Public Release

Health Effects of Cannabis and Cannabinoids

Current State of Evidence and Recommendations for Research

This report is available to download as a free pdf: **Nationalacademies.org/CannabisHealthEffects**

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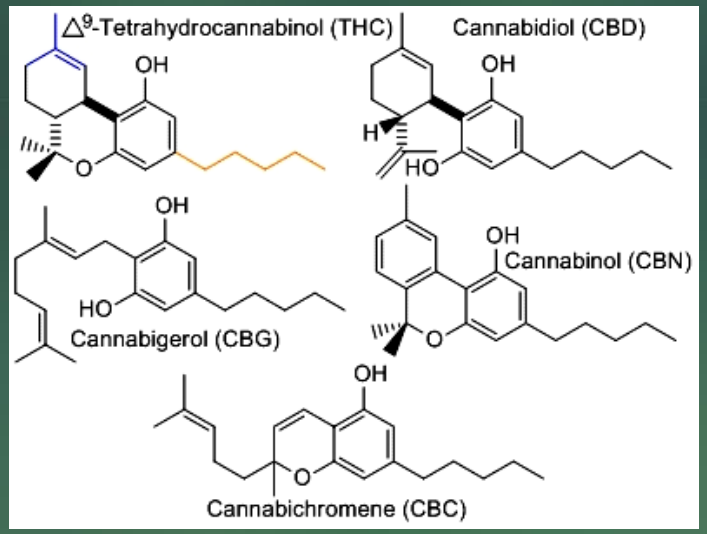
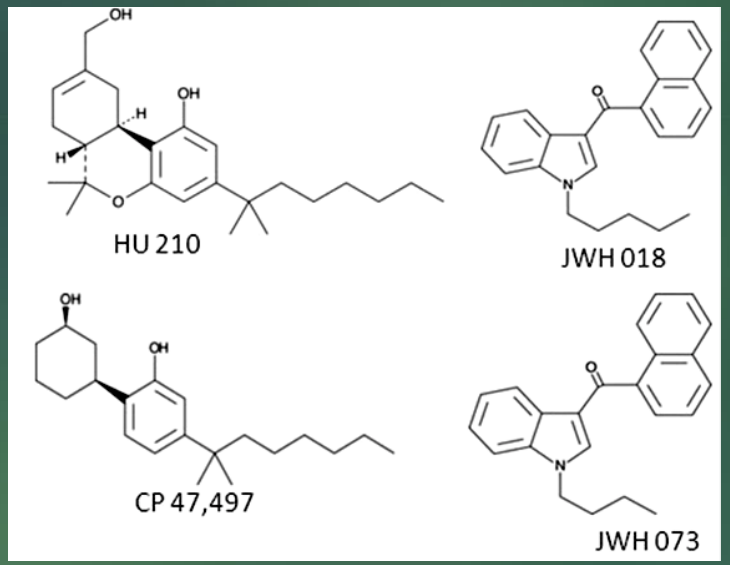
Outline of Presentation

- Background on cannabis and cannabinoids
- Brief overview of study context and statement of task
- Overview of study approach
- Therapeutic effects of Cannabis and Cannabinoids
- Overview of key mental health effects of Cannabis
- Identified research barriers and recommendations

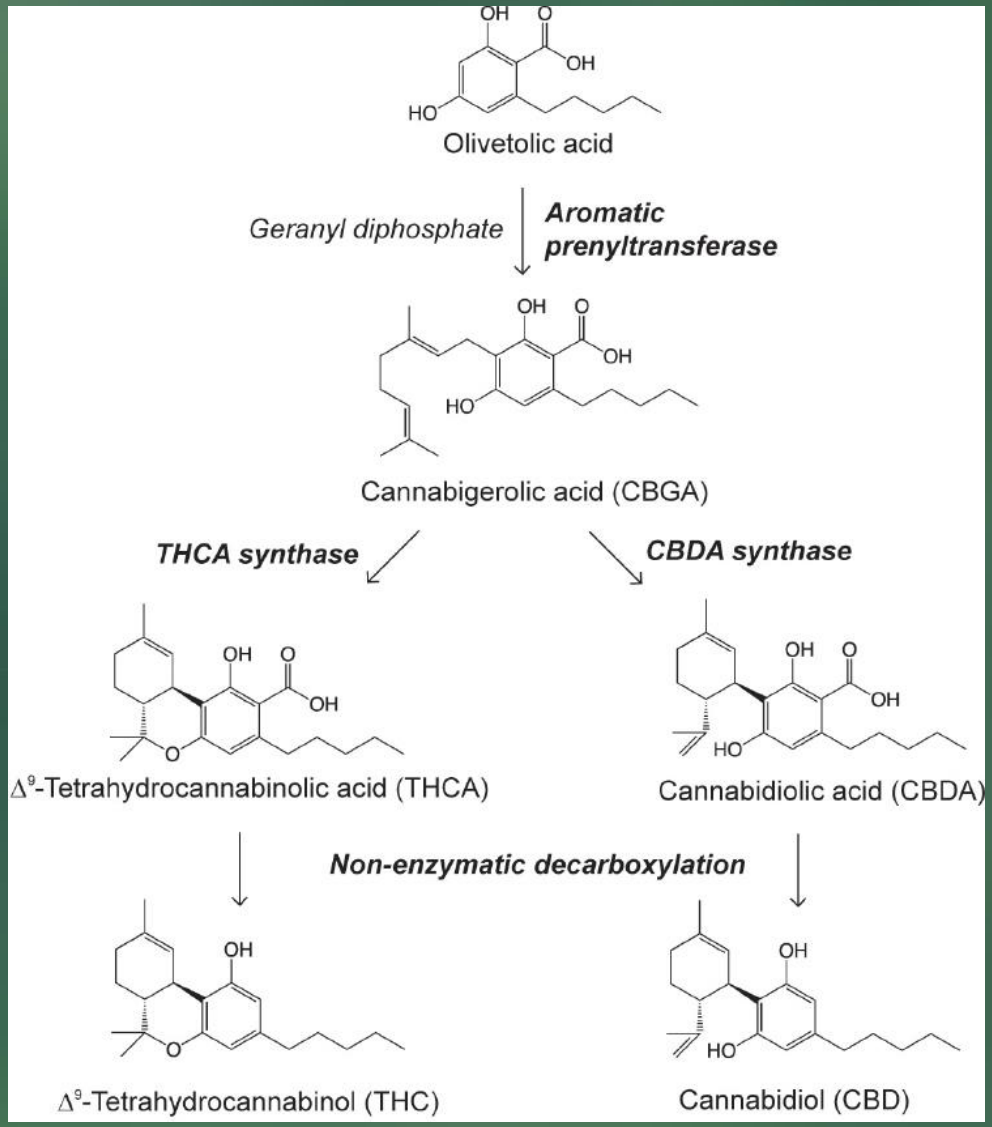
Natural vs. Synthetic



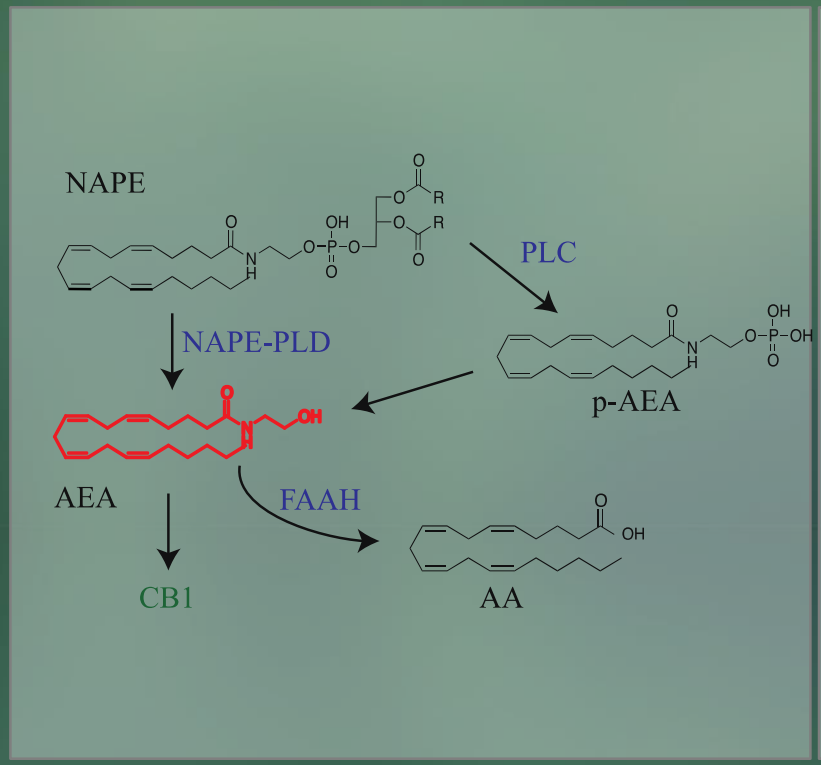
Marijuana, hashish



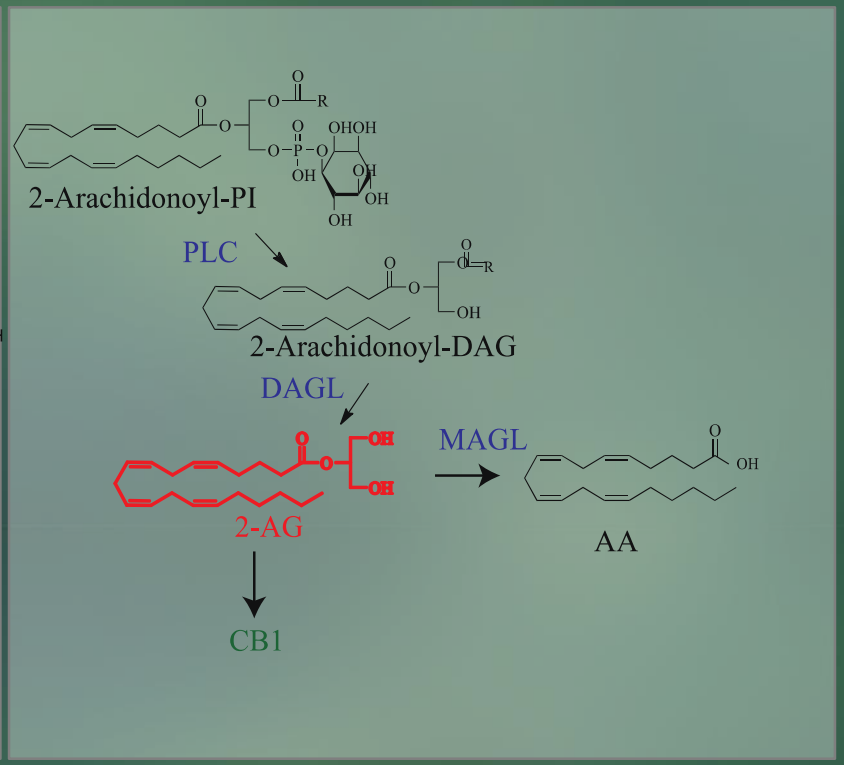
Spice, spike 99, K2


Olivetolic acid
Geranyl diphosphate
Aromatic prenyltransferase
Cannabigerolic acid (CBGA)
THCA synthase
CBDA synthase
Δ9-Tetrahydrocannabinolic acid (THCA)
Cannabidiolic acid (CBDA)
Non-enzymatic decarboxylation
Δ9-Tetrahydrocannabinol (THC)
Cannabidiol (CBD)

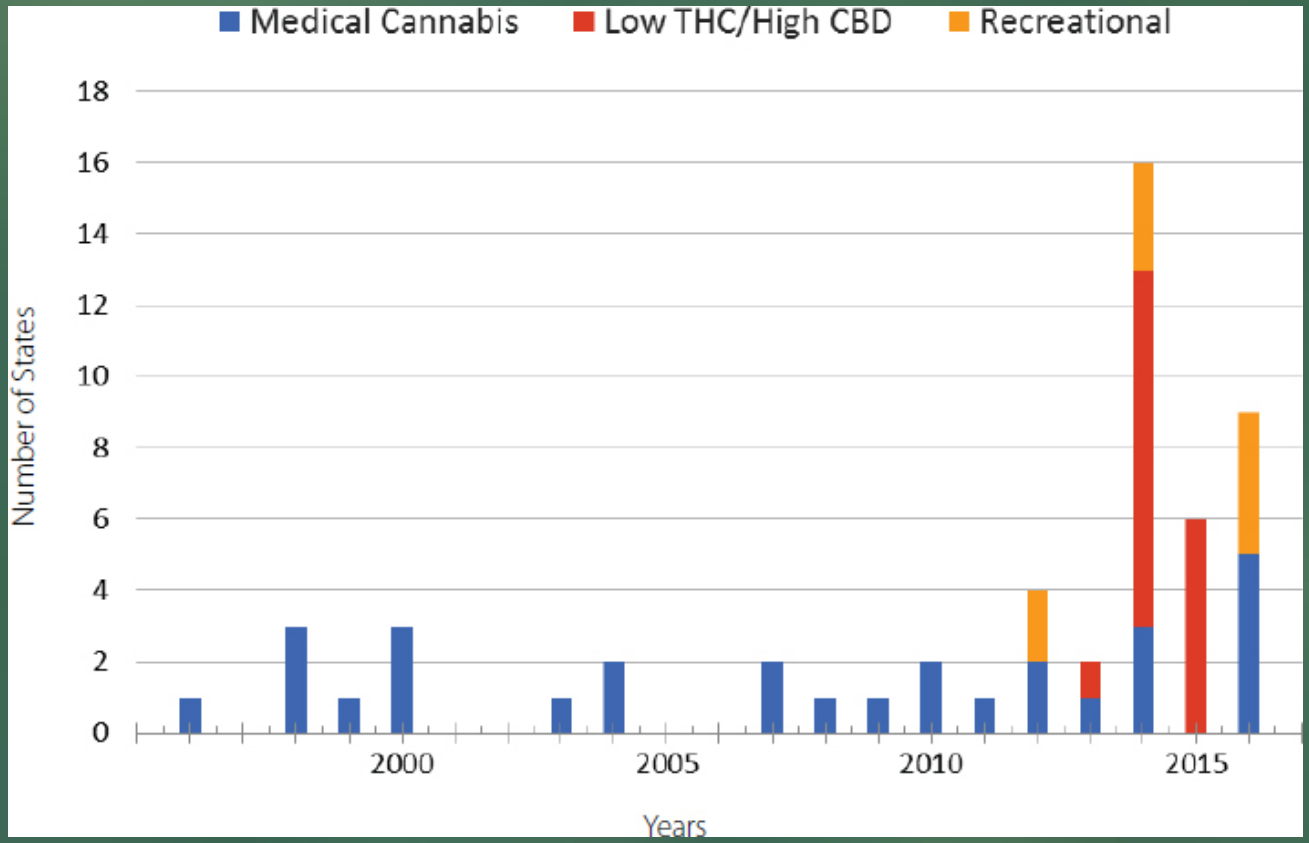
Endogenous cannabinoids

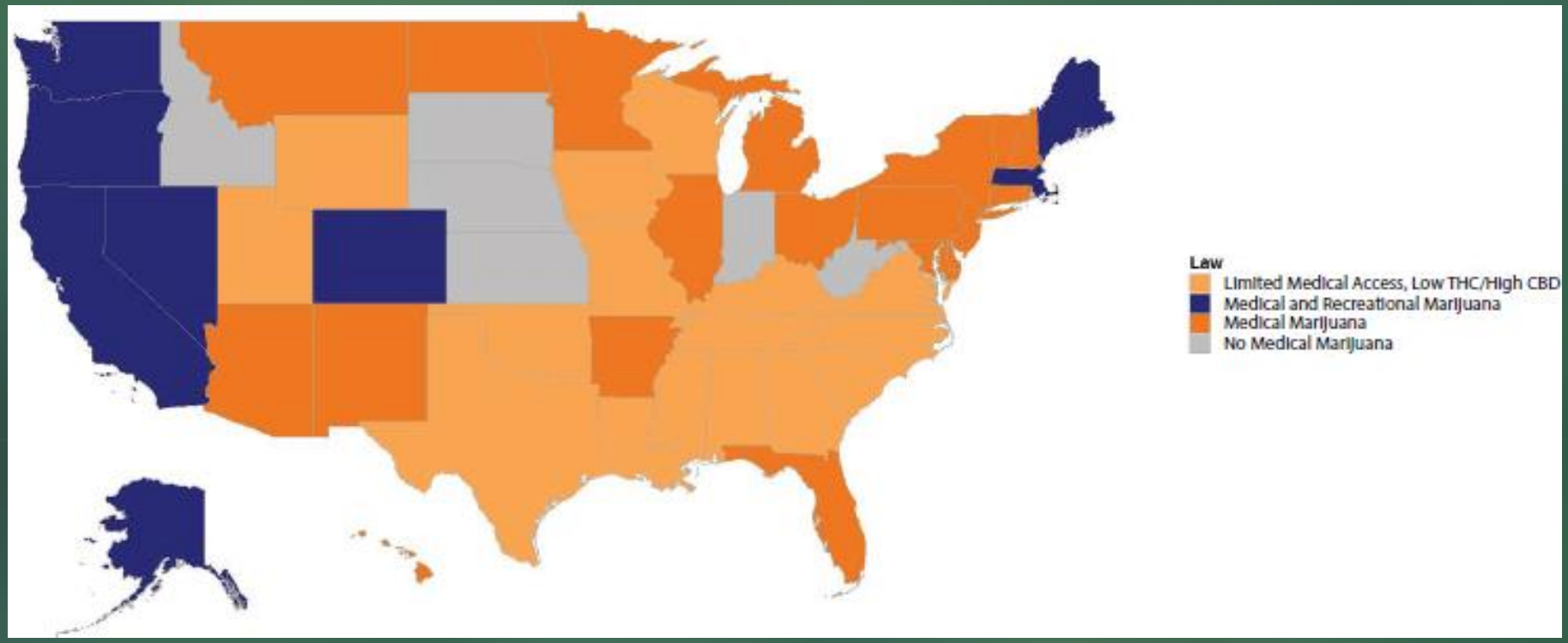


Anandamide (AEA)



2-arachidonoylglycerol (2-AG)


Medical Cannabis
Low THC/High CBD
Recreational
Number of States
18
16
14
12
10
8
6
4
2
0
2000
2005
2010
2015
Years


Law
Limited Medical Access, Low THC/High CBD
Medical and Recreational Marijuana
Medical Marijuana
No Medical Marijuana

Brief Overview of Study Context and Statement of Task

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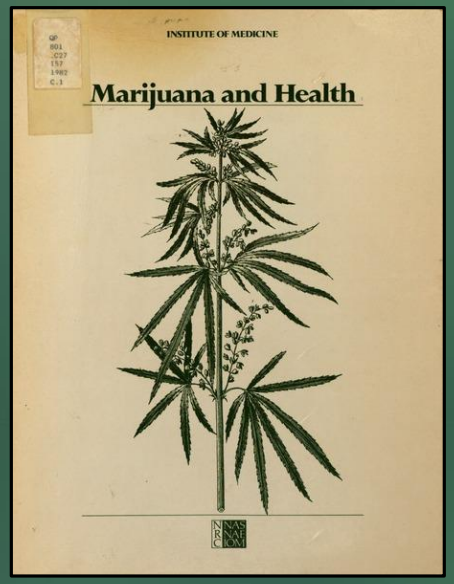
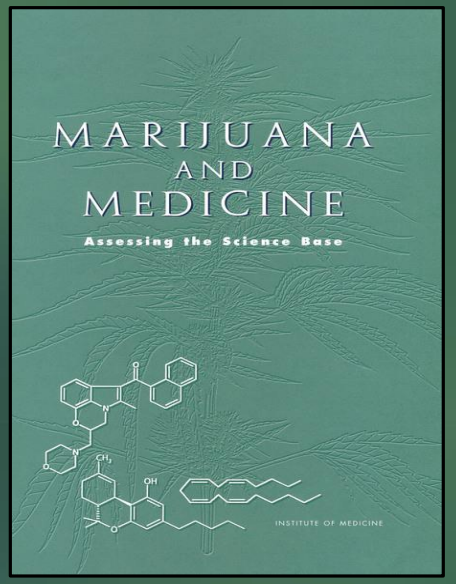
Study Context



Marijuana and Health
(1982)



Marijuana and Medicine:
Assessing the Science Base
(1999)

Summary of Statement of Task

Develop a comprehensive, in-depth review of existing evidence regarding the health effects (both harms and benefits) of cannabis and cannabinoids use

Make short- and long-term recommendations regarding a research agenda to identify the most critical research questions and advance the cannabis and cannabinoid research agenda

Study Sponsors

- Alaska Mental Health Trust Authority
- Arizona Department of Health Services
- California Department of Public Health
- CDC Foundation
- Centers for Disease Control and Prevention (CDC)
- Food and Drug Administration
- Mat-Su Health Foundation
- National Cancer Institute - National Institutes of Health
- National Highway Traffic Safety Administration
- National Institute on Drug Abuse- National Institutes of Health
- Oregon Health Authority
- Robert W. Woodruff Foundation
- The Colorado Health Foundation
- Truth Initiative
- Washington State Department of Health

Committee on the Health Effects of Marijuana: An Evidence Review and Research Agenda

MARIE C. MCCORMICK *(chair),* Harvard T.H. Chan School of Public Health, MA

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MARGARITA ALEGRÍA, Massachusetts General Hospital

WILLIAM CHECKLEY, Johns Hopkins University, MD

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ZIVA D. COOPER, Columbia University Medical Center, NY

ADRE J. DU PLESSIS, Children National Health System, D.C.

SARAH FELDSTEIN EWING, Oregon Health and Science University

SEAN HENNESSY, University of Pennsylvania

KENT HUTCHISON, University of Colorado Boulder

NORBERT E. KAMINSKI, Michigan State University

SACHIN PATEL, Vanderbilt University Medical Center, TN

DANIELE PIOMELLI, University of California, Irvine

STEPHEN SIDNEY, Kaiser Permanente Northern California

ROBERT B. WALLACE, University Of Iowa College of Public Health

JOHN WILLIAMS, Duke University Medical Center, NC

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Overview of Study Approach

Study Approach

Committee member expertise included:

- substance abuse
- cardiovascular health
- general epidemiology
- immunology
- pharmacology
- pulmonary health
- neurodevelopment
- oncology
- pediatrics
- public health
- systematic review methodology
- and others…

Between June and December 2016, the committee held 5 in-person meetings and 1 virtual meeting

The committee held 2 open session meetings

Study Approach
(further detailed in the full report)

- Adopted key features of a systematic review process
- Conducted an extensive search of relevant databases (e.g., Medline, Embase, the Cochrane Database of Systematic Reviews, PsycINFO)
  - Initial search resulted in more than 24, 000 articles
  - Committee considered more than 10,000 abstracts to determine relevance for the report
- Primacy given to recently published systematic reviews and high-quality primary research that studied one or more of the committee's 11 prioritized health endpoints

Study Approach– 11 prioritized health endpoints

- Therapeutic effects
- Cancer incidence
- Cardiometabolic risk
- Respiratory disease
- Immune function
- Injury and death
- Prenatal, perinatal, and postnatal outcomes
- Psychosocial outcomes
- Mental health
- Problem cannabis use
- Cannabis use and abuse of other substance

Study approach
(further detailed in the full report)

- Standardized language to categorize the weight of evidence
- 5 levels of evidence
  - CONCLUSIVE
  - SUBSTANTIAL
  - MODERATE
  - LIMITED
  - NO or INSUFFICIENT

Review of Select Chapter Highlights

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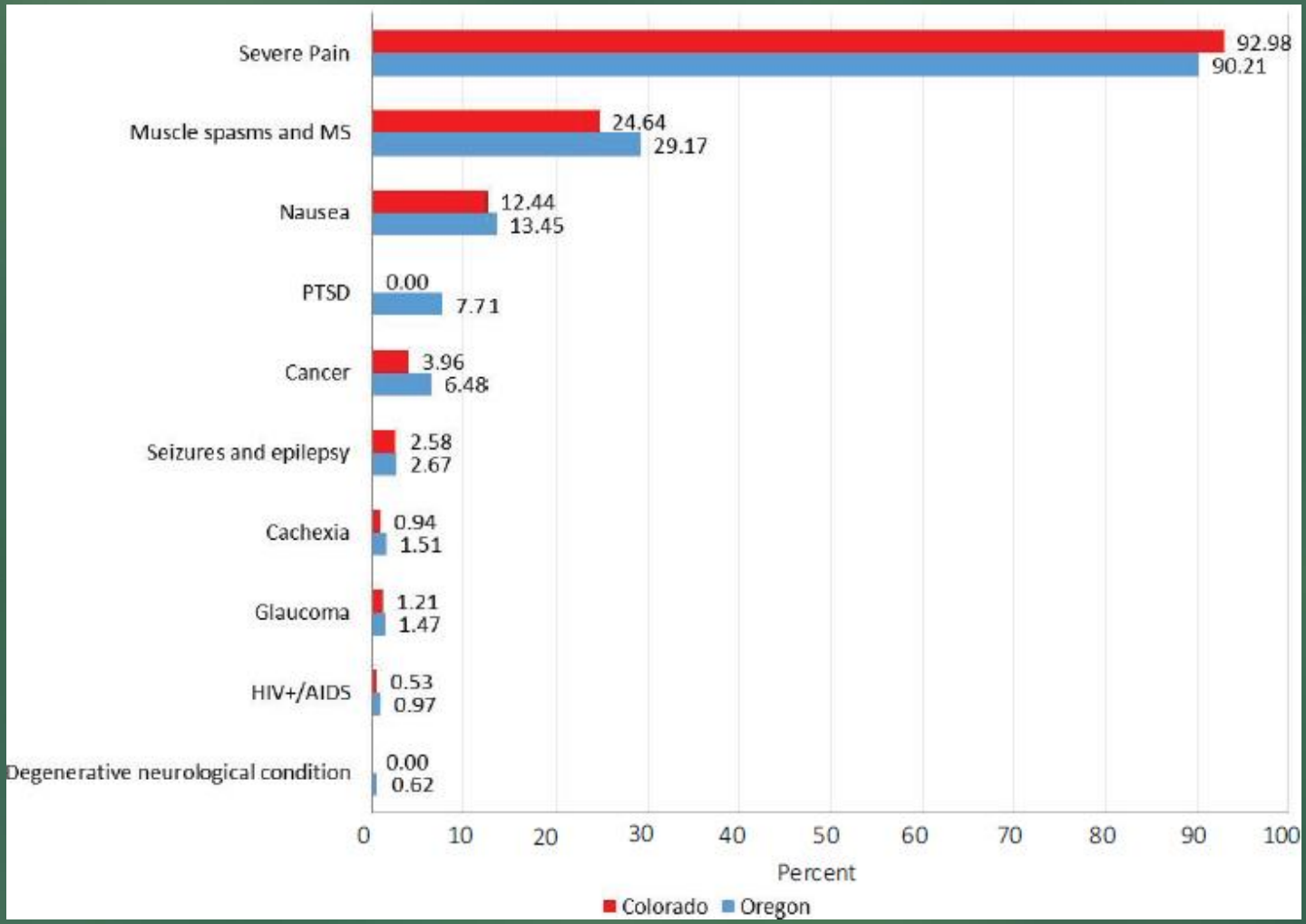

Severe Pain
92.98
90.21
Muscle spasms and MS
24.64
29.17
Nausea
12.44
13.45
PTSD
0.00
7.71
Cancer
3.96
6.48
Seizures and epilepsy
2.58
2.67
Cachexia
0.94
1.51
Glaucoma
1.21
1.47
HIV+/AIDS
0.53
0.97
Degenerative neurological condition
0.00
0.62
0
10
20
30
40
50
60
70
80
90
100
Percent
Colorado
Oregon

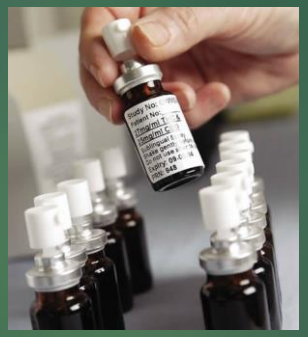
Therapeutics

- In adults with chemotherapy induced nausea and vomiting, oral cannabinoids are effective antiemetics.
- In adults with chronic pain, patients who were treated with cannabis or cannabinoids are more likely to experience a clinically significant reduction in pain symptoms
- In adults with multiple sclerosis (MS) related spasticity, short-term use of oral cannabinoids improves patient-reported spasticity symptoms.
- For these conditions the effects of cannabinoids are modest; for all other conditions evaluated there is inadequate information to assess their effects.

Chronic Pain

- The majority of studies on pain cited in Whiting et al. (2015) evaluated nabiximols outside the United States. In their review, the committee found that only a handful of studies have evaluated the use of cannabis in the United States, and all of them evaluated cannabis in flower form provided by the National Institute on Drug Abuse that was either vaporized or smoked.
- Thus, while the use of cannabis for the treatment of pain is supported by well-controlled clinical trials as reviewed above, very little is known about the efficacy, dose, routes of administration, or side effects of commonly used and commercially available cannabis products in the United States.

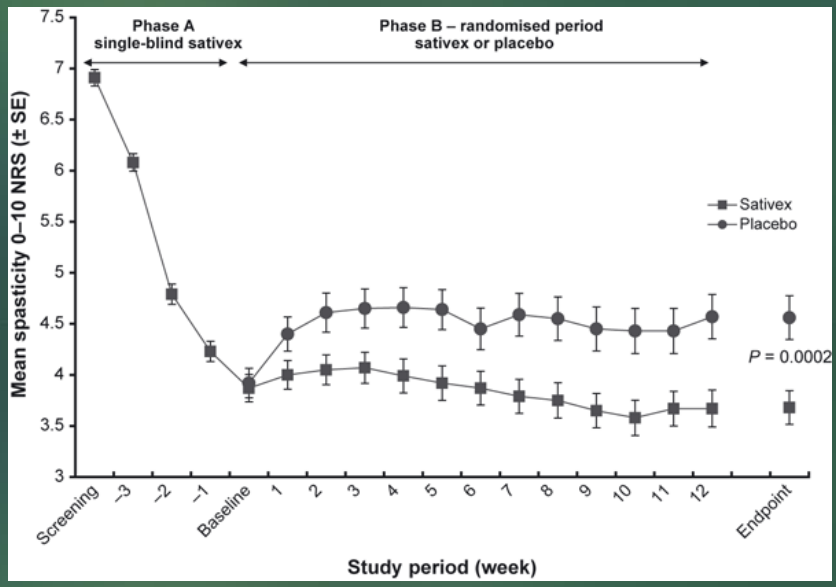
Multiple Sclerosis



Produced and marketed by GW Pharmaceuticals. Approved in the UK for the treatment of pain and spasticity associated with MS

Extracted from pharma grown cannabis in the UK.

Sublingual preparation of THC:CBD in a 1:1 ratio. Also contains >100 trace cannabinoids



PTSD

- We identified a fair-quality double-blind, randomized crossover trial (Jetly et al., 2015)
- Ten participants were randomized to either nabilone 0.5 mg that was titrated to a daily maximum of 3.0 mg or else to a placebo for 7 weeks. Nightmares, global clinical state, and general well-being were improved more with nabilone treatment than with the placebo treatment ($p < 0.05$). Global clinical state was rated as very much improved or much improved for 7 of 10 subjects in the nabilone treatment period and 2 of 10 subjects in the placebo treatment period.
- **CONCLUSION 4-20 There is limited evidence (a single, small fair-quality trial) that nabilone is effective for improving symptoms of posttraumatic stress disorder.**

Seizures

- Recent systematic reviews were unable to identify any randomized controlled trials evaluating the efficacy of cannabinoids for the treatment of epilepsy. Currently available clinical data therefore consist solely of uncontrolled case series, which do not provide high-quality evidence

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 25, 2017 VOL. 376 NO. 21

Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome

Orrin Devinsky, M.D., J. Helen Cross, Ph.D., F.R.C.P.C.H., Linda Laux, M.D., Eric Marsh, M.D., Ian Miller, M.D., Rima Nabbout, M.D., Ingrid E. Scheffer, M.B., B.S., Ph.D., Elizabeth A. Thiele, M.D., Ph.D., and Stephen Wright, M.D., for the Cannabidiol in Dravet Syndrome Study Group*

Table 2. Primary Efficacy End Point of Percentage Change in Convulsive-Seizure Frequency in Each Trial Group.*

Variable	Cannabidiol	Placebo	Adjusted Median Difference (95% CI)	P Value†
			percentage points	
No. of convulsive seizures per mo — median (range)				
Baseline	12.4 (3.9 to 1717)	14.9 (3.7 to 718)		
Treatment period	5.9 (0.0 to 2159)	14.1 (0.9 to 709)		
Percentage change in seizure frequency — median (range)	−38.9 (−100 to 337)	−13.3 (−91.5 to 230)	−22.8 (−41.1 to −5.4)	0.01

Devinsky et al. (May 25 issue)1 present data showing that 65% of patients in their trial of cannabidiol as treatment for seizures in the Dravet syndrome were taking clobazam. We are concerned about a potential drug–drug interaction between clobazam and cannabidiol. Cannabidiol is a potent inhibitor of CYP3A4 and CYP2C19, which can increase concentrations of several other antiepileptic drugs, including clobazam.2 A previous study showed that, during cannabidiol treatment, clobazam levels increased by a mean of 60%, and levels of its active metabolite, *N*-desmethylclobazam, increased by a mean of 500%.3 Moreover, studies have shown that raising clobazam concentrations is likely to have an effect on seizure frequency.4 Thus, this interaction may lead to an overestimation of cannabidiol efficacy in patients who are receiving clobazam.

Health Effects of Cannabis

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Respiratory Disease

- Percentage of past month cannabis usage has steadily increased between 2002-2015.
- According to a recent nationwide survey published in 2016, 22.2 million Americans (12+) reported using cannabis in past 30 days.
- Estimated that more than 40% of current users smoke cannabis on a daily or near daily basis.

CBHSQ, 2015; Douglas et al., 2015

Respiratory Disease

- There is substantial evidence of a statistical association between long-term cannabis smoking and worse respiratory symptoms and more frequent chronic bronchitis episodes.

- There is moderate evidence of a statistical association between *cessation* of cannabis smoking and improvements in respiratory symptoms.

Respiratory Disease

- There is limited evidence of a statistical association between occasional cannabis smoking and an increased risk of developing chronic obstructive pulmonary disease (COPD) when controlled for tobacco use.
- There is insufficient evidence to support or refute a statistical association between cannabis smoking and hospital admissions for COPD.
- There is insufficient evidence to support or refute a statistical association between cannabis smoking and asthma development or asthma exacerbation.

Cancer

- Leading cause of disease and death among Americans.
  - Estimated that in 2016:
    - 1,685,210 new cancer cases
    - 595,690 cancer-related deaths

- Like tobacco smoke, cannabis smoke does contain carcinogens.

Tashkin, 2013; Lortet-Tieulent et al., 2016; NCI, 2016

Cancer

- There is moderate evidence of *no* statistical association between cannabis smoking and the incidence of lung cancer.
- There is moderate evidence of *no* statistical association between cannabis use and the incidence of head and neck cancers.
- There is limited evidence of a statistical association between current, frequent, or chronic cannabis smoking and non-seminoma-type testicular germ cell tumors.

Cancer

- There is insufficient evidence to support or refute a statistical association between cannabis smoking and the incidence of esophageal cancer.
- There is insufficient evidence to support or refute a statistical association between cannabis use and the incidence of prostate cancer, cervical cancer, malignant gliomas, non-Hodgkin lymphoma, penile cancer, anal cancer, Kaposi's sarcoma, or bladder cancer.
- There is insufficient evidence to support or refute a statistical association between parental cannabis use and a subsequent risk of developing acute myeloid leukemia/acute non-lymphoblastic leukemia, acute lymphoblastic leukemia, rhabdomyosarcoma, astrocytoma, or neuroblastoma in offspring.

Prenatal, Perinatal, and Neonatal Outcomes

- Concerns stem from previous research showing that:
  - Tetrahydrocannabinol (THC) crosses the placenta.
  - THC can be secreted in breast milk with the ability to accumulate in high concentrations.
- In 2015, 3.4 percent of pregnant women (15-44) reported using marijuana in the previous month.
  - This is compared to the 0.8 percent of pregnant women who reported using pain relievers - the next most used drug in this population.

Prenatal, Perinatal, and Neonatal Outcomes

- Smoking cannabis during pregnancy is linked to lower birth weight in the infant.
- The relationship between smoking cannabis during pregnancy and other pregnancy and childhood outcomes is unclear.

Psychosocial

- Adolescence and emerging adulthood are the periods where most youths begin to experiment with substances of abuse, including cannabis.
- 24.9% of youths report having used cannabis at least once by 8th grade.
- 51.4% of youths report having tried cannabis by the time they graduate high school.

Johnston et al., 2015

Psychosocial

- Recent cannabis use impairs the performance in cognitive domains of learning, memory, and attention. Recent use may be defined as cannabis use within 24 hours of evaluation.
- A limited number of studies suggest that there are impairments in cognitive domains of learning, memory, and attention in individuals who have stopped smoking cannabis.
- Cannabis use during adolescence is related to impairments in subsequent academic achievement and education, employment and income, and social relationships and social roles.

Mental Health

- Relationship between substance use and mental health has been a long-standing and complex public health issue.

- In 2014, SAMHSA found that 20.2 million adults had a substance use disorder.
  - Of these individuals, 7.9 million had both a mental health and substance use disorder.

Mental Health: Depression & Suicide

- Cannabis use does not appear to increase the likelihood of developing depression.
- However, heavy cannabis users are more likely to report thoughts of suicide than non-users.
- Moderate evidence of a statistical association between cannabis use and increased incidence of suicide completion.

Mental Health: Bipolar Disorder

- Limited evidence of a statistical association between cannabis use and the likelihood of developing bipolar disorder, particularly among regular or daily users.

- For individuals diagnosed with bipolar disorders, near daily cannabis use may be linked to greater symptoms of bipolar disorder than non-users.

Mental Health: Anxiety Disorders & PTSD

- Cannabis use does not appear to increase the likelihood of developing any anxiety disorder, except social anxiety disorder.

- Cannabis use does not appear to increase the likelihood of developing posttraumatic stress disorder.

Mental Health: Schizophrenia

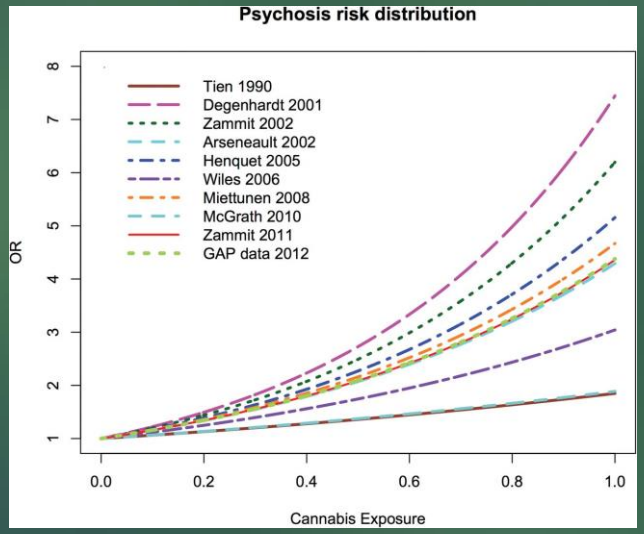
- Schizophrenia spectrum disorders and other psychotic disorders are characterized by three classes of symptoms:
  - **Positive symptoms** (e.g., delusions, hallucinations, or disorganized or abnormal motor behavior)
  - **Negative symptoms** (e.g., diminished emotional expression, lack of interest of motivation to engage in social settings, speech disturbance, or anhedonia)
  - **Impaired cognition**

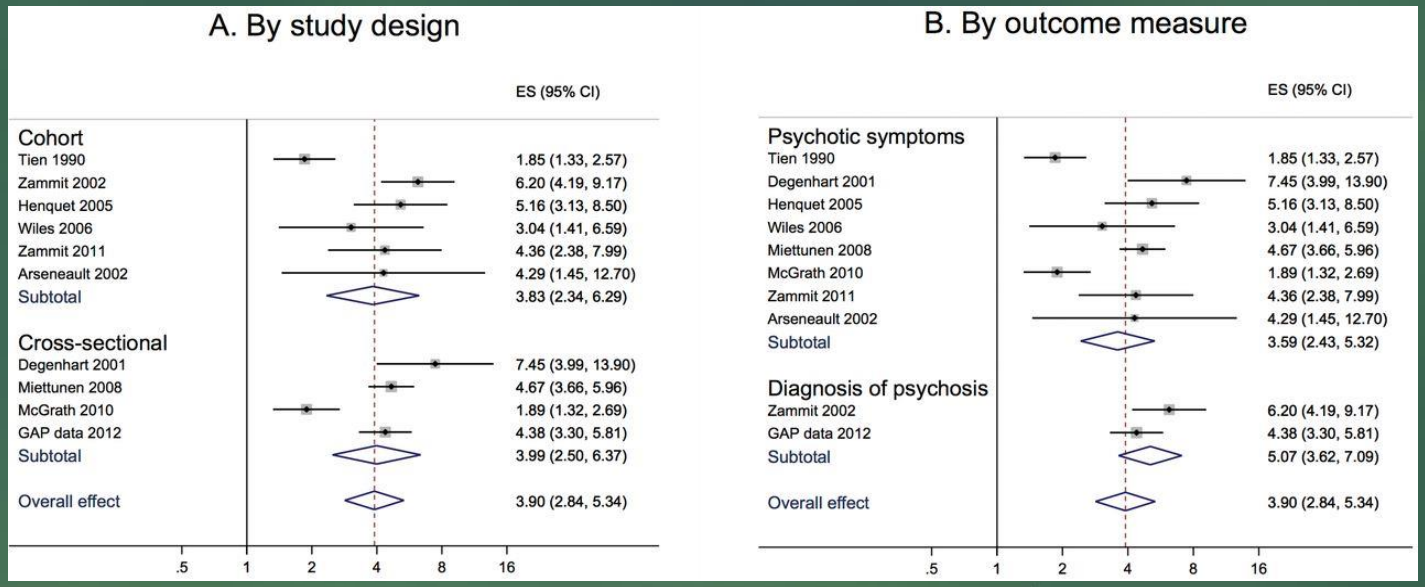
- Evidence suggests that the prevalence of cannabis use among people with schizophrenia is generally higher than among the general population.

APA, 2013, p. 87; McLaughlin et al., 2014; NIMH, 2015

Mental Health: Schizophrenia

There is substantial evidence of a statistical association between cannabis use and the development of schizophrenia or other psychoses, with the highest risk among the most frequent users.





Marconi et al., 2016 Schizophrenia Bulletin

Mental Health: Schizophrenia

- There is moderate evidence that, among individuals with psychotic disorders, there is a statistical association between history of cannabis use and better cognitive performance (learning and memory tasks).

- Among those with psychotic disorders:

  - Limited evidence of a statistical association between cannabis use and an increase in positive symptoms (e.g., hallucinations).

  - Moderate evidence for no statistical association between cannabis use and worsening of negative symptoms (e.g., blunted affect).

Problem Cannabis Use

- 4.2 million Americans reported experiencing symptoms in the past year that would qualify them for **cannabis use disorder**.
- Symptoms of cannabis use disorder include:
  - Disruptions in functioning
  - Development of a tolerance or cravings for cannabis
  - Withdrawal symptoms within a week of cessation
    - Include: inability to sleep, restlessness, depression etc.

Substance Abuse and Mental Health Services Administration; Center for Behavioral Health Statistics and Quality, 2015

Problem Cannabis Use

- 4.2 million Americans reported experiencing symptoms in the past year that would qualify them for cannabis use disorder.

- Risk factors include:
  - **Initiating cannabis use at a young age.**
  - Being male and smoking cigarettes.

Greater frequency of cannabis use also increases likelihood of developing problem cannabis use.

Center for Behavioral Health Statistics and Quality, 2015

Cannabis Use and Abuse of Other Substances

- Gateway Hypothesis suggests that individuals rarely use harder substances, such as heroin or cocaine, without having first used “gateway” substances, such as alcohol, tobacco, or cannabis.

- There is moderate evidence of a statistical association between cannabis use and the development of substance dependence and/or a substance abuse disorder for substances including, alcohol, tobacco, and other illicit drugs.

Cannabis Use and Abuse of Other Substances

- There is limited evidence of a statistical association between cannabis use and changes in the rates and use patterns of other licit and illicit substances.

- There is limited evidence of a statistical association between cannabis use and the initiation of tobacco use.

Immunity

- There exists a paucity of data on the effects of cannabis or cannabinoid-based therapeutics on the human immune system.
- There is insufficient data to draw overarching conclusions concerning the effects of cannabis smoke or cannabinoids on immune competence.
- There is limited evidence to suggest that regular exposure to cannabis smoke may have anti-inflammatory activity.
- There is insufficient evidence to support or refute a statistical association between cannabis or cannabinoid use and adverse effects on immune status in individuals with HIV.

Injury and Death

- Cannabis use prior to driving increases the risk of being involved in a motor vehicle accident.
- In states where cannabis use is legal, there is increased risk of unintentional cannabis overdose injuries among children.
- It is unclear whether and how cannabis use is associated with all-cause mortality or with occupational injury.

Barriers to Cannabis Research

- There are specific regulatory barriers, including the classification of cannabis as a Schedule I substance, that impede the advancement of cannabis and cannabinoid research.
- It is often difficult for researchers to gain access to the quantity, quality, and type of cannabis product necessary to address specific research questions on the health effects of cannabis use.
- A diverse network of funders is needed to support cannabis and cannabinoid research that explores the beneficial and harmful health effects of cannabis use.
- To develop conclusive evidence for the effects of cannabis use on short- and long-term health outcomes, improvements and standardization in research methodology (including those used in controlled trials and observational studies) are needed.

Report Recommendations

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Recommendation 1: Address Research Gaps

To develop a comprehensive evidence base on the short- and long-term health effects of cannabis use (both beneficial and harmful effects), public agencies, philanthropic and professional organizations, private companies, and clinical and public health research groups should provide funding and support for a national cannabis research agenda that addresses key gaps in the evidence base. Prioritized research streams and objectives should include, but need not be limited to:

- Clinical and Observational Research
- Health Policy and Health Economics Research
- Public Health and Public Safety Research

Recommendation 2: Improve Research Quality

To promote the development of conclusive evidence on the short- and long-term health effects of cannabis use (both beneficial and harmful effects), agencies of the United States Department of Health and Human Services, including the National Institutes of Health and the Centers for Disease Control and Prevention should jointly fund a workshop to develop a set of research standards and benchmarks to guide and ensure the production of high-quality cannabis research.

Recommendation 3: Improve Surveillance Capacity

To ensure that sufficient data are available to inform research on the short- and long-term health effects of cannabis use (both beneficial and harmful effects), the Centers for Disease Control and Prevention, the Substance Abuse and Mental Health Services Administration, the Association of State and Territorial Health Officials, National Association of County and City Health Officials, the Association of Public Health Laboratories, and state and local public health departments should fund and support improvements to federal public health surveillance systems and state-based public health surveillance efforts.

Recommendation 4: Address Research Barriers

The Centers for Disease Control and Prevention, National Institutes of Health, Food and Drug Administration, industry groups, and nongovernmental organizations should fund the convening of a committee of experts tasked to produce an objective and evidence-based report that fully characterizes the impacts of regulatory barriers to cannabis research and that proposes strategies for supporting development of the resources and infrastructure necessary to conduct a comprehensive cannabis research agenda.

This report is now available and can downloaded as a free pdf at: **nationalacademies.org/CannabisHealthEffects**

Thank you for your support of this important study.

Questions?