE OF CANNABIS AND THE ENDOCANNABINOID SYSTEM



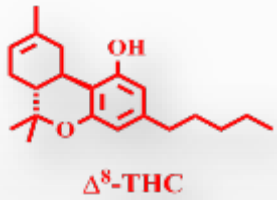
CANNABIS CONTAINS ~100 CANNABINOIDS PLUS OTHER CHEMICALS IN VARYING CONCENTRATIONS



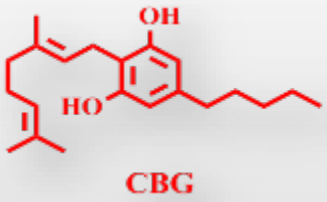
delta-9-tetrahydrocannabinol



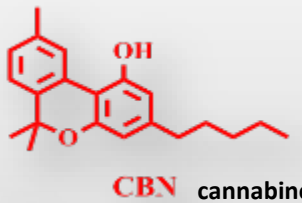
delta-9-tetrahydrocannabivarin



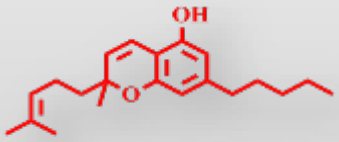
delta-8-tetrahydrocannabinol



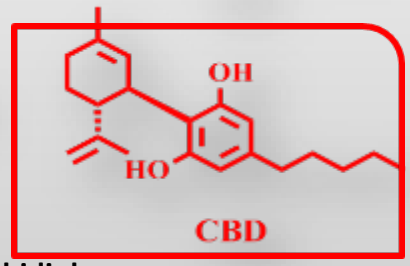
cannabigerol



cannabinol



cannabichromene



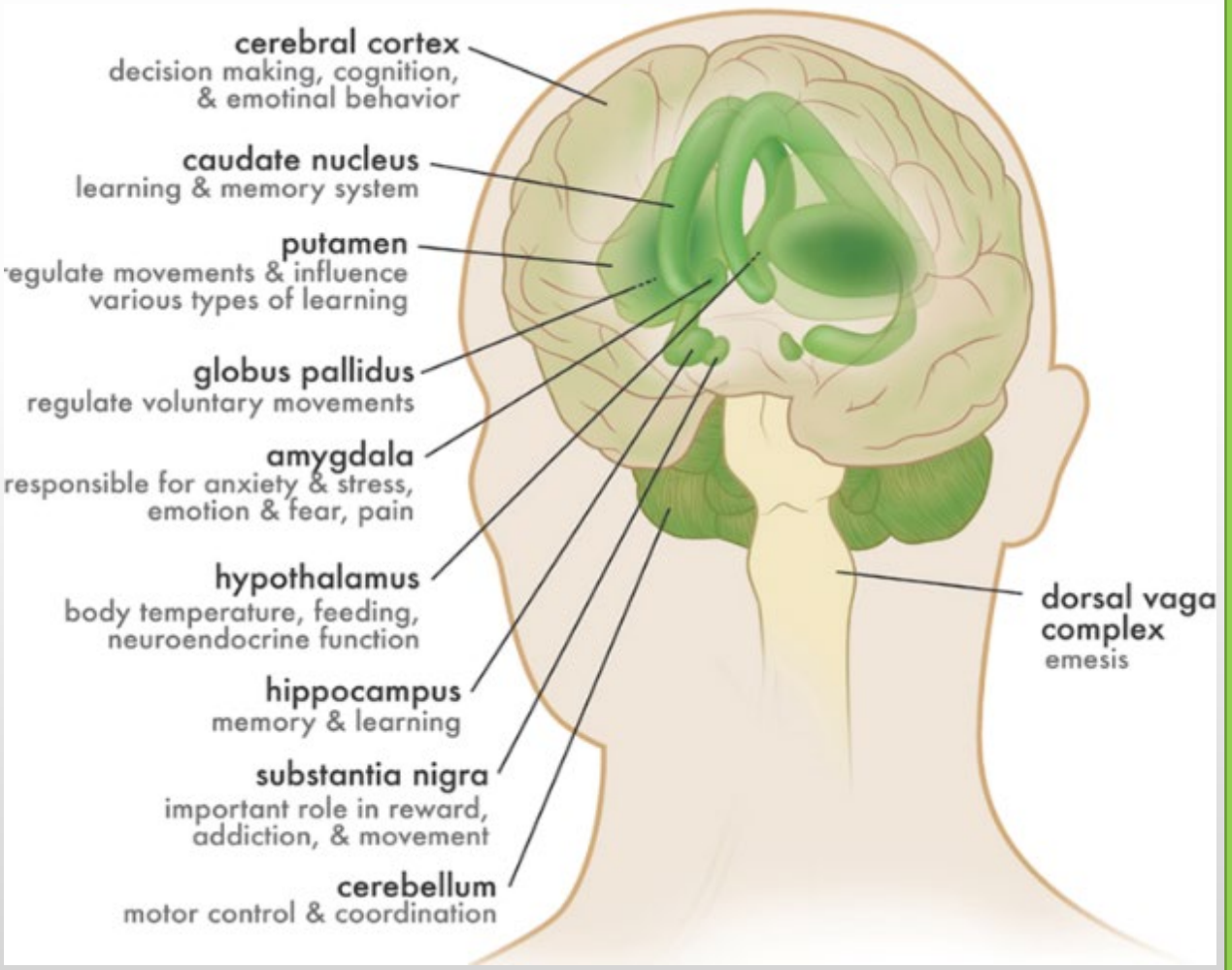
cannabidiol

- Plant with long history of use worldwide
- Illegal under Federal law (Schedule I substance—not FDA approved)
- Legal for medical use in 31 States + D.C.
- High CBD variety (or extracts) legal in 17 states for medical use
- 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, waiting for Scheduling decision)*

CANNABINOID RECEPTORS ARE LOCATED THROUGHOUT THE BRAIN

Regulation of:

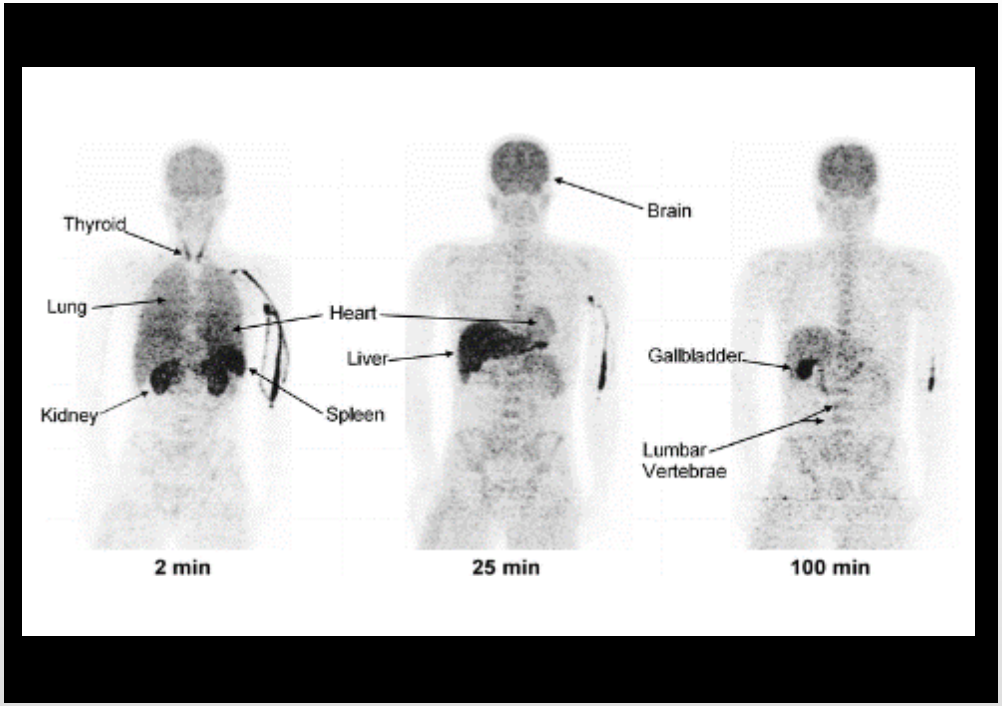
- Brain Development
- Memory and Cognition
- Movement Coordination
- Pain Regulation & Analgesia
- Immunological Function
- Appetite
- Motivational Systems & Reward



Source: Canadian Consortium for the Investigation of Cannabinoids, http://www.ccic.net/

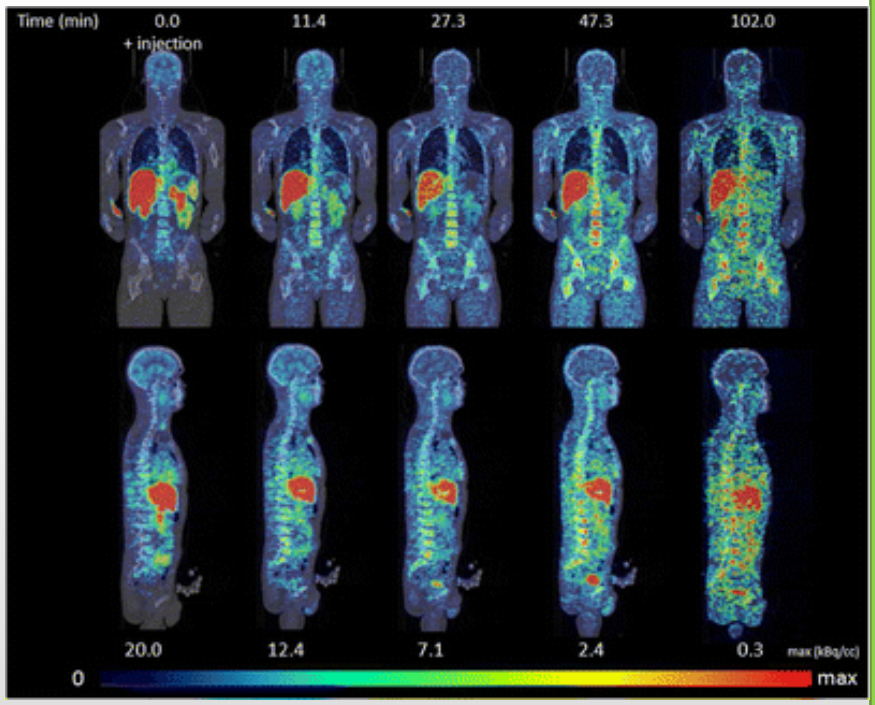
CANNABINOID RECEPTORS ARE ALSO LOCATED THROUGHOUT THE BODY

Whole Body Distribution of CB1 Receptors (11C-MePPEP)



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

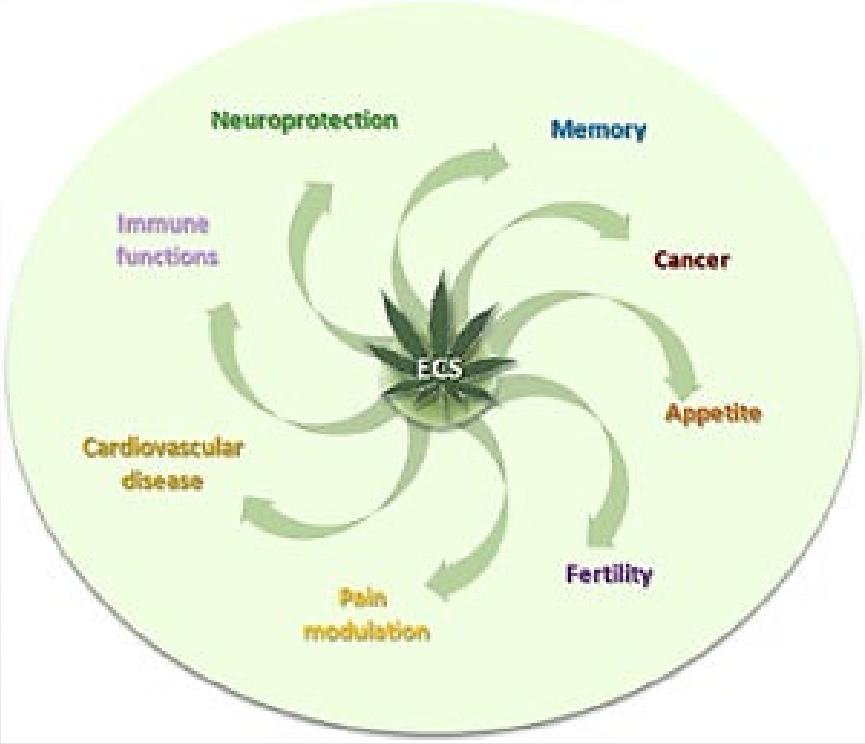
Distribution of CB2 Receptors [11C]-NE40



Source: Ahmad et al., Mol Imaging Biol. 2013 A

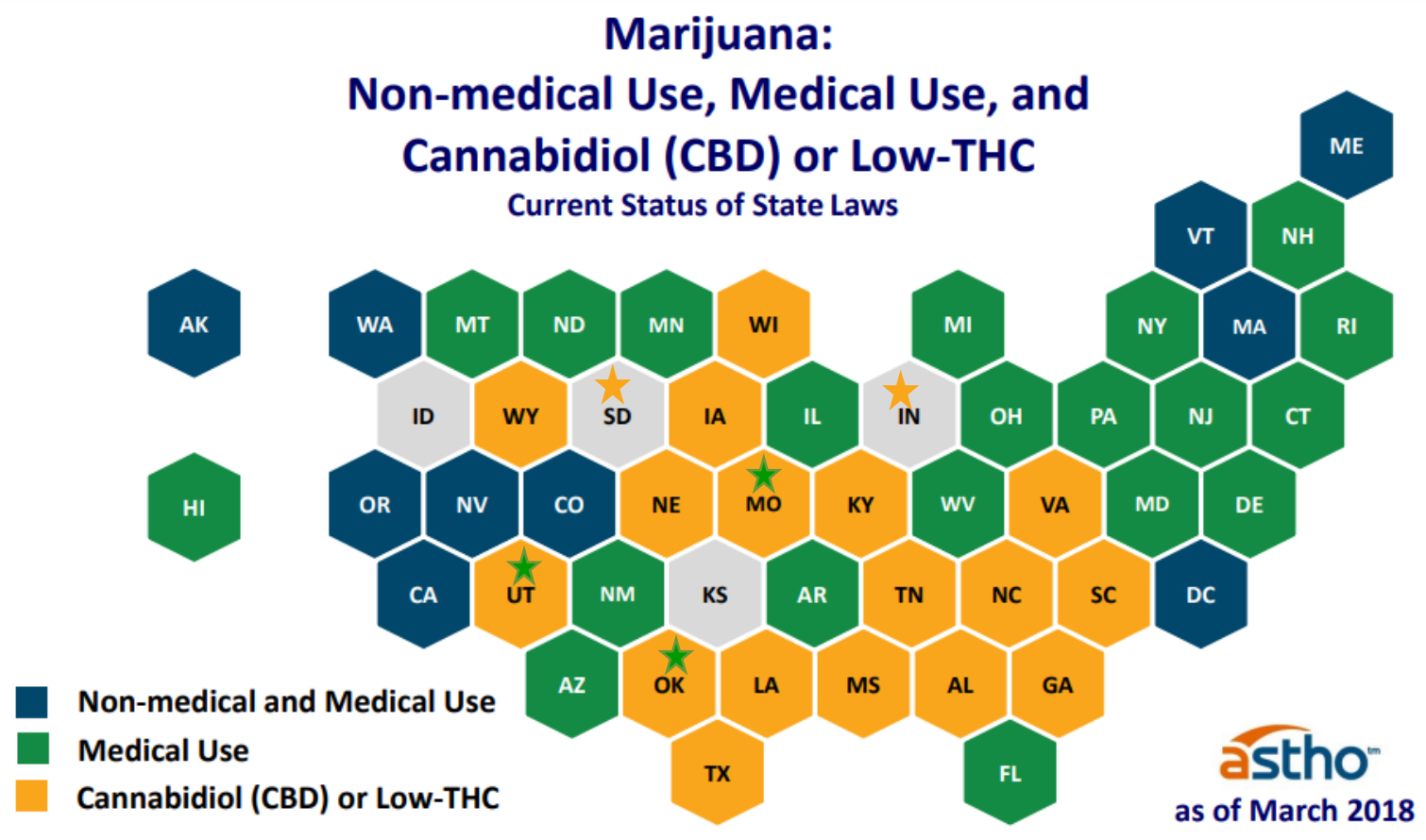
EXPLOITING THE CANNABINOID SYSTEM FOR THERAPEUTIC PURPOSES

- Exogenous compounds
  - Phytocannabinoids
    - THC, CBD, combinations
  - Synthetic cannabinoids
    - Dronabinol, Nabilone
- Endogenous manipulation
  - FAAH inhibitors
  - MAGL inhibitors
  - Allosteric modulators
- Receptor targets
  - CB1, CB2, TRPV1, PPAR, 5-HT, peripheral, others…



Source: Canadian Consortium for the Investigation of Cannabinoids, http://www.ccic.net/

CANNABIS LAWS IN THE US



Changes in 2018

Approved Medical Use
- Missouri
- Oklahoma
- Utah

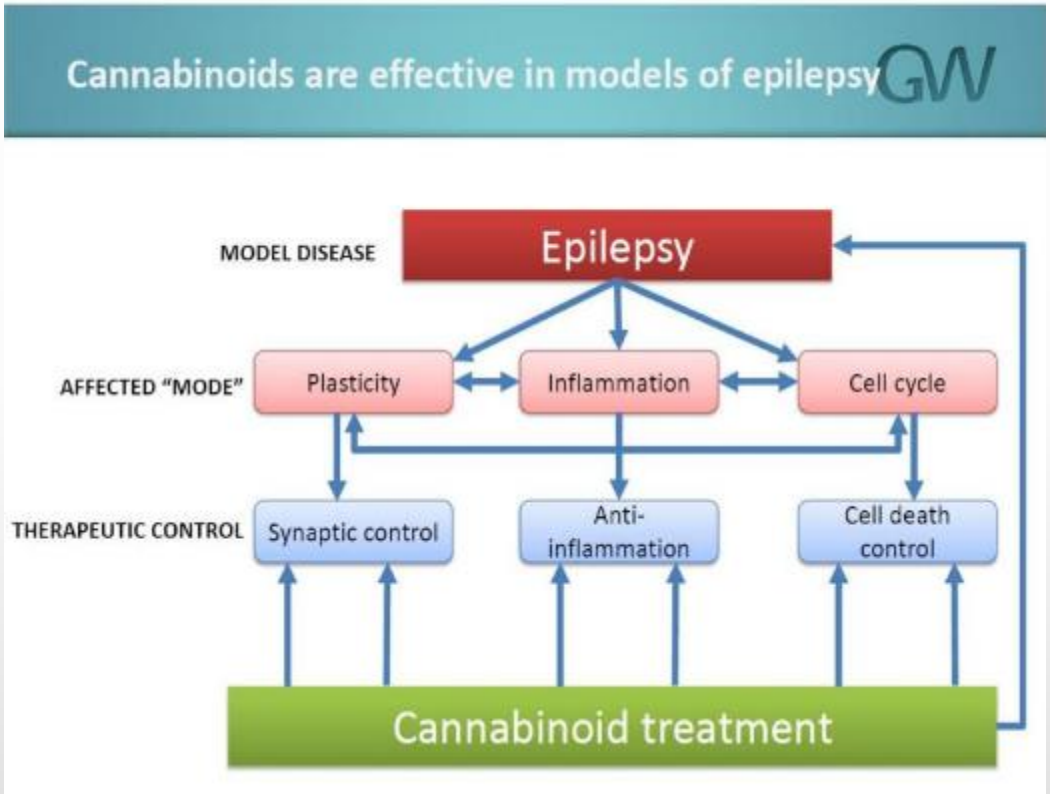
Approved CBD or Low-THC Use
- Indiana
- South Dakota

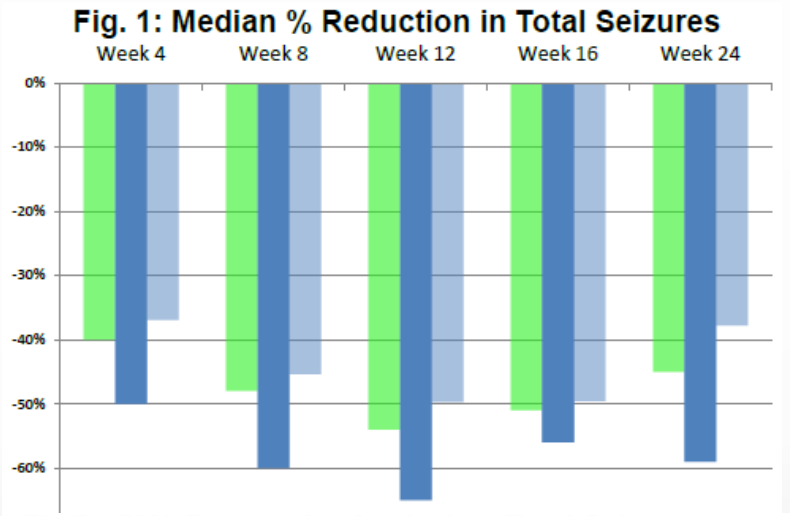
States with MML vary on:
- CBD only vs. broad medical use
- Allowable conditions and routes of administration
- Dispensaries/home growth and registries
- Testing, regulatory requirements

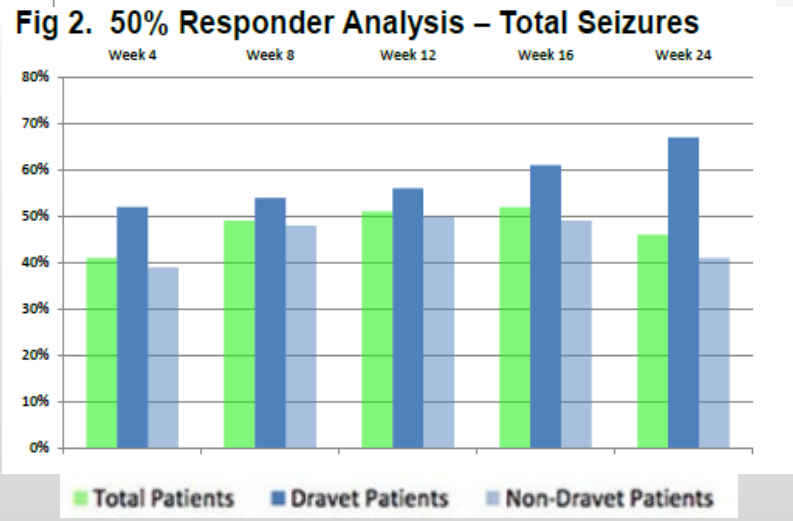
What is Cannabidiol (CBD)?

- Schedule 1 controlled substance (for now)
- *Doesn't* act directly on CB1 or CB2 receptors
- Potential mechanisms of action: 5HT1a receptors; glycine receptors; orphan G-protein coupled receptors; FAAH inhibition; more…
- Does not have rewarding effects
- May counteract some effects of THC
  - Bred out of "high potency" cannabis
- May have a wide range of medical uses
- Strongest evidence of medical benefit: childhood epilepsy (Epidiolex recently approved by FDA; awaiting scheduling decision)

Epidiolex (Cannabidiol) in Tx Resistant Epilepsy







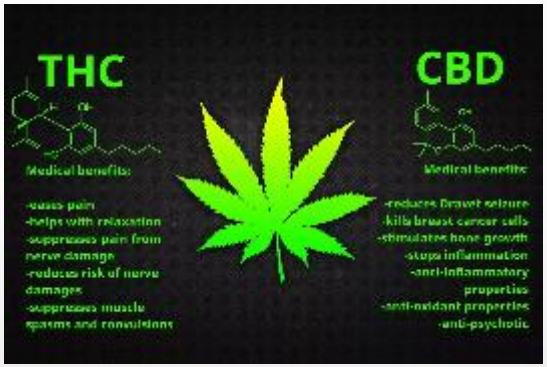
Source: Devinsky O et al., Poster presented at the 2015 Annual Meeting of the American Epilepsy Society.
Funded by GW Pharmaceuticals, the company developing Epidiolex

MYTHS: AT LEAST 50 CONDITIONS THAT CBD IS PURPORTED TO TREAT

- Acne
- ADD and ADHD
- Addiction
- AIDS
- ALS
- Alzheimer's
- Anorexia
- Antibiotic Resistance
- Anxiety
- Atherosclerosis
- Arthritis
- Asthma
- Autism
- Bipolar
- Cancer
- Multiple Sclerosis (MS)
- Digestive Issues
- Depression
- Diabetes
- Endocrine Disorders
- Epilepsy and Seizures
- Fibromyalgia
- Glaucoma
- Heart Disease
- Huntington's Disease
- Inflammation
- Irritable Bowel Syndrome
- Kidney Disease
- Liver Disease
- Metabolic Syndrome
- Migraine
- Mood Disorders
- Neurodegeneration
- Motion Sickness
- Nausea
- Chronic Pain
- Obesity
- OCD
- Osteoporosis/Bone Health
- Parkinson's Disease
- Prion/Mad Cow disease
- PTSD
- Rheumatism
- Schizophrenia
- Sickle Cell Anemia
- Skin Conditions
- Sleep Disorders
- Spinal Cord Injury
- Stress
- Stroke and TBI

At Least 52 Medical Conditions For Which **Marijuana** Is Approved by States

1. Alzheimer's Disease
2. Anorexia
3. Arnold-Chiari malformation
4. Arthritis
5. Ataxia
6. Cachexia
7. Cancer
8. Cardiopulmonary respiratory syndrome
9. Causalgia
10. Cervical dystonia
11. Crohn's disease
12. Decompensated cirrhosis
13. Dystonia
14. Epilepsy
15. Fibromyalgia
16. Glaucoma
17. Hepatitis C
18. HIV/AIDS
19. Huntington’s disease
20. Hydrocephalus
21. Inflammatory autoimmune-mediated arthritis
22. Inflammatory bowel disease (IBS)
23. Inflammatory demyelinating polyneuropathy
24. Interstitial cystitis
25. Lou Gehrig’s disease (amyotrophic lateral sclerosis, ALS)
26. Lupus



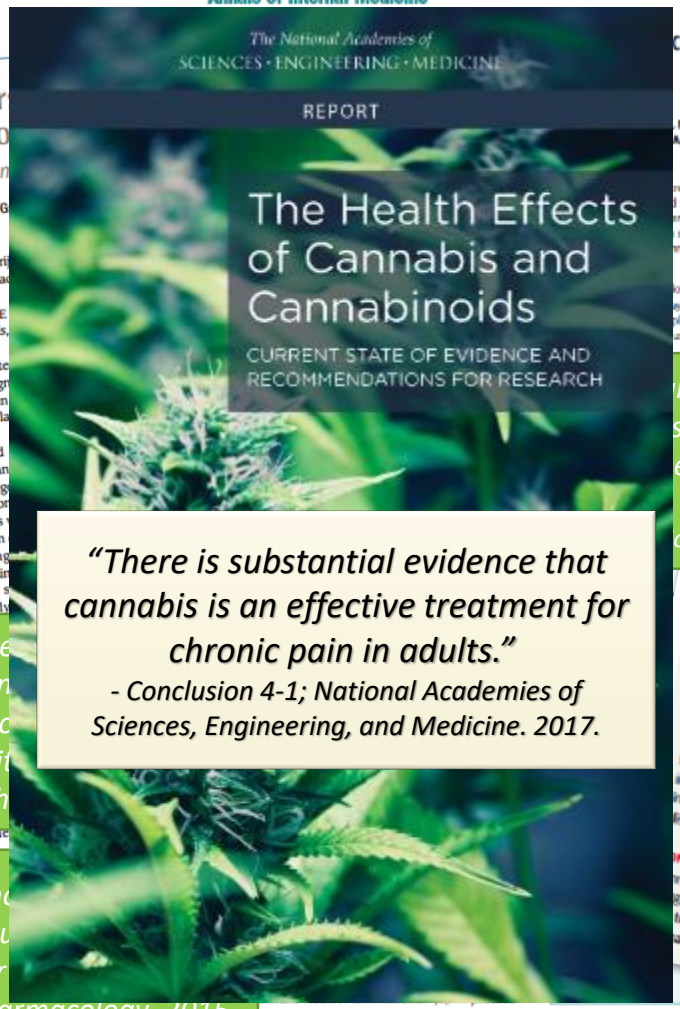
27. Migraines
28. Multiple Sclerosis
29. Muscle spasms
30. Muscular dystrophy
31. Myasthenia gravis
32. Myoclonus
33. Nail-patella syndrome
34. Nausea or vomiting
35. Neurofibromatosis
36. Neuropathy
37. Pain
38. Pancreatitis
39. Parkinson's disease
40. Peripheral neuropathy
41. Post-traumatic stress disorder (PTSD)
42. Reflex sympathetic dystrophy
43. Residual limb pain from amputation
44. Seizure disorders
45. Sjogren's syndrome
46. Spasticity
47. Spinal cord damage with intractable spasticity
48. Syringomyelia
49. Terminal illness
50. Tourette’s syndrome
51. Traumatic brain injury
52. Opioid Use Disorder

Strength of the Evidence For **Marijuana/Cannabinoid** Medical Applications

Some human Evidence	Preclinical Evidence	Weakest Evidence
• Nausea (Cancer chemotherapy) • Spasticity and Pain (MS) • Appetite Stimulant (AIDS-associated wasting) • **Pain** esp. neuropathic • Anticonvulsant (CBD) • Glaucoma (decreases intraocular pressure; no evidence it slows disease progression; and short acting)	• Anti-inflammatory (CBD) • Antitumor (THC/CBD) (animal models/cell cultures: glioblastoma; breast cancer cells; others (mechanisms: apoptosis; inhibition of tumor angiogenesis)	• PTSD • ADHD • Alzheimer's • Depression

RECENT META-ANALYSES SUPPORT THE USE OF **CANNABINOIDS** FOR CHRONIC NEUROPATHIC NON CANCER PAIN, BUT…..

- Studies generally short, small, with modest effect sizes.



"There is substantial evidence that cannabis is an effective treatment for chronic pain in adults."
- Conclusion 4-1; National Academies of Sciences, Engineering, and Medicine. 2017.

"There is evide… medical r… neuropathic… tradit…
- A. Desh…

"currently available cannabinoids are safe, m… analgesics that provide a reasonable therapeu… management of chronic non-cancer…
- M.E. Lynch & M.A. Ware; J Neuroimmune Pharmacology 2015

…nnabis some exists …cine 2017

There was moderate-quality evidence to support the use of cannabinoids for the treatment of chronic pain and spasticity.
- P.F. Whiting et al; JAMA 2015

Urgent Need for Alternative Pain Management, but The Medical **Cannabis** "Store"…

States with MML/ Dispensaries report:

- Decreasing rates OD deaths
- Fewer opioid treatment admissions
- Fewer opioid Rxs: Medicaid and Medicare Part D
- Savings in Medicare spending
- Patient – reported decreases in opioid and other pain medication use*

** This was not confirmed in a recent prospective study in Australia (Campbell, et al 2018)*

Counterargument: Cannabis use precedes and increases the risk for opioid misuse and OUD

JAMA®
The Journal of the American Medical Association

Evidence Missing for Cannabis as Medication

- **Cannabis research is low quality**
  - No randomized clinical trials
  - Uses population-level data
    - Results may be opposite of those from individual-level analyses
  - Unregulated products, doses, frequencies, and routes of administration
    - 58 of 84 (69%) cannabidiol extracts purchased online mislabeled cannabinoid content
  - Small sample sizes
  - Short follow-up period
  - Confuse correlation with causation
  - Do not control for other factors that may influence results
    - Changes in prescribing guidelines, opioid rescheduling, Good Samaritan laws, incarceration practices, and availability of methadone, buprenorphine, or naloxone

- **Cannabis for pain**
  - **Low-strength evidence** that cannabis alleviates neuropathic pain
  - **Insufficient evidence** that cannabis alleviates other types of pain
- **Cannabis to treat opioid addiction**
  - **No prospective evidence** to demonstrate any benefit
  - Substituting cannabis for methadone or buprenorphine **may increase risks**
  - **31%** of people reporting any past-year cannabis use meet criteria for cannabis use disorder

Humphreys K and Saitz R. (2019). JAMA 321:7(639-640)

MEDICAL CANNABIS USE: WHAT DO WE NEED TO KNOW?

- What dose/components/formulations are effective, for what conditions
- What people are currently using; effects on the symptoms or condition being treated
- What other medications are being used
- The link between cannabis and opioid use for pain
- Whether users are strictly medicinal or combined recreational/medicinal users
- Whether tolerance develops
- Long term adverse effects/addiction/cognitive or motivational impairments
- How States are regulating dosing, labels, pesticide use, etc.
- What to tell physicians—no guidelines; insufficient data, except on FDA approved medications

CANNABIS RESEARCH BARRIERS

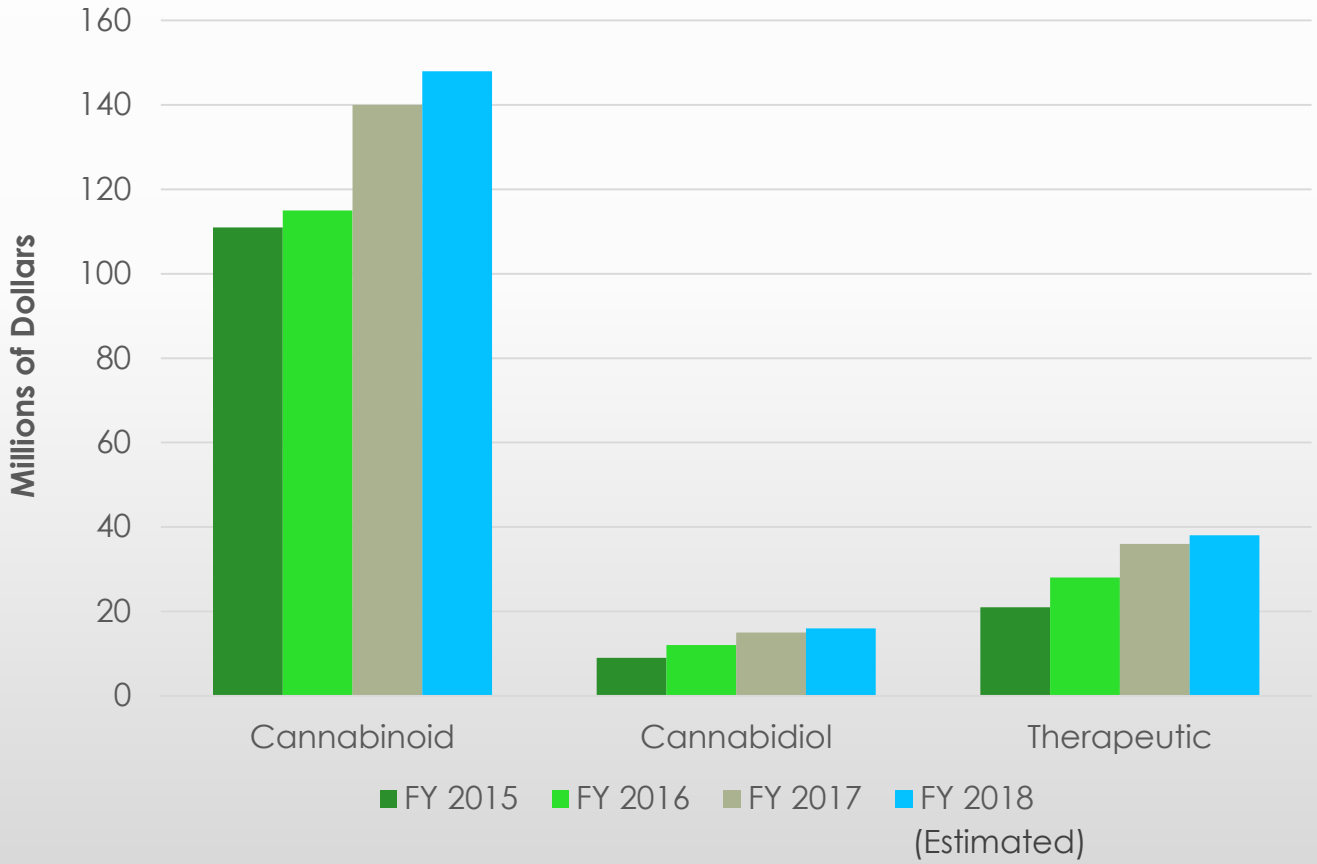
ADMINISTRATIVE

- Schedule I: Complex and lengthy registration process.
- Single Source: NIDA supply has diversified, but costly and time consuming to grow new products, doesn't represent diversity of products/formulation currently available.
- Schedule I status of non-intoxicating components of cannabis (e.g. CBD).

SCIENTIFIC

- Complexity of plant (100 cannabinoids + other components), entourage effect?
- Route of administration.
- Need proper controls, sufficient study duration (blinding, driving…)
- Should be taking advantage of what is already happening in the states and in other countries (e.g., patient registries; adverse outcomes).
- Should be studying products that people are using to understand full range of health consequences.

NIH Spending on Cannabis Research



NIH RePORT: Categorical Spending

- NIH tracks research area expenditures year-by-year
- 285 categories reported online
  - https://report.nih.gov/categorical_spending.aspx
  - Standardized categories defined by NIH experts
  - Individual projects may be included in multiple research categories
- **Primary categories related to cannabis**
  - Cannabinoid Research
    - Therapeutic Cannabinoid Research
    - Cannabidiol Research
    - Endocannabinoid Research

Cannabinoid Research – FY17 $140M

- Basic research
  - Receptors, ligands, and synthetic chemistry
  - Brain circuitry and morphology, mechanism of action, receptor physiology, genetics, and physiological effects of exogenous cannabinoid-related molecules
- Applied research
  - Behavior and decision-making
  - How cannabis use disorder (CUD) develops, the impact of social networks/environments, epidemiology studies, how changes in laws or policies affect crime and cannabis use, and clinical/research training in addiction science
  - Treatment of adverse health effects due to cannabis use and CUD
  - Prevention of cannabis use and CUD
  - Therapeutic benefit or impact of cannabinoid use on disease state within human or animal models
  - Pharmacological research

Therapeutic Cannabinoid Research - FY17 $36M

- Subset of Cannabinoid Research Category
  - All projects must first be assigned to the full Cannabinoid Research category
- Research on therapeutic use of the cannabinoid system
  - Synthetic
  - Plant-based
  - Endogenous
  - Not focused on treating CUD, but does investigate use of cannabinoids to treat substance use disorders

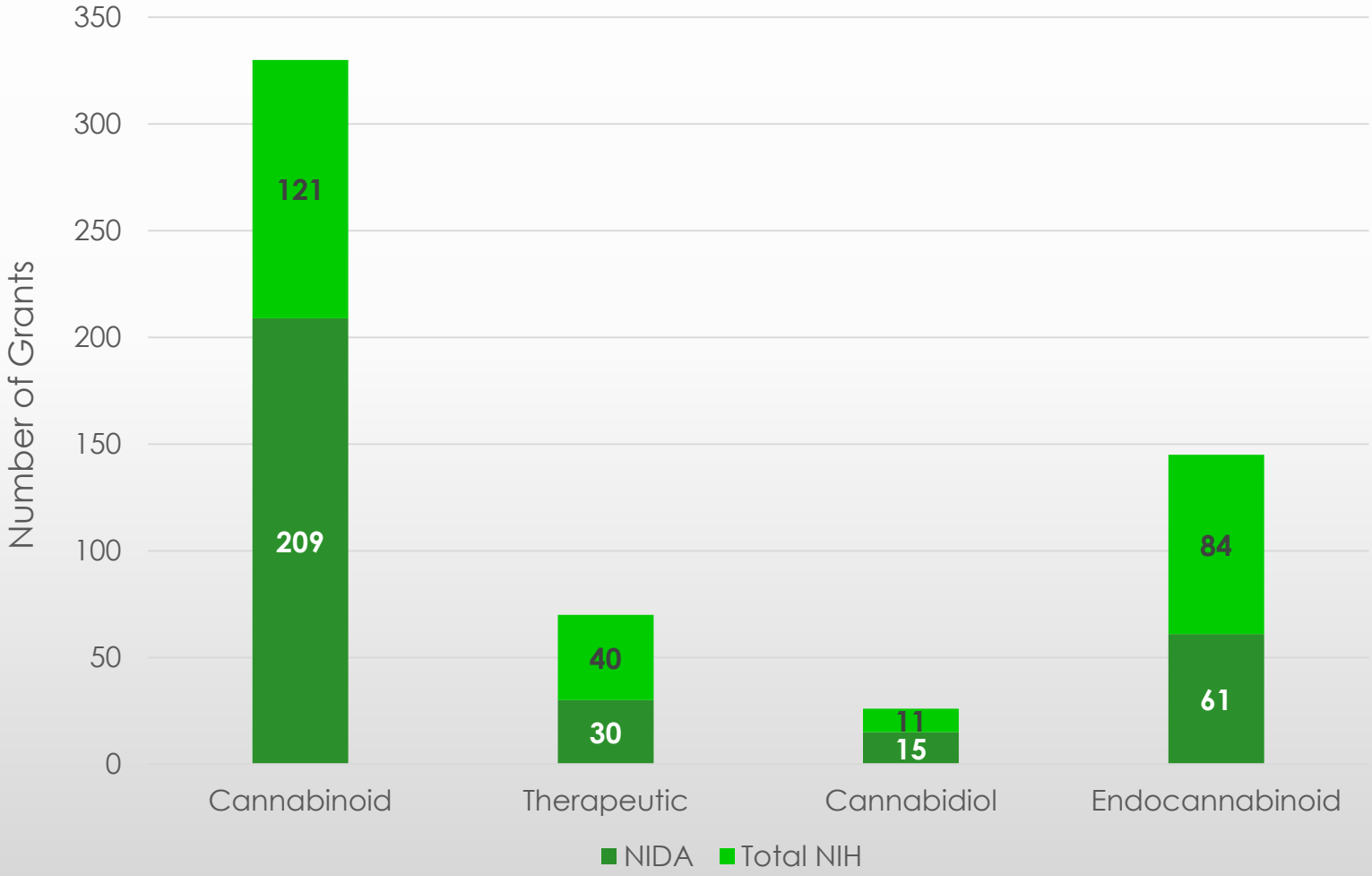
Cannabidiol (CBD) – FY17 $15M

- All CBD research
  - Medicinal applications
  - Basic research
  - Industrial synthesis of CBD

Endocannabinoid System – FY17 $63 M

- Physiological and/or mechanistic explorations of the ECS
  - ECS animal model development and use
  - Research on anandamide, even if being used exogenously
  - Research concerning the modulation of the ECS in alcohol and/or other drug rehabilitation
  - Genomic studies and studies of splice variants
  - Therapeutic potential of the ECS
  - Research that has an endocannabinoid end goal or outcome

FY 2017 NIH Grants on Cannabis Research



NIH RePORT: Categorical Spending