The Great American Cannabis Experiment: Medicinal/Recreational Use and Abuse

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Assistant Professor: IM, WVSOM

ACOi 2023 October 11-14 Tampa • Hybrid

AMERICA IS TRANSITIONING TOWARD ENDING THE PROHIBITION OF MARIJUANA

- CANNABIS went from having "*No Medical Value*" to a "***CURE for just about everything***"!

- **No reliable method to characterize Impairment**

Bloomberg.com

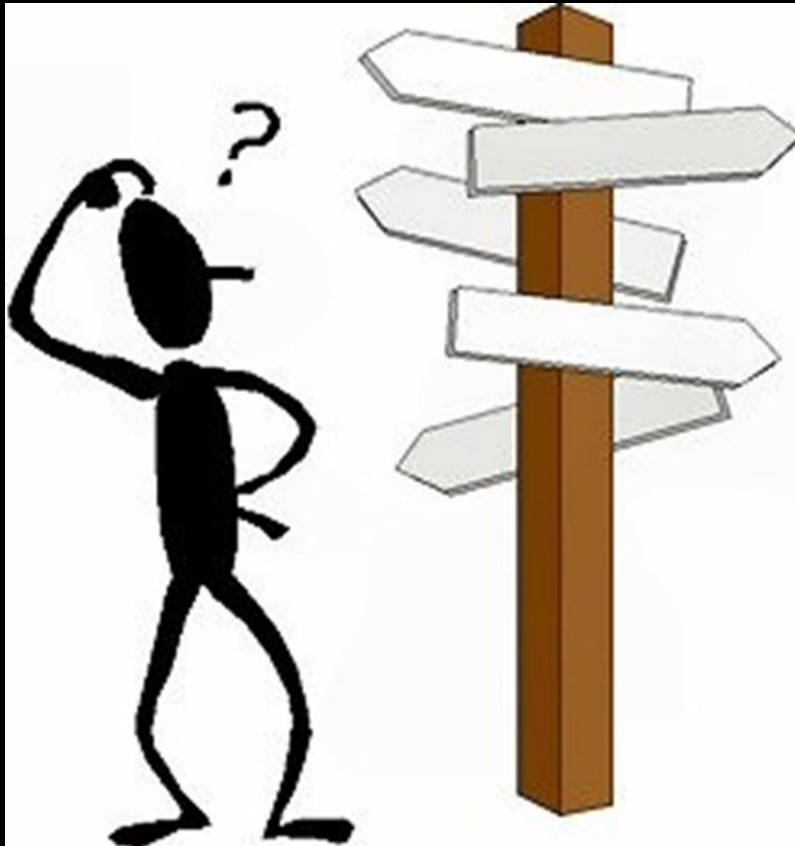**HHS Calls for Moving Marijuana to Lower-Risk US Drug Category**

US health officials are recommending easing restrictions on marijuana, a move that sets the stage for potentially expanding the cannabis...

FOR MEDICAL USE ONLY
as per CA Health & Safety Code sections 11362.5 and 11362.7
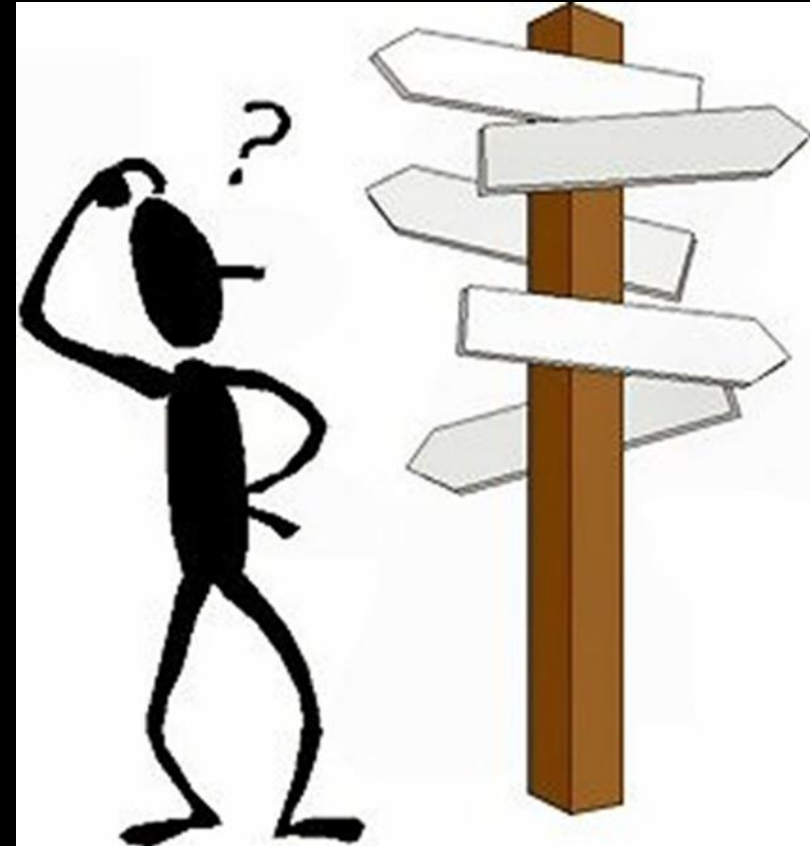
CANNABIS CONFUSION

AIDS	amyotrophic lateral sclerosis
Alzheimer's disease	cachexia
cancer	chronic traumatic encephalopathy
Crohn's disease	epilepsy or another seizure disorder
fibromyalgia	glaucoma
hepatitis C	Huntington's disease
inflammatory bowel disease	irritable bowel syndrome
multiple sclerosis	pain that is either chronic and severe or intractable
Parkinson's disease	positive status for HIV
post-traumatic stress disorder	sickle cell anemia
spasticity	spinal cord disease or injury
terminal illness	Tourette syndrome
traumatic brain injury	ulcerative colitis

EVIDENCE vs. BELIEF

Medical Marijuana Advocates "Believe"

- Therapy for "Intractable Medical Problems"
- Safety
- Effective Treatments

Opponents "Believe"

- Benefits are Overblown
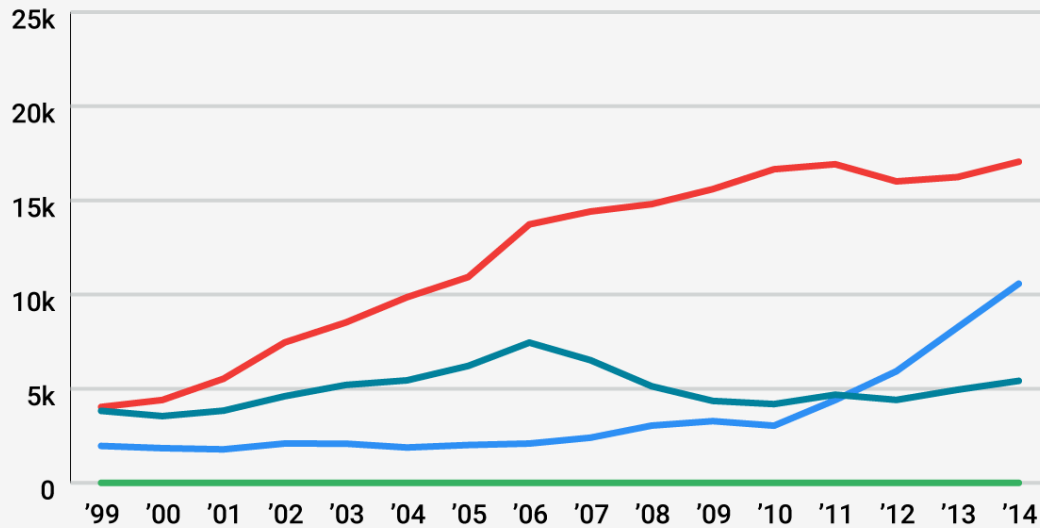- Ignoring the "Harms" of medical marijuana

"HIGH HOPES RIDE ON LEGAL MARIJUANA AMID OPIOID CRISIS"

OVERDOSE DEATH RATES IN AMERICA

Opioid Pain Relievers · Heroin · Cocaine · Marijuana
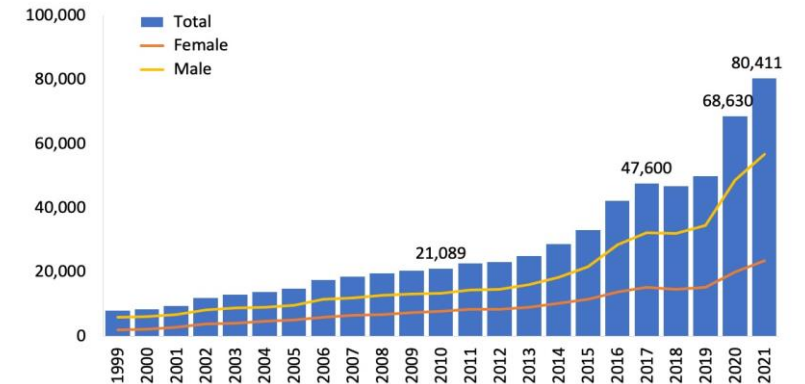
All underlying causes of death*

*Includes deaths from unintentional drug poisoning, suicide drug poisoning, homicide drug poisoning or drug poisoning of undetermined intent.

SOURCE: Wonder.cdc.gov; drugabuse.gov — BUSINESS INSIDER

Figure 3. National Overdose Deaths Involving Any Opioid*, Number Among All Ages, by Gender, 1999-2021

*Among deaths with drug overdose as the underlying cause, the "any opioid" subcategory was determined by the following ICD-10 multiple cause-of-death codes: natural and semi-synthetic opioids (T40.2), methadone (T40.3), other synthetic opioids (other than methadone) (T40.4), or heroin (T40.1). Source: Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2021 on CDC WONDER Online Database, released 1/2023.

Figure 1. National Drug-Involved Overdose Deaths*, Number Among All Ages, by Gender, 1999-2021
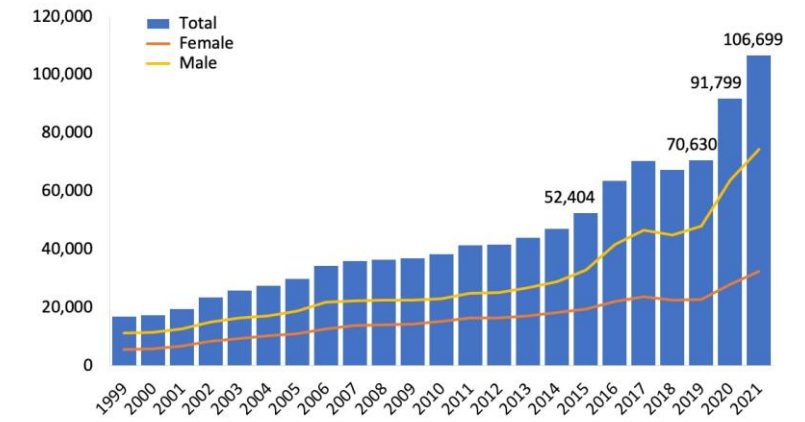
*Includes deaths with underlying causes of unintentional drug poisoning (X40–X44), suicide drug poisoning (X60–X64), homicide drug poisoning (X85), or drug poisoning of undetermined intent (Y10–Y14), as coded in the International Classification of Diseases, 10th Revision. Source: Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2021 on CDC WONDER Online Database, released 1/2023.

LEARNING OBJECTIVES

- Medicine by "Popular-vote" vs. Evidence-based and the State-based Cannabis Initiatives: Follow the Money

- Review the History of Botanical/Medicinal Cannabis

- Mention the Components of the Human Endocannabinoid System and Promising Pharmacologic Applications of Phytocannabinoids

- Review the Recent Evidence-based Research of Cannabinoid Compounds

- Discuss the Use and Potential Abuse of Cannabinoids

NO DISCLOSURES TO REPORT
ONLY FDA APPROVED INDICATIONS

Medical-Use Update

As of Apr. 24, 2023, 38 states, three territories and the District of Columbia allow the medical use of cannabis products. See Table 1 below for additional information.

Non-Medical/Adult-Use Update

As of June 1, 2023, 23 states, two territories and the District of Columbia have enacted measures to regulate cannabis for adult non medical use.

Low-THC Update

Approved measures in 9 states allow the use of "low THC, high cannabidiol (CBD)" products for medical reasons in limited situations or as a legal defense. (See Table 2 below for more information). Low-THC programs are not counted as comprehensive medical cannabis programs. NCSL uses criteria similar to other organizations tracking this issue to determine if a program is "comprehensive":

1. Protection from criminal penalties for using cannabis for a medical purpose.
2. Access to cannabis through home cultivation, dispensaries or some other system that is likely to be implemented.
3. It allows a variety of strains or products, including those with more than "low THC."
4. It allows either smoking or vaporization of some kind of cannabis products, plant material or extract.
5. Is not a limited trial program. (Nebraska has a trial program that is not open to the public.)

MAP: State Regulated Cannabis Programs

Notes: The District of Columbia allows limited adult possession and growing, no regulated production or sales.

ROLLING STONE

- *Cannabis sativa/Indica*
- *400 chemical compounds*
- 66 different cannabinoids
- 104 Unique to Cannabis Plant
- Phytocannabinoids: delta9-THC: Cannabidiol (CBD)
- Tetrahydrocannabivarin (THCV), Cannabichromene (CBC), Cannabigerol (CBG)
- All are lipophilic
- Amounts vary in growing conditions
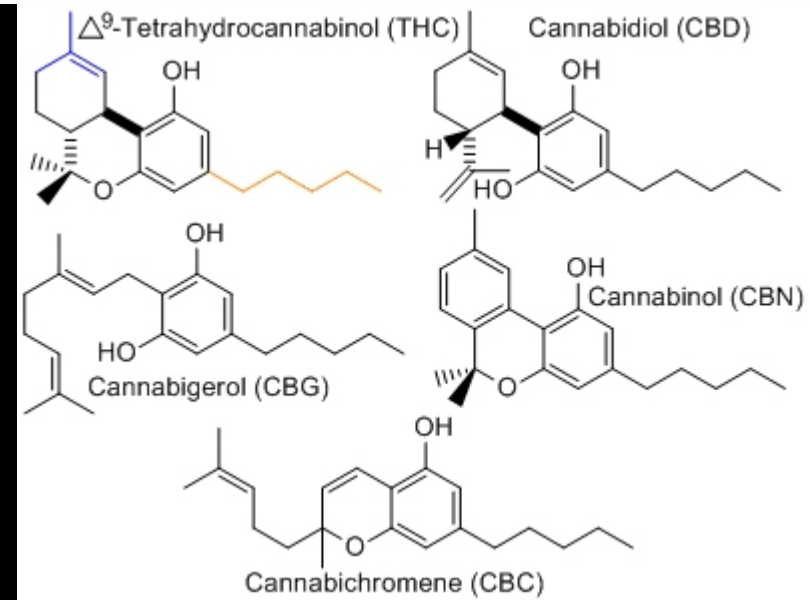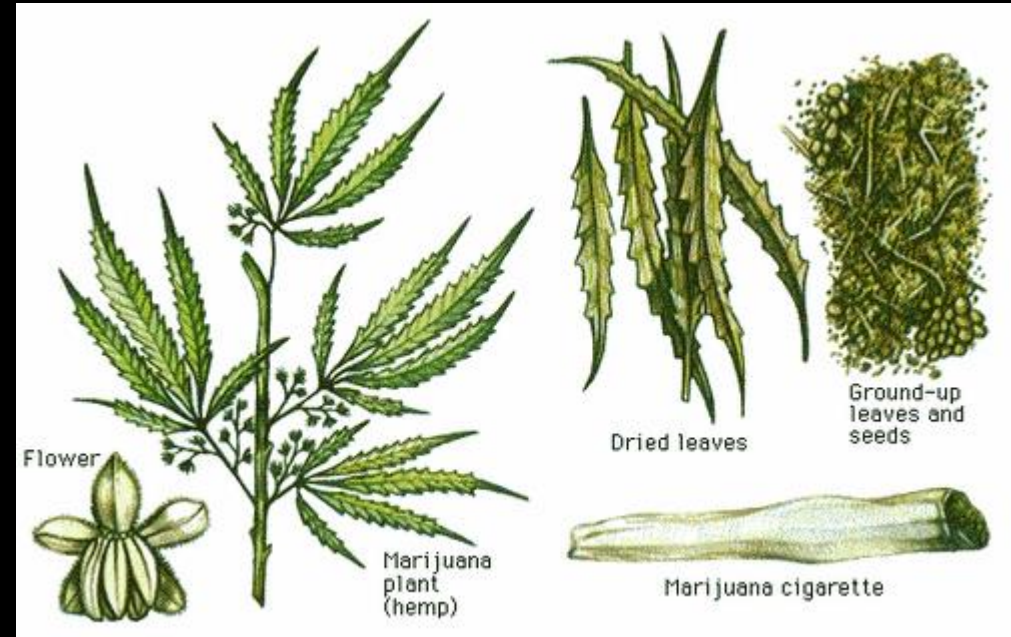
TERPENES

- Aromatic compounds produced in the glandular flower bud
- Not phytocannabinoids
- Limonene, pinene, myrcene, etc
- Responsible for aromatic/odorous character
- *May involve modulating effects of THC and CBD*
- *Content ? Related to distinction of sativa vs indica*

SATIVA

DAY TIME USE

CEREBRAL HIGH

ENERGETIC

STIMULATE APPETITE

ENHANCES CREATIVY

RELIEVES DEPRESSION

HIGHER THC LEVEL

INDICA

NIGHT TIME USE

BODY HIGH

SEDATIVE

RELIEVES ANXIETY

CAUSES SLEEPINESS

RELIEVES PAIN

HIGHER CBD LEVEL

CANNABINOID BIOLOGY

- Cannabinoid receptors characterized in 1980-90's (CB1 and CB2)

- Likely have a natural role in pain modulation, movement control, and memory

- Role in immune systems is likely multi-faceted and remains unclear

- Brain develops tolerance

- Animal research demonstrates potential for dependence

- Withdrawal symptoms can be observed in animals but appear to be mild compared to opiates and benzos

The cannabinoid receptors are further divided into 2 main subtypes, known as cb1 and cb2.

CB1 is found mostly in the brain.

CB2 receptors are mostly found within the immune system.

Endocannabinoid Receptors

- CB1: Brain, spinal cord, connective tissue, reproductive organs, glands, internal organs

- CB2: Spleen, tonsils, GI, thymus gland. White blood cells: T-cells, B-cells, macrophages

- GPR55, GPR18: Regulator of neuroimmune function

- GPR3, GPR6 and GPR12 orphan receptors

RETROGRADE SIGNALING

ENDOCANNABINOID SYSTEM

NOT NEW!

Cannabis Timeline & Important Periods

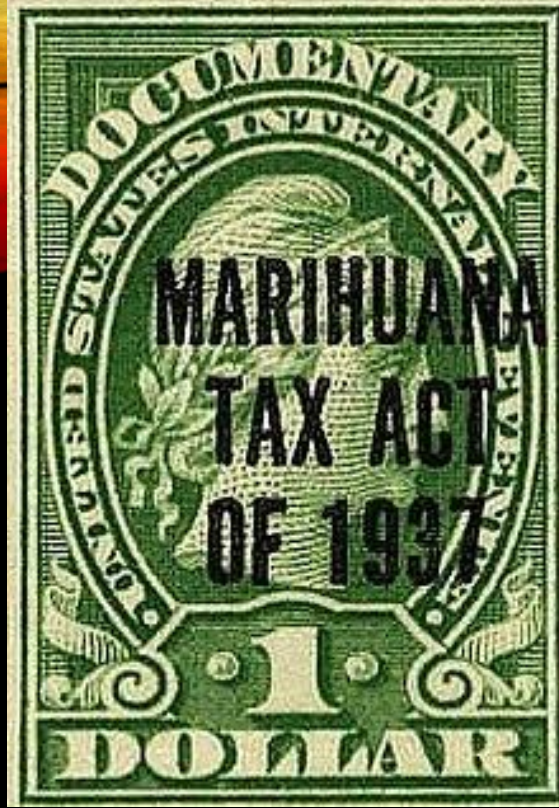| ancient times		recent history		drug discovery		legalization	
Hemp farming in China	6500 BCE	Hemp In Americas	1500's	Marijuana Act	1938	Oregon Decriminalizes	1973
Carbon Dating Fiber Use	4000 BCE	Cannabis Sativa	1737	Hemp Stopped	1958	California Goes Medical	1996
Hindi Texts Reference	2000 BCE	Cannabis Indica	1785	THC Discovered	1960's	First Rec. States Pass	2012
Auryvedic Medicine Uses	900 BCE	Heavy Textile Use	1800's	Dranabinol Used	1986	Hemp Farm Bill	2014
European Cultivation	500 BCE	American Farming	1900's	Endocannabinoid System	1988	FDA Approves Epidiolex	2020
Greek Physicians Recommend	200 CE	Dr. Recommended	1915	Endocannabinoids	1992	House Passes decriminalization	2021

There's certainly room for debate on this, but the researchers said that the timeline started about 5,000 years ago in China. The so-called "father" of Chinese agriculture, emperor Chen Nung, included the plant in the first Chinese pharmacopeia. That text said cannabis was prescribed for "fatigue, rheumatism and malaria."
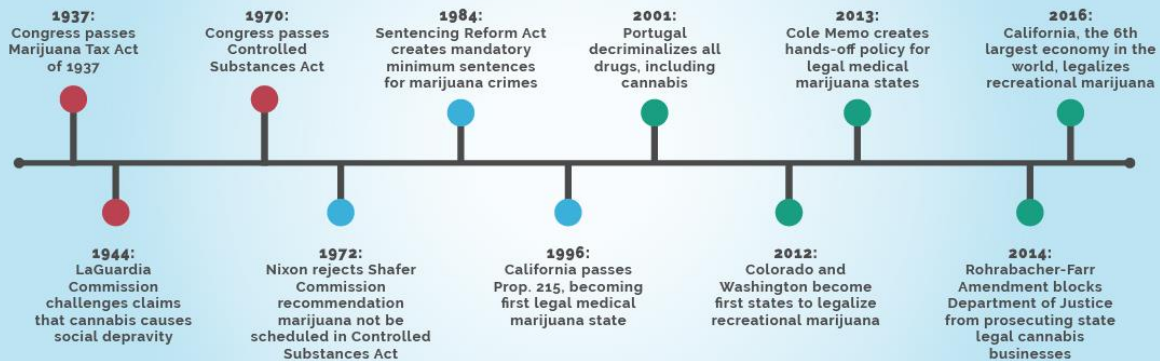
Via the Journal of Ethnophamacology.
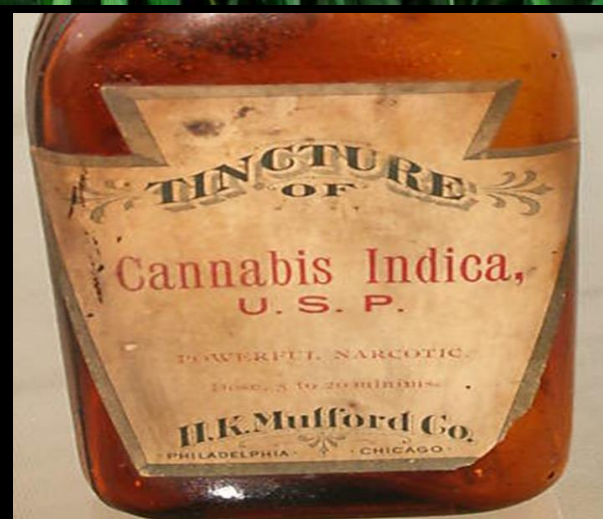
The Legalization of Marijuana

1937: Congress passes Marijuana Tax Act of 1937

1944: LaGuardia Commission challenges claims that cannabis causes social depravity

1970: Congress passes Controlled Substances Act

1972: Nixon rejects Shafer Commission recommendation marijuana not be scheduled in Controlled Substances Act

1984: Sentencing Reform Act creates mandatory minimum sentences for marijuana crimes

1996: California passes Prop. 215, becoming first legal medical marijuana state

2001: Portugal decriminalizes all drugs, including cannabis

2012: Colorado and Washington become first states to legalize recreational marijuana

2013: Cole Memo creates hands-off policy for legal medical marijuana states

2014: Rohrabacher-Farr Amendment blocks Department of Justice from prosecuting state legal cannabis businesses

2016: California, the 6th largest economy in the world, legalizes recreational marijuana

1. **California's Proposition 215 (1996)**. With this ballot initiative, California became the first state to legalize medical marijuana. California was the first domino to fall and gave organizers outside the state the confidence to push for the legalization of medical marijuana in their states.

2. **Colorado's Amendment 64 (2012)**. Colorado became one of the first two states to legalize recreational marijuana through a ballot initiative. The state also set the standard for others in how to regulate recreational marijuana, with sales of both medical and recreational cannabis of $1.5 billion in 2017.

3. **Washington's Initiative 502 (2012)**. Washington state residents voted to legalize recreational marijuana at the same time Colorado did. While Washington's recreational cannabis market hasn't been quite as large as in its fellow pioneer state, total marijuana spending last year in the state was $934 million.

4. **California's Proposition 64 (2016)**. California's passage of a ballot initiative to legalize recreational marijuana is important because of the state's size. The medical marijuana market in California was nearly $3 billion last year, roughly twice the size of Colorado's total marijuana market. By 2022, California's total marijuana market could be in the ballpark of $7.7 billion, according to projections from Arcview Market Research and BDS Analytics.

When Gallup first asked about legalizing marijuana in 1969, 12% of Americans were in favor. Support grew from there, reaching 31% in 2000 and surpassing the majority level in 2013. Since 2016, at least six in 10 have been in favor.

The latest results are based on an Oct. 3-20 Gallup poll.

Americans' Support for Legal Marijuana

Do you think the use of marijuana should be legal, or not?
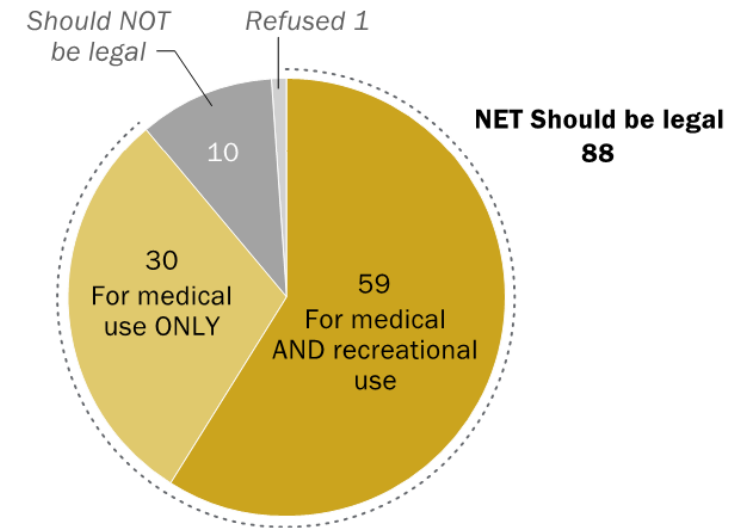
— % Yes, legal
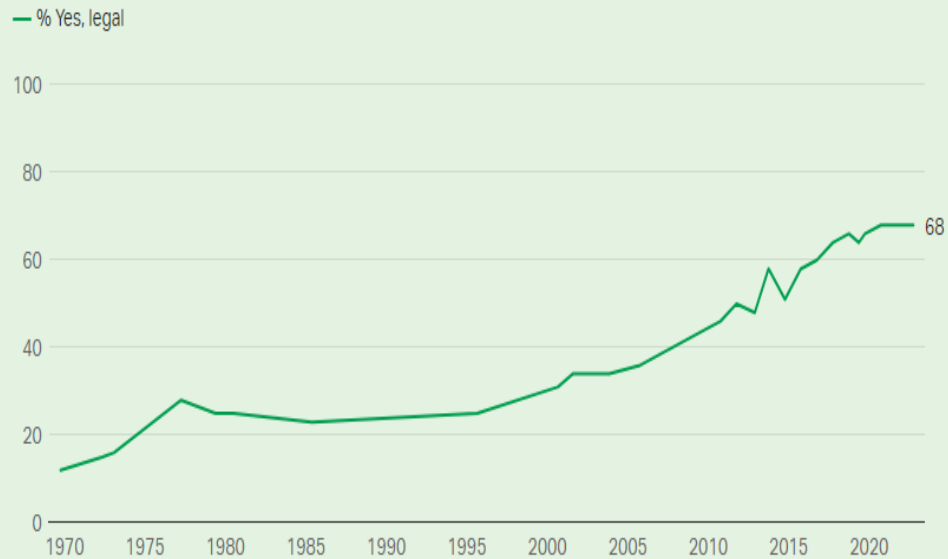
Get the data • Download image

GALLUP

Just one-in-ten U.S. adults say marijuana should not be legal at all

Just one-in-ten U.S. adults say marijuana should not be legal at all

% of U.S. adults who say marijuana …

Should NOT be legal — 10

Refused 1

NET Should be legal 88

30 For medical use ONLY

59 For medical AND recreational use

Source: Survey of U.S. adults conducted Oct. 10-16, 2022.

PEW RESEARCH CENTER
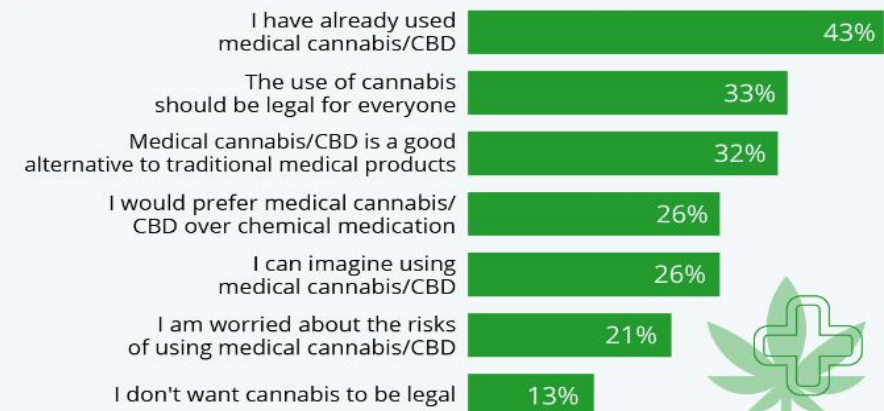
There's No Stopping the Cannabis Revolution

BY NORML | JULY 19, 2023
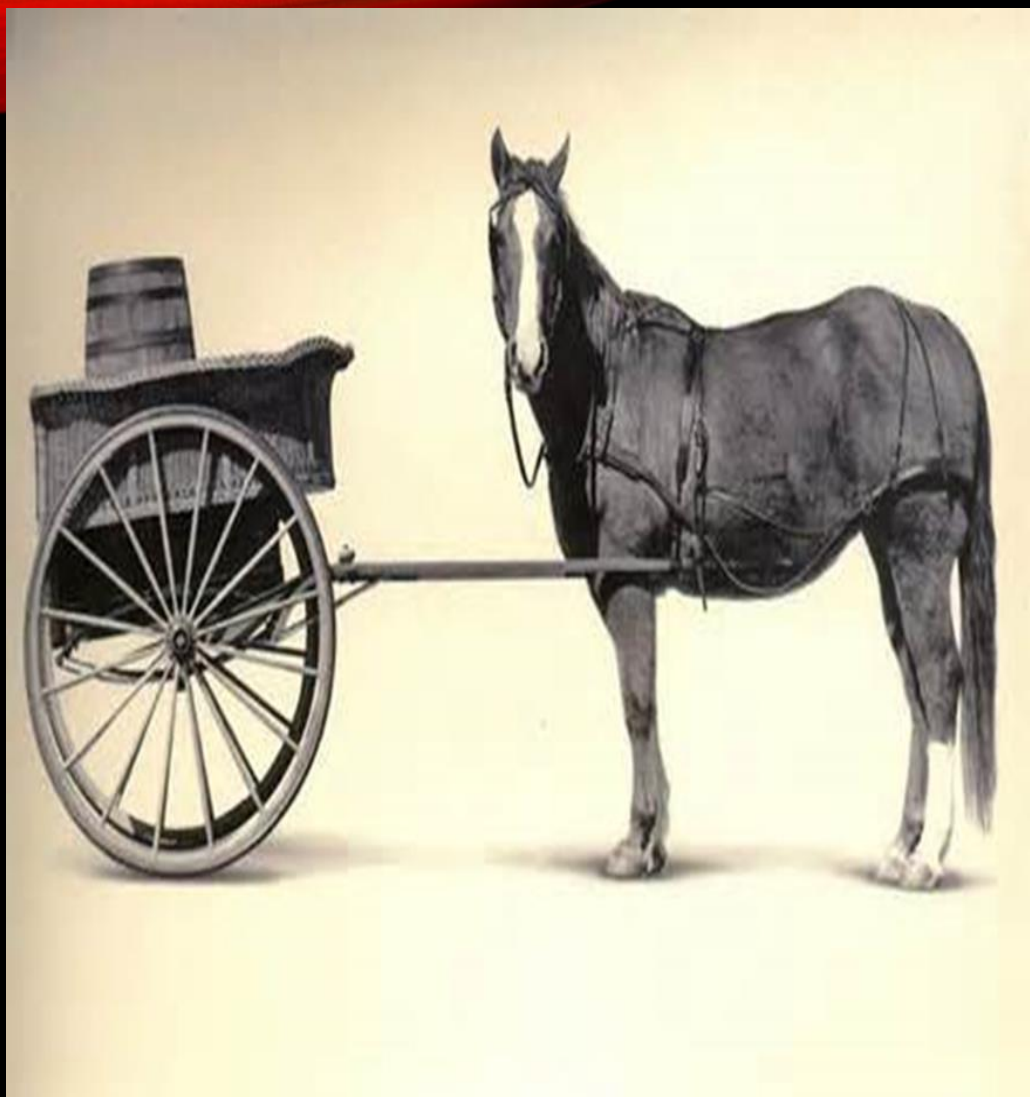
We are in the midst of a cannabis revolution.

Twenty-three states have legalized the use of cannabis for responsible adults, and nearly 70 percent of Americans now support this common-sense policy.

Earlier this month, Marylanders experienced their first taste of cannabis freedom. In a few weeks, Minnesotans will join them.

Who will be the next?

U.S. DEA DRUG SCHEDULING

Schedule	Definition	Examples
I	Drugs, substances, or chemicals are defined as **drugs with no currently accepted medical use and a high potential for abuse.**	Cannabis Heroin LSD

Dec. 1, 2022

Less than two miles from Ryan McLaughlin's cannabis research lab at Washington State University (WSU) in Pullman, there are dispensaries that legally sell cannabis products many times stronger than what his lab can obtain through the federal government for research.

"It's very frustrating for me in a state that has legal recreational cannabis," says McLaughlin, PhD, an associate professor of integrative physiology and neuroscience and part of WSU's Center for Cannabis Policy, Research, and Outreach. "I could go to a cannabis store and … [find] everything under the sun and different ways of consuming it. But for me, as a researcher, my hands are tied."

McLaughlin uses animal models to study the effects of cannabis use on the brain and behavior. But because cannabis is labeled a Schedule 1 drug by federal law, meaning it is considered to have high potential for abuse and no accepted medical benefits, McLaughlin can only obtain his product from the University of Mississippi, the sole grower authorized by the U.S. Drug Enforcement Agency.
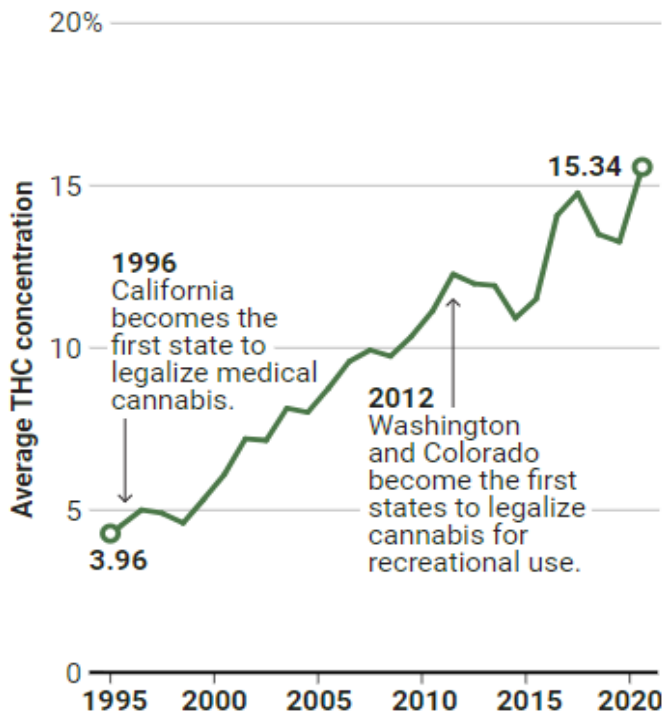
AAMCNEWS

How risky is recreational marijuana use? No one really knows.

As more states legalize recreational cannabis, physicians and scientists still know very little about its risks and benefits. That's largely due to federal restrictions on research.

WHERE WAS/IS THE IRB?

As of May 2023, 23 states and the District of Columbia have already been down this path. Their experiences implementing new laws can serve as a potential roadmap for other states considering legalization. To paraphrase US Supreme Court Justice Louis Brandeis, states can serve as "laboratories of democracy" that can inform legislation in other states.

- Legalized recreational and medical marijuana
- Legalized medical marijuana

Higher times

Cannabis plants, resins, and oils have gotten far more potent over the past quarter-century, according to an analysis of illegal samples seized by the U.S. Drug Enforcement Administration. Concentrations of tetrahydrocannabinol (THC), the main psychoactive ingredient, have risen as states have legalized cannabis use.

1996 California becomes the first state to legalize medical cannabis.

2012 Washington and Colorado become the first states to legalize cannabis for recreational use.

3.96

15.34

(GRAPHIC) D. AN-PHAM/*SCIENCE*; JULIA GREENWOOD/*SCIENCE*;
(DATA) *POTENCY MONITORING PROGRAM QUARTERLY REPORT #153,*
NATIONAL INSTITUTE ON DRUG ABUSE

Jan 14, 2021).

A standard THC unit for reporting of health research on cannabis and cannabinoids

Cannabis is widely used worldwide, with an estimated 200 million people reporting past year use. However, our knowledge about the health effects of cannabis use is limited, in part due to the absence of standardised measures for quantifying and reporting delta-9-tetrahydrocannabinol (THC), the primary psychoactive cannabinoid in cannabis products. Current reporting practice often includes frequency of use but lacks a suitable measure of dose (ie, how much is consumed). Common measures of dose (eg, weight of cannabis in grams, number of joints smoked) have important limitations. First, these measures are unable to capture the increasingly diverse range of cannabis products and methods of use (eg, edibles, drinks, vaping, and dabbing).[1] Second, concentrations of THC have increased internationally and vary substantially across different cannabis products,[2] which limits the precision of these measures (eg, grams of cannabis or number of joints smoked) for estimating the dose of THC. Third, inconsistencies in methodology and reporting practice hinder our understanding of the health effects of THC, both in terms of adverse outcomes (eg, psychotic disorders, neuroanatomical alterations)[3] and potential benefits (eg, treatment of chronic pain).

In 2018, the need to establish a standardised dose for cannabis was identified as the top priority of the US National Institute on Drug Abuse Cannabis Policy Research Workgroup,[4] on the premise that standardised measures had proved useful for alcohol and other drugs. Yet, because of the range of different cannabis products and formulations, there was no similar concept or measure for cannabis available.[4] In 2019, we proposed the standard THC unit: a dose of 5 mg of THC.[5] Similar to standard alcohol units, which are measured in
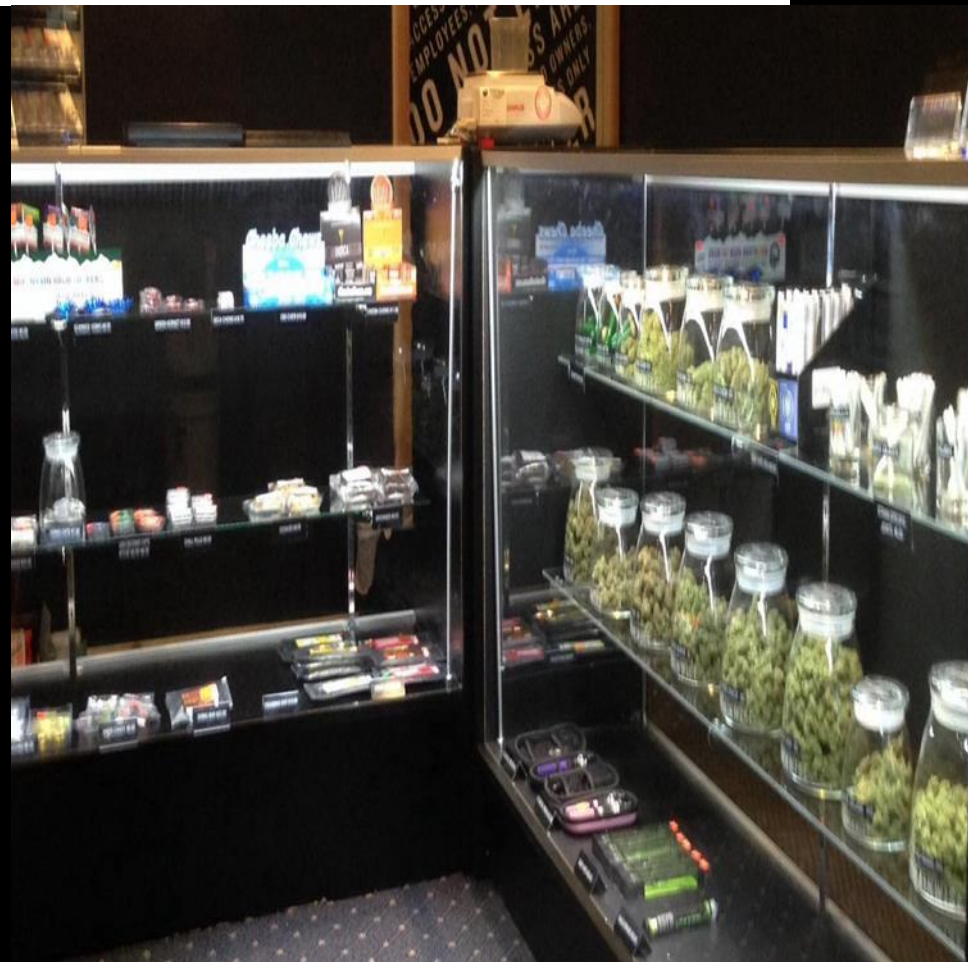

Vaping oil: *"Filthy Laboratory"*

Cannabinoid Dose and Label Accuracy in Edible Medical Cannabis Products

Ryan Vandrey, PhD[1]; Jeffrey C. Raber, PhD[2]; Mark E. Raber[2]; et al

≫ Author Affiliations | Article Information

Results

Of 75 products purchased (47 different brands), 17% were accurately labeled, 23% were underlabeled, and 60% were overlabeled with respect to THC content (Table 1). The greatest likelihood of obtaining under-labeled products was in Los Angeles and overlabeled products in Seattle (x^2=12.94, P=.01).

Non-THC content was generally low (Table 2). Forty-four products (59%) had detectable levels of CBD; only 13 had CBD content labeled. Four products were underlabeled and 9 were overlabeled for CBD. The median THC:CBD ratio of products with detectable CBD was 36:1, 7 had ratios of less than 10:1, and only 1 had a 1:1 ratio.

ACOi **2023** October 11-14
Tampa • Hybrid

Despite Some Stumbles, Total Sales In U.S. Cannabis Market Could Soar To $50.7 Billion By 2028, Says Top Researcher

- Retail cannabis sales in the U.S. are on pace to surpass $33 billion by the end of 2022 and more than $52 billion by the end of 2026. (MJBiz Factbook)
- U.S. medical and recreational cannabis sales saw noticeable jumps in 2021 by approximately 34% and 43%, respectively, compared to 2020 sales. (MJBiz Factbook)
- 46% of consumers get their cannabis products from a dispensary. (Leafly – Seeds of Change)
- 20% of dispensary shoppers say that mood-specific labeling influences their purchase decision. (Cannabis Products)
- Female consumers account for less than one-third of total U.S. cannabis sales. But their sales are growing faster than those of male consumers. (Headset)
- Marijuana sales soared during the first year of the pandemic. Americans spent more than $18 billion on cannabis in 2020 – a 71% increase over 2019 sales. (Leafly)
- In 2021, U.S. cannabis sales for 4/20 reached $175.6 million. (Statista)
- After 4/20, occasions with the highest cannabis sales during 2021 were: Green Wednesday, Memorial Day weekend, Valentine's Day, and New Year's Eve. (Eaze)
- Almost half (45%) of current consumers purchase cannabis at least once per week. (New Frontier Data – Cannabis Consumers in America)
- Consumer spending, on average, is highest for flower ($98) and vapes ($92) and lowest for topicals ($57) and pre-rolls ($38). (New Frontier Data – 2022 U.S. Cannabis Report)

- Approximately 52 million U.S. adults will consume cannabis at least once in 2022 in both legal and unregulated markets. (New Frontier Data – 2022 U.S. Cannabis Report)
- The number of cannabis consumers in the U.S. is expected to grow by about 4% every year for the next eight years, reaching an estimated 71 million consumers by 2030. (New Frontier Data – 2022 U.S. Cannabis Report)
- The United Nations estimated that 192 million people globally used cannabis in 2018, making it the most used substance worldwide. (United Nations Office on Drugs and Crime)
- In 2021, nearly half of U.S. adults (49%) said they have tried marijuana, up from 45% in 2019. (Gallup)
- Generation Z is the age demographic to keep an eye on – the U.S. market share of this age group has more than doubled in the last two years, rising from 8.3% in Q1 2020 to 15% in Q4 2021. (Headset)
- When asked why they use cannabis, more people cited stress (21.9%) and mental health (21.5%) management than any other reason. (Eaze)
- 37% of consumers use cannabis with workout routines. (Eaze)
- 55% of current consumers are dual-use consumers, meaning their cannabis use is both medical and recreational. (New Frontier Data – Cannabis Consumers in America)
- For many consumers, cannabis has become part of their regular routine – 47% of consumers use cannabis daily, and 67% consume it more than once a week. (New Frontier Data – Cannabis Consumers in America)
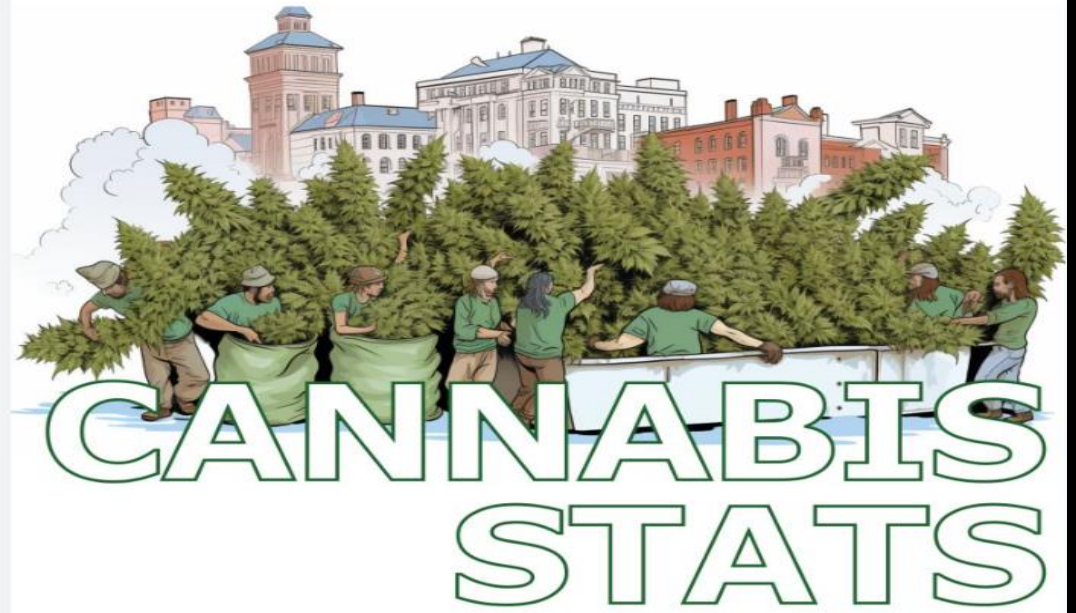
CANNABIS STATS

- The cannabis industry could add nearly $100 billion to the American economy by the end of 2022 and around $155 billion by 2026. (MJBizDaily)
- In 2020, North America had the largest share of legal cannabis sales worldwide, accounting for nearly the entire market. (Statista)
- California is the single largest cannabis market in the world – larger ev than all of Canada. (Statista)
- North American cannabis companies raised more than $1.6 billion in January 2021 alone. (MJBizDaily)

Cannabis Industry Statistics on Product Trends

- Flower is still the most purchased cannabis product, but its market share is declining. Flower sales in the U.S. increased from $4.92 billion in 2020 to $5.49 billion in 2021, but its overall market share dropped. ([MJBiz Daily](#))
- Vapes came in second for product revenue in 2021 in the U.S., with nearly $2.6 billion in retail sales and 28% year-over-year growth. ([Headset](#))
- Marijuana-infused beverages are gaining popularity, with a 45% jump in year-over-year growth in 2021. ([Headset](#))
- Pre-roll sales went from $1.02 billion in 2020 to $1.42 billion in 2021, a 38.9% increase. ([Headset](#))
- 37% of U.S. consumers say that taste/flavor is the most important factor in deciding what cannabis products to buy, followed by high THC content (33%) and low price (27%). ([Deloitte](#))
- Edibles are expected to make up 15% of the cannabis market by 2025. ([Cannabis Products](#))
- Around half (51%) of all consumers – and 61% of those under 35 – say they are interested in trying new cannabis products. ([New Frontier Data – Cannabis Consumers in America](#))

BUSINESS

States Have Generated Over $15 Billion In Marijuana Tax Revenue Since 2014, Though Earnings Declined Last Year, Report Finds

Published 4 months ago on May 1, 2023

- As of April 2022, 77% of the U.S. population live in a state with some form of legalized cannabis. (MJBiz Factbook)
- 91% of Americans favor some type of marijuana legalization. 60% say it should be legal for medical and recreational use, while 31% think it should only be made legal for medical reasons. Just 8% of Americans don't support any legalization. (Pew Research Center)
- 77% of consumers think there should be public spaces (like cafes) where cannabis use is allowed. (New Frontier Data – Cannabis Consumers in America)
- Every state without legalization shares at least one border with a state that has legalized cannabis. (MJBiz Factbook)
- Texas accounts for more than one-third of the population without legal access to cannabis. (MJBiz Factbook)
- The transition between medical and recreational markets has accelerated. California took 7,308 days between the legalization of medical marijuana to the first recreational sale. In 2020, South Dakota became the first state to have medical and recreational use approved at the same time. (MJBizDaily and MJBiz Factbook)
- Eighteen more states are poised to legalize medical or recreational cannabis over the next decade. (New Frontier Data – 2022 U.S. Cannabis Report)
- If all 18 potential states pass legalization measures, 96% of Americans will live in a state with some form of legal cannabis access. (New Frontier Data – 2022 U.S. Cannabis Report)

The Economist

After New Hampshire: now what?
The great bank scare
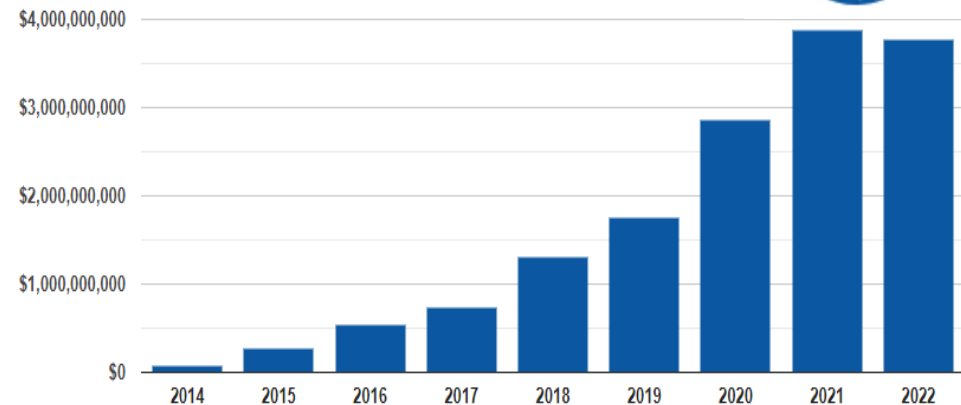Einstein's triumph
Don't dam the Mekong
The dismal science of love

FEBRUARY 13TH–19TH 2016

The right way to do drugs

fig.3

Legalising cannabis safely

Combined Totals By Year (All States)

MPP — We Change Laws, We Change Lives
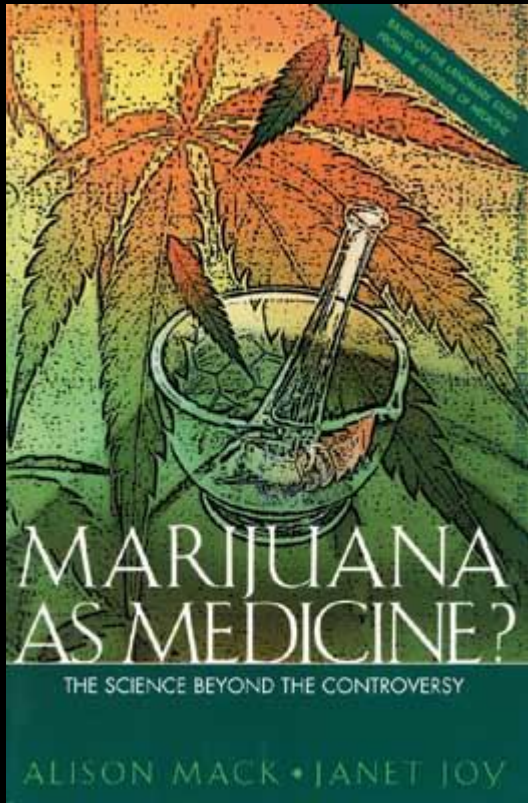
Science of Cannabis
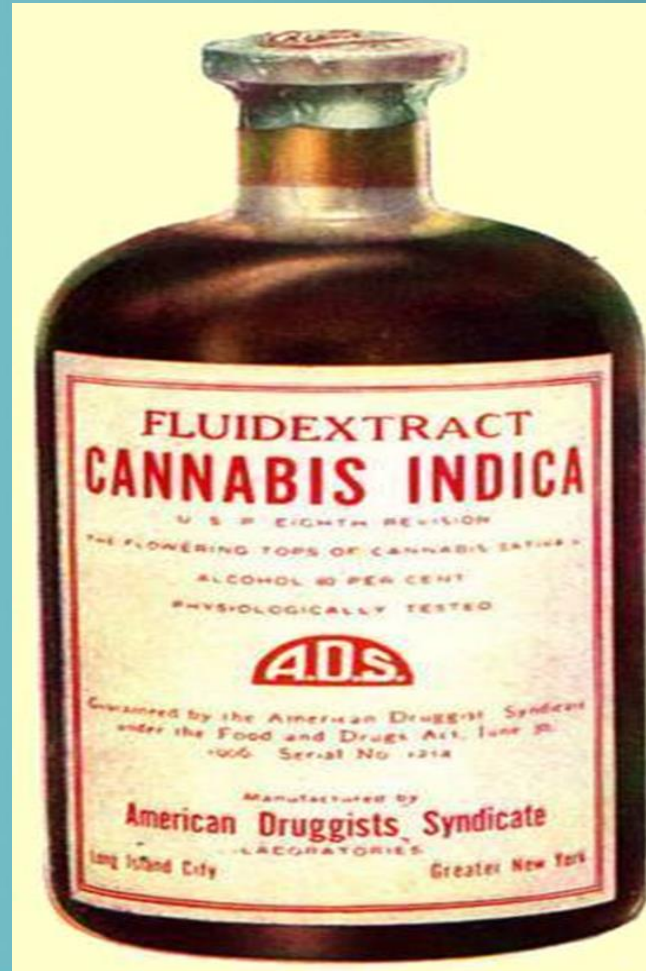
INSTITUTE OF MEDICINE: 1997 & 2003

SUMMARY OF RESEARCH

- More than 30 yrs of clinical research
- Only small number of randomized, controlled trials of "smoked cannabis"
- Short term with a total of about 300 patients
- Indicate: reduction in neuropathic pain
- Improves appetite and caloric intake
- Spasticity relief in MS
- Better alternatives are available to Rx glaucoma and chemo-induced N & V

MARIJUANA AS MEDICINE?
THE SCIENCE BEYOND THE CONTROVERSY

ALISON MACK • JANET JOY

CANNABINOIDS FOR MEDICAL USE: 23 JUNE 2015

- Systemic Review and Meta-Analysis

- 79 Trials: (6462 participants)

- Study Selection: "Randomized clinical trials of cannabinoids for the following indications:

- 1. Nausea and vomiting associated with ChemoRX

- 2. Appetite Stimulation in HIV/SIDS

- 3. Chronic Pain

- 4. Spasticity due to MS/paraplegia

- 5. Anxiety/Depression: Sleep Disorder

- 6. Psychosis: glaucoma, Tourette Syndrome

CANNABINOIDS FOR MEDICAL USE (CONT)

- Most trials showed improvement in "SYMPTOMS"…Did NOT meet statically significance in all trials
- N&V: greater than average showing response comp. with placebo
- Pain: greater than average reduction in numerical pain scale rating
- Spascity: Average reduction
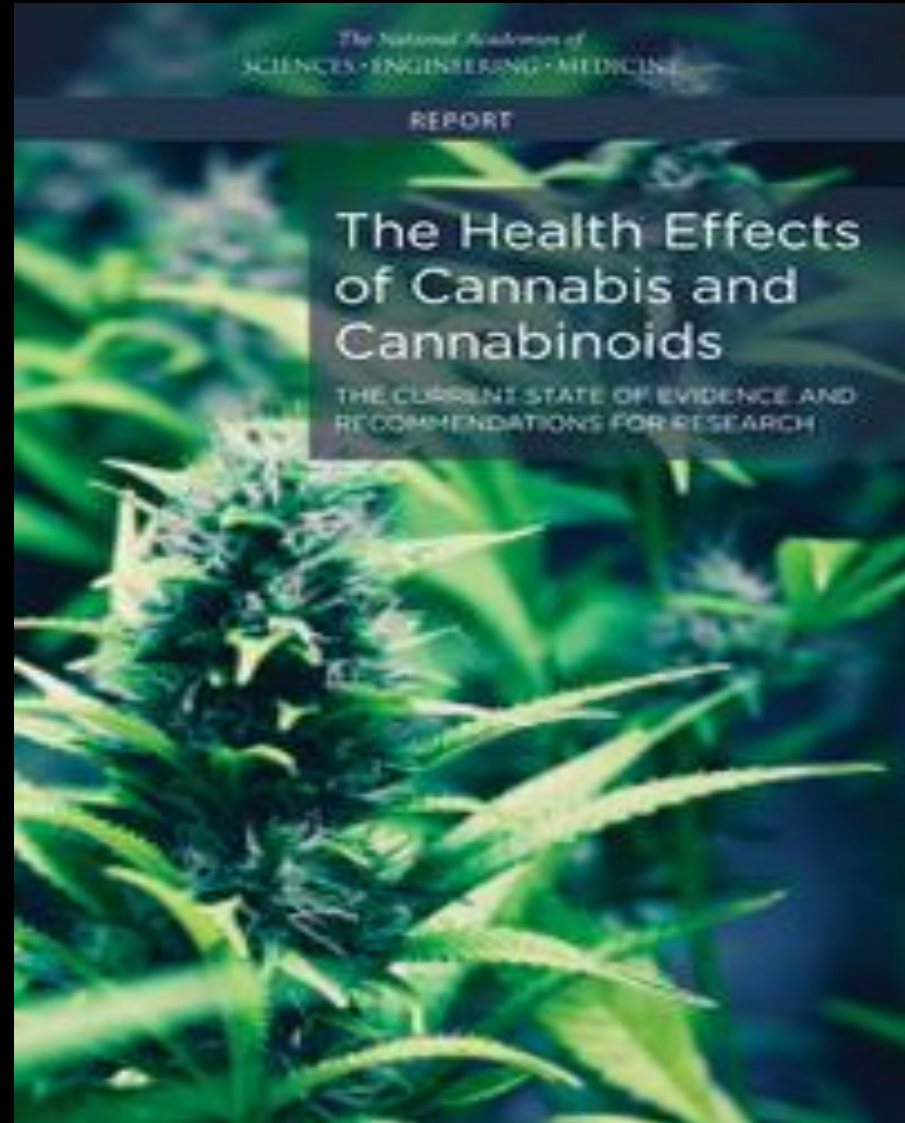
CONCLUSIONS AND RELEVANCE

- Moderate-quality evidence to Support cannabinoid use for Chronic Pain and Spascity

- Low-Quality evidence: Suggesting that Cannabinoids were associated with Improvements in N&V due to ChemoRx, Weight gain in HIV, Sleep Disorders, and Tourettes

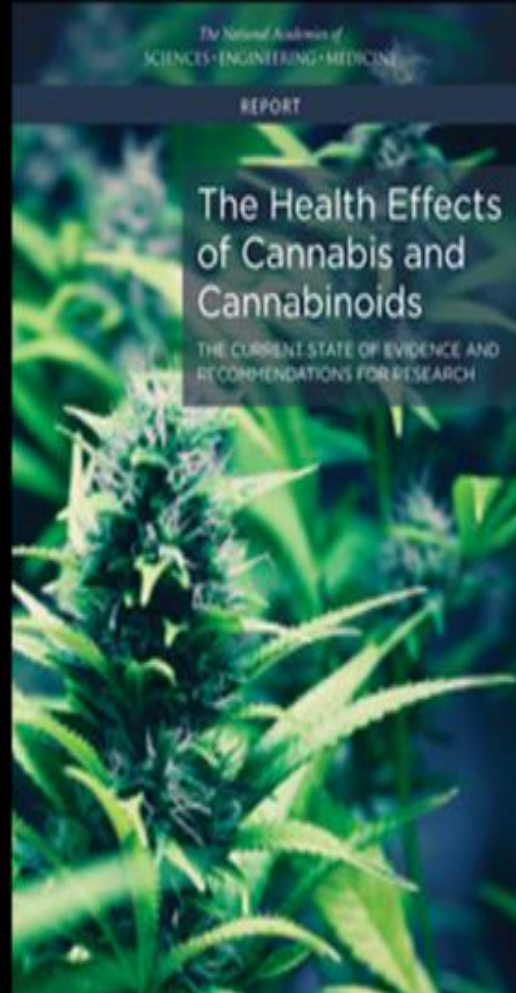- Cannabinoids were associated with an Increase risk of short term AE

12 JANUARY 2017

The National Academies of
SCIENCES · ENGINEERING · MEDICINE

- "Conclusive or Substantial":   Can treat chronic pain in adults

Nausea and vomiting in ChemoRx

Improve reported MS spasticity

"Substantial Evidence"   Smoking: worse respiratory S/S

Increase bronchitis

Risk MVC

Low Birth weight pregnancy

Increase psychosis/frequent use

Use at "earlier age" problematic

- "No Evidence":   In Rx Depressive Disorders and PTSD

- "Limited Evidence":   Associated impaired academic performance and social functioning: nor increased rates of unemployment and low income

   Research Barriers: Schedule I

                       Difficulty "to gain access to quantity, quality, and type of cannabis product necessary to address specific research questions on health effects"

TRIAL OF CBD FOR DRUG-RESISTENT SEIZURES IN DRAVET SYNDROME

- 31 May 2017
- Complex childhood epilepsy disorder
- Double blind placebo controlled
- 120 participants: 20mg/kg
- 14 weeks
- With CBD decreased seizures/month12.5 to 9
- Placebo 14.9 to 14.1
- AE: CBD diarrhea, vomiting, fatigue, pyrexia, somnolence, LFT
- More withdrawals in CBD
- Greater reduction in seizure frequency
- Funded by GW Pharm

19 APRIL 2018: FDA ADVISORY PANEL UNANIMOUSLY RECOMMENDS APPROVAL

A Mapping Literature Review of Medical Cannabis Clinical Outcomes and Quality of Evidence in Approved Conditions in the USA from 2016 to 2019

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Abstract
In 2017, a National Academies of Sciences, Engineering, and Medicine (NASEM) report comprehensively evaluated the body of evidence regarding cannabis health effects through the year 2016. The objectives of this study are to identify and map the most recently (2016–2019) published literature across approved conditions for medical cannabis and to evaluate the quality of identified recent systematic reviews, published following the NASEM report. Following the literature search from 5 databases and consultation with experts, 11 conditions were identified for evidence compilation and evaluation: amyotrophic lateral sclerosis, autism, cancer, chronic noncancer pain, Crohn's disease, epilepsy, glaucoma, human immunodeficiency virus/AIDS, multiple sclerosis (MS), Parkinson's disease, and posttraumatic stress disorder. A total of 198 studies were included after screening for condition-specific relevance and after imposing the following exclusion criteria: preclinical focus, non-English language, abstracts only, editorials/commentary, case studies/series, and non-U.S. study setting. Data extracted from studies included: study design type, outcome definition, intervention definition, sample size, study setting, and reported effect size. Few completed randomized controlled trials (RCTs) were identified. Studies classified as systematic reviews were graded using the Assessing the Methodological Quality of Systematic Reviews-2 tool to evaluate the quality of evidence. Few high-quality systematic reviews were available for most conditions, with the exceptions of MS (9 of 9 graded moderate/high quality; evidence for 2/9 indicating cannabis improved outcomes; evidence for 7/9 indicating cannabis inconclusive), epilepsy (3 of 4 graded moderate/high quality; 3 indicating cannabis improved outcomes; 1 indicating cannabis inconclusive), and chronic noncancer pain (12 of 13 graded moderate/high quality; evidence for 7/13 indicating cannabis improved outcomes; evidence from 6/7 indicating cannabis inconclusive). Among RCTs, we identified few studies of substantial rigor and quality to contribute to the evidence base. However, there are some conditions for which significant evidence suggests that select dosage forms and routes of administration likely have favorable risk-benefit ra-

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A Mapping Literature Review of Medical Cannabis Clinical Outcomes and Quality of Evidence in Approved Conditions in the USA from 2016 to 2019

Subject Area: General Medicine , Pharmacology , Public Health

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Article history

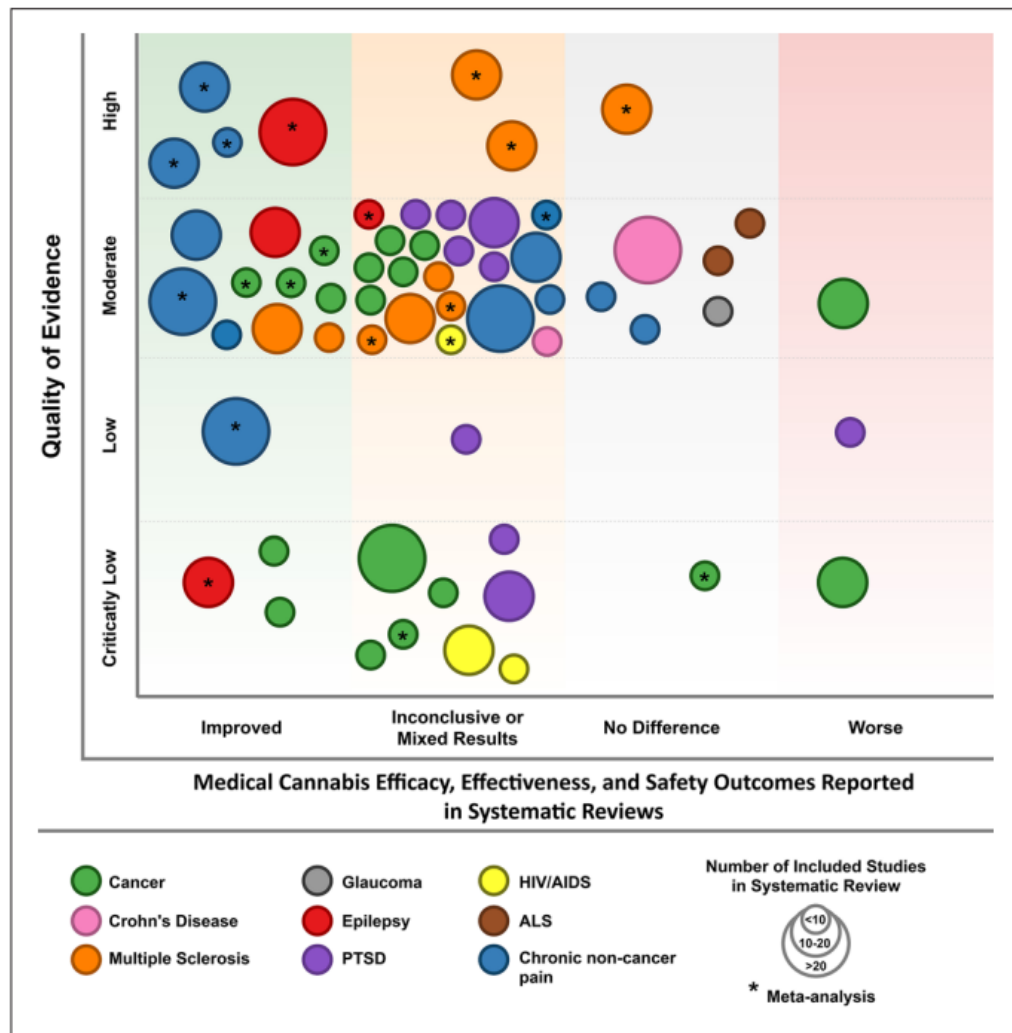**ARTICLE CONTENTS**
Abstract

Contents

Fig. 1. Quality of evidence among systematic reviews assessing medical cannabis efficacy, effectiveness, and safety outcomes in selected conditions. MS, multiple sclerosis; ALS, amyotrophic lateral sclerosis; PTSD, posttraumatic stress disorder; HIV, human immunodeficiency virus.

Limitations and Strengths

Our review has several limitations that should be considered in the interpretation of the findings. First, we restricted our search strategy to studies published between July 2016 and October 2019 and for our rapid review to studies published between 2000 and October 2019. Therefore, we assessed only a narrow period of the most recently available literature. Second, we excluded articles reporting primary research conducted exclusively outside the USA, in order to account for differences in cannabis product availability internationally as well as differences in regulatory barriers and access. We, therefore, have excluded potentially relevant recent literature conducted in countries with robust scientific and clinical research programs evaluating cannabis efficacy and safety. However, studies originating from the USA accounted for almost 2/3 of all publications between 2000 and 2017 [219]. Third, even though we conducted pilot runs and training with reviewers on the use of the data extraction tool, the data extraction step was only conducted by one reviewer with review by a second reviewer in cases of uncertainty. In addition, the screening process for each topic area was only conducted by a second reviewer for those articles categorized as "uncertain"; thus, selection bias might have been introduced during both stages. However, weekly meetings throughout the review process were used to clarify any questions and uncertainties throughout the screening and extraction process. Fourth, systematic reviews and meta-analyses were not excluded if they partially included studies that were not matching our criteria (e.g., a systematic review consisting of studies that were conducted between 2016 and 2019 but also prior to 2016 was still considered as eligible, since it was not feasible to disentangle the evidence synthesis without examining the underlying primary study). Therefore, our findings based on systematic reviews and meta-analyses might not be restricted to our

There are also several strengths of this review to consider, including the broad scope of assessed medical conditions, comprehensive search strategy that extended beyond RCTs, and adherence to the PRISMA statement for gathering and reporting findings. Furthermore, this review highlights recent research efforts by medical condition, and directions of findings, thus creating a comprehensive picture of the scientific landscape of clinical studies about cannabis. Moreover, we also identified several literature gaps that could be addressed in future research, and we assessed the quality of evidence available, which is essential information for policymaking. Additionally, input from an external expert panel ensured a wide range in scope of the literature covered, and this review gives an up-to-date overview about the current state of evidence quality in a readily interpretable map.

Conclusion

The large body of the literature recently published regarding medical cannabis masks a paucity of evidence related to efficacy and safety as treatment options for several conditions for which it is commonly prescribed. Across 11 conditions, we identified few studies of substantial rigor and quality to contribute to the evidence base. However, there are some conditions for which significant evidence suggests that certain dosage forms and routes of medical cannabis products likely have favorable risk-benefit ratios (i.e., epilepsy and chronic noncancer pain). Gaps in the evidence remain significant for most examined conditions, but the identification of several registered forthcoming RCTs suggests that improved evidence will be available in the coming years.

Check for updates

Balancing risks and benefits of cannabis use: umbrella review of meta-analyses of randomised controlled trials and observational studies

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Additional material is published online only. To view please visit the journal online.

ABSTRACT

OBJECTIVE
To systematically assess credibility and certainty of associations between cannabis, cannabinoids, and cannabis based medicines and human health, from observational studies and randomised controlled trials (RCTs).

DESIGN
Umbrella review.

DATA SOURCES
PubMed, PsychInfo, Embase, up to 9 February 2022.

ELIGIBILITY CRITERIA FOR SELECTING STUDIES
Systematic reviews with meta-analyses of observational studies and RCTs that have reported on the efficacy and safety of cannabis, cannabinoids, or cannabis based medicines were included. Credibility was graded according to convincing, highly suggestive, suggestive, weak, or not significant (observational evidence), and by GRADE (Grading of Recommendations, Assessment, Development and Evaluations) (RCTs). Quality was assessed with AMSTAR 2 (A Measurement Tool to Assess Systematic Reviews 2). Sensitivity analyses were conducted.

RESULTS
101 meta-analyses were included (observational=50,

RCTs=51) (AMSTAR 2 high 33, moderate 31, low 32, or critically low 5). From RCTs supported by high to moderate certainty, cannabis based medicines increased adverse events related to the central nervous system (equivalent odds ratio 2.84 (95% confidence interval 2.16 to 3.73)), psychological effects (3.07 (1.79 to 5.26)), and vision (3.00 (1.79 to 5.03)) in people with mixed conditions (GRADE=high), improved nausea/vomit, pain, spasticity, but increased psychiatric, gastrointestinal adverse event, and somnolence among others (GRADE=moderate). Cannabidiol improved 50% reduction of seizures (0.59 (0.38 to 0.92)) and seizure events (0.59 (0.36 to 0.96)) (GRADE=high), but increased pneumonia, gastrointestinal adverse events, and somnolence (GRADE=moderate). For chronic pain, cannabis based medicines or cannabinoids reduced pain by 30% (0.59 (0.37 to 0.93), GRADE=high), across different conditions (n=7), but increased psychological distress. For epilepsy, cannabidiol increased risk of diarrhoea (2.25 (1.33 to 3.81)), had no effect on sleep disruption (GRADE=high), reduced seizures across different populations and measures (n=7), improved global impression (n=2), quality of life, and increased risk of somnolence (GRADE=moderate). In the general population, cannabis worsened positive psychotic symptoms (5.21 (3.36 to 8.01)) and total psychiatric symptoms (7.49 (5.31 to 10.42)) (GRADE=high), negative psychotic symptoms, and cognition (n=11) (GRADE=moderate). In healthy people, cannabinoids improved pain threshold (0.74 (0.59 to 0.91)), unpleasantness (0.60 (0.41 to 0.88)) (GRADE=high). For inflammatory bowel disease, cannabinoids improved quality of life (0.34 (0.22 to 0.53)) (GRADE=high). For multiple sclerosis, cannabinoids improved spasticity, pain, but increased risk of dizziness, dry mouth, nausea, somnolence (GRADE=moderate). For cancer, cannabinoids improved sleep disruption, but had gastrointestinal adverse events (n=2) (GRADE=moderate). Cannabis based medicines, cannabis, and cannabinoids resulted in poor tolerability across various conditions (GRADE=moderate). Evidence was convincing from observational studies (main and sensitivity analyses) in pregnant women, small for gestational age (1.61 (1.41 to 1.83)), low birth weight (1.43 (1.27 to 1.62));

WHAT IS ALREADY KNOWN ON THIS TOPIC

Observational evidence reported that cannabinoids were associated with numerous health outcomes and have been tested for several conditions in randomised controlled trials

Credibility and coherence of findings from different sources of evidence on the same outcomes have not been assessed to date

WHAT THIS STUDY ADDS

Most outcomes associated with cannabinoids are supported by weak evidence (observational studies), low to very low certainty (randomised controlled trials), or are not significant (observational studies, randomised controlled trials)

Convincing or converging evidence recommends avoiding cannabis during adolescence and early adulthood in people prone to have or have mental health disorder, who are pregnant, and while driving

Cannabidiol is effective for epilepsy, notably in children, while other cannabinoids can be effective in use for multiple sclerosis, chronic pain, inflammatory bowel disease, and palliative care

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median Newcastle-Ottawa score of case-control and cohort studies was 7 (interquartile range 7-9).

Among the 187 randomised controlled trials, 64 reported on tetrahydrocannabinol, 32 on nabilone, 26 on nabiximols, 22 on cannabis, 18 on cannabidiol, and the remaining on various combinations of cannabis-based medicines, or other individual cannabis based medicines. Of these, 186 focused on medical use of cannabinoids, and one on recreational use; the route of administration was oral in 121, oral spray in 29, inhaled in 21, intravenous in six, intramuscular in four, oral and inhaled in three, and transdermal in two studies. The risk of bias was high in 79 randomised controlled trials, unclear in 55, low in 48, and moderate in five.

Discussion

Principal findings

This umbrella review grades the credibility and certainty of evidence on the effect of cannabinoid use, encompassing observational and interventional evidence.

Regarding harmful outcomes, among all meta-analytical associations supported by at least suggestive evidence in observational studies and moderate certainty in randomised controlled trials, converging evidence supports an increased risk of psychosis associated with cannabinoids in the general population. Specifically, cannabis use was associated with psychosis in adolescents (highly suggestive credibility, convincing in main sensitivity analyses) and adults (suggestive credibility, suggestive certainty), and with psychosis relapse in people with a psychotic disorder (weak credibility, suggestive certainty). Use of cannabinoids in adult non-clinical and clinical populations was associated with positive (high certainty) and negative (moderate certainty) psychotic symptoms in randomised controlled trials.

Evidence from observational studies (weak credibility, suggestive certainty) and randomised controlled trials (high credibility, moderate certainty) show an association between cannabis and general psychiatric symptoms, including depression and mania, as well as detrimental effects on prospective memory, verbal delayed recall, verbal learning, and visual immediate recall (weak credibility, highly suggestive in observational evidence, moderate certainty in randomised controlled trials). Across different clinical and non-clinical populations, observational evidence suggests an association between cannabis use and motor vehicle accidents (weak credibility, convincing certainty). Additionally, evidence from randomised controlled trials shows an association with somnolence (cannabinoids (moderate certainty) and cannabidiol (high certainty)),[103] and cannabis based medicines and visual impairment (high certainty), disorientation, dizziness, sedation, and vertigo (moderate certainty), among others.

These associations are of particular concern given the epidemiology and age pattern of cannabis use disorders, and the population attributable fraction of cannabis for schizophrenia, which is almost 10%.[152]

According to the Global Burden of Disease 2019, cannabis use disorders are associated with 690000 (95% uncertainty interval 421000-1080000) disability adjusted life years per 100000 individuals globally.[9] Prevalence and disability related to cannabis start to be measurable at ages 10-14 years (11900 disability adjusted life years), peak at ages 20-24 years (163000 disability adjusted life years), then gradually decrease.[9][12][153] The age pattern of cannabis use disorders coincide with the peak age at onset of mental health disorders. According to the largest meta-analysis on the age at onset of mental disorders published to date, which pooled 192 studies and 708561 individuals, around 34.6% of mental health disorders have onset by age 14 years, 48.4% by 18 years, and 62.5% by 25 years; the age that any mental health disorder onset peaks is at 14.5 years.[154] For cannabis use disorders, 66% of people will have onset by age 25 years, with age of peak onset 20.5 years. Of note, age at peak onset of schizophrenia spectrum disorders is also in the early 20s, with a slightly lower proportion of people with onset by 25 years (47.8%). In addition to the association between cannabis and psychosis, cannabis is also associated with a worse outcome after onset, including poorer cognition,[87] lower adherence to antipsychotics,[56] and higher risk of relapse.[85] In other words, use of cannabis when no psychotic disorder has already occurred increases the risk of its onset, and using cannabis after its onset, worsens clinical outcomes. Mood disorders also have their peak of onset close to that for cannabis use, which is of concern given the associations shown in this work between cannabis and depression, mania, and suicide attempt. Moreover, high tetrahydrocannabinol content cannabis could serve as a so-called gateway to other substances, particularly in younger people: this effect has been shown in humanss[155] and animal models,[156][157] strengthening the recommendation to avoid cannabis use in adolescents and young adulthood.

Evidence suggests detrimental effects on cognition, an association with motor vehicle accidents, together with the age pattern of cannabis use (disorder), and related burden, which raise two additional matters. Firstly, given the adverse effects of cannabis on verbal delayed recall, verbal learning, visual immediate recall, and mental health, negative effects on scholastic or academic performance are reasonably expected, particularly in people who heavily use. Secondly, psychiatric symptoms such as suicide ideation and attempt, mania, and poor cognition, among other adverse events (eg, somnolence, disorientation, dizziness, sedation, vertigo, and visual impairment) might mediate the association between cannabis and increased risk of motor vehicle accidents. According to the DRUID project (driving under the influence of drugs, alcohol, and medicines in Europe), tetrahydrocannabinol ((0.5-2.2), measured as tetrahydrocannabinol or carboxy-tetrahydrocannabinol, in oral fluid or blood) is the second most frequent compound detected in seriously injured drivers, after alcohol (14.1-30.2%), then cocaine and amphetamines.[158]

NATURAL EXTRACT FROM PLANT SOURCE

- THC and CBD (nabiximols) Oraomucosal spray
- 2.7mgTHC/2.5mg CBD: 2.5-120mg in divided doses
- Neuropathic pain/spasticity of MS
- Analgesia: advanced CA-mod/severe
- UK, Canada 2010: First Cannabis based med
- US: Phase III trials in CA pain initial results in 2014
- GW Pharm/ Otsuka
- New Drug app: 2013 spasticity of MS

Table 2

Cannabis Medications Currently in Use

Agent	Cannabis Element	Intended Indication(s)	Important Information
Epidiolex (CBD) oral solution	CBD	FDA-approved for treating seizures associated with Lennox-Gastaut syndrome or Dravet syndrome in patients aged ≥2 years	Classified as a Schedule V substance[a]
Marinol (dronabinol) oral capsule	Synthetic THC	FDA-approved for treating anorexia associated with weight loss in AIDS patients and for treatment-resistant N/V associated with cancer chemotherapy	Classified as a Schedule III substance[b]
Cesamet (nabilone) oral capsule	Synthetic cannabinoid similar to THC	FDA-approved for treatment of treatment-resistant N/V associated with cancer chemotherapy	Classified as a Schedule II substance[c]
Sativex (THC and CBD) oromucosal spray	THC + CBD	Approved in other countries for symptom improvement in adults with treatment-refractory MS spasticity	Not approved for use in the U.S.; also called *nabiximols* in the U.S.; the only cannabis-based medication intended for use in pain management

[a] Schedule V: least potential for abuse.
[b] Schedule III: less potential for abuse and may lead to moderate or low physical dependence or high psychological dependence.
[c] Schedule II: high potential for abuse and may lead to severe psychological or physical dependence.
CBD: cannabidiol; MS: multiple sclerosis; N/V: nausea/vomiting; THC: delta-9-tetrahydrocannabinol.
Source: References 13, 16-19.

Comparison of Medical Cannabis Use Reported on a Confidential Survey vs Documented in the Electronic Health Record Among Primary Care Patients

Gwen T. Lapham, PhD, MPH, MSW[1,2]; Theresa E. Matson, MPH[1,2]; David S. Carrell, PhD[1]; et al

❯ Author Affiliations | Article Information

🔗 Related Articles

Key Points

Question What is the prevalence of patient-reported explicit (ie, medical use) and implicit (ie, health reasons for use) medical cannabis use, and how does electronic health record documentation compare with patient report of medical use?

Findings In this survey study, among 1688 primary care patients, 26.5% reported explicit and 35.1% reported implicit medical use of cannabis. The prevalence of medical use documented in the electronic health record was 4.8%, missing most medical cannabis use reported by patients.

Main Outcomes and Measures Survey data were linked to EHR data in the year before screening. EHR measures included documentation of explicit and/or implicit medical cannabis use. Analyses estimated the primary care prevalence of cannabis use and compared EHR-documented with patient-reported medical cannabis use, accounting for stratified sampling and nonresponse.

Results Overall, 1688 patients responded to the survey (34% response rate; mean [SD] age, 50.7 [17.5] years; 861 female [56%], 1184 White [74%], 1514 non-Hispanic [97%], and 1059 commercially insured [65%]). The primary care prevalence of any past-year patient-reported cannabis use on the survey was 38.8% (95% CI, 31.9%-46.1%), whereas the prevalence of explicit and implicit medical use were 26.5% (95% CI, 21.6%-31.3%) and 35.1% (95% CI, 29.3%-40.8%), respectively. The prevalence of EHR-documented medical cannabis use was 4.8% (95% CI, 3.45%-6.2%). Compared with patient-reported explicit medical use, the sensitivity and specificity of EHR-documented medical cannabis use were 10.0% (95% CI, 4.4%-15.6%) and 97.1% (95% CI, 94.4%-99.8%), respectively.

Conclusions and Relevance These findings suggest that medical cannabis use is common among primary care patients in a state with legal use, and most use is not documented in the EHR. Patient report of health reasons for cannabis use identifies more medical use compared with explicit questions about medical use.

Prevalence of Cannabis Use Disorder and Reasons for Use Among Adults in a US State Where Recreational Cannabis Use Is Legal

Gwen T. Lapham, PhD, MPH, MSW[1,2]; Theresa E. Matson, PhD, MPH[1,2]; Jennifer F. Bobb, PhD[1]; et al

》 Author Affiliations | Article Information

Introduction

Cannabis use is prevalent and increasing in the US.[1-3] As of June 2023, 38 states have legalized medical cannabis use; among these, 23 have legalized recreational use.[4] Cannabis use is most prevalent in states with legal recreational use, where now more than half of US adults have legal access to cannabis.[5-8] Medical use of cannabis is also growing,[9] although prevalence varies depending on state law, clinician recommendation, and patient viewpoints.[10-13] Among primary care patients who used cannabis in a state with legal recreational use, where provider recommendation is unnecessary for medical use, the prevalence of patient-reported medical cannabis use was 67%.[13]

Greater cannabis use is associated with an increase in risk of cannabis use disorder (CUD),[14-17] and legalization has contributed to increases,[18-20] with 17% of individuals who use cannabis having CUD.[21] Among veteran outpatients who used cannabis in a state with legal medical use, the prevalence of CUD varied by reasons for use and was lowest among those who reported medical use only.[12] This study assessed whether CUD prevalence varied for patients by self-reported reason for cannabis use in a state with legal recreational use. We estimated the prevalence of CUD based on a diagnostic questionnaire on a confidential cannabis survey among patients who used cannabis, overall and by 3 categories of patient-reported reasons for use: medical use only, nonmedical use only, and both.

Main Outcomes and Measures Patient responses to the Composite International Diagnostic Interview-Substance Abuse Module for CUD, corresponding to *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* CUD severity (0-11 symptoms) were categorized as any CUD (≥2 symptoms) and moderate to severe CUD (≥4 symptoms). Adjusted analyses were weighted for survey stratification and nonresponse for primary care population estimates and compared prevalence of CUD across reasons for cannabis use.

Results Of 1463 included primary care patients (weighted mean [SD] age, 47.4 [16.8] years; 748 [weighted proportion, 61.9%] female) who used cannabis, 42.4% (95% CI, 31.2%-54.3%) reported medical use only, 25.1% (95% CI, 17.8%-34.2%) nonmedical use only, and 32.5% (95% CI, 25.3%-40.8%) both reasons for use. The prevalence of CUD was 21.3% (95% CI, 15.4%-28.6%) and did not vary across groups. The prevalence of moderate to severe CUD was 6.5% (95% CI, 5.0%-8.6%) and differed across groups: 1.3% (95% CI, 0.0%-2.8%) for medical use, 7.2% (95% CI, 3.9%-10.4%) for nonmedical use, and 7.5% (95% CI, 5.7%-9.4%) for both reasons for use (*P* = .01).

Conclusions and Relevance In this cross-sectional study of primary care patients in a state with legal recreational cannabis use, CUD was common among patients who used cannabis. Moderate to severe CUD was more prevalent among patients who reported any nonmedical use. These results underscore the importance of assessing patient cannabis use and CUD symptoms in medical settings.

What Is Cannabis Use Disorder? DSM-5 Definition. According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), cannabis use disorder is characterized by "a problematic pattern of cannabis use leading to clinically significant impairment or distress." Nov 7, 2022
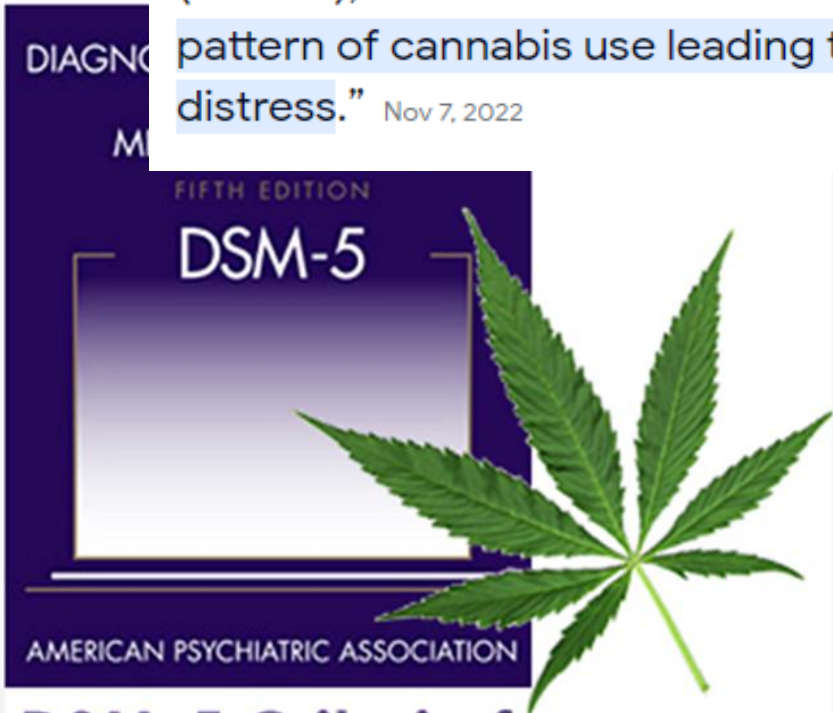
efits, its use in excess by some individuals and occupational functioning. Published in *nd Statistical Manual of Mental Disorders*

(DSM-5) included significant changes to substance-related and addictive disorders. *DSM-5* combined the previously separate categories of substance abuse and dependence into a single disorder of substance use, specific to the substance (eg, Alcohol Use Disorder, Cannabis Use Disorder). The Text Revision of the *DSM-5* was published in 2022. It recognizes the following 5 cannabis-associated disorders: [12]

- Cannabis Use Disorder

- Cannabis Intoxication

- Cannabis Withdrawal

- Cannabis-Induced Mental Disorders

- Unspecified Cannabis-Related Disorder

DIAGN

M

FIFTH EDITION

DSM-5

AMERICAN PSYCHIATRIC ASSOCIATION

DSM-5 Criteria for Cannabis Use Disorder

ΛCOi **2023** October 11-14
Tampa • Hybrid

Cannabis/Marijuana Use Disorder

KEYWORDS: **CANNABIS/MARIJUANA USE DISORDER**
SUBSTANCE USE DISORDER

- The continued use of cannabis despite significant negative impact on one's life and health

- About 10 percent of people who begin smoking cannabis will become addicted

- Treatment includes motivational interviews, contingency management and cognitive behavioral therapy

Nondisordered Cannabis Use Among US Adolescents

Ryan S. Sultan, MD[1,2,3]; Alexander W. Zhang, BA[1,2]; Mark Olfson, MD, MPH[1,2,4]; et al

≫ Author Affiliations | Article Information

Key Points

Question Is nondisordered cannabis use (NDCU) among US adolescents associated with adverse psychosocial events?

Findings In this cross-sectional study of 68 263 adolescents, NDCU was approximately 4 times more common than cannab use disorder (CUD). NDCU and CUD were both significantly associated with adverse psychosocial events in a stepwise gradient manner.

Meaning These findings suggest that adolescents with NDCU or CUD had increased odds of adverse psychosocial events.

Objective To describe the prevalence and demographics of NDCU and to compare associations of cannabis use with adverse psychosocial events among adolescents with no cannabis use, NDCU, and CUD.

Design, Setting, and Participants This cross-sectional study used a nationally representative sample derived from the 2015 to 2019 National Survey on Drug Use and Health. Participants were adolescents aged 12 to 17 years, separated into 3 distinct groups: nonuse (no recent cannabis use), NDCU (recent cannabis use below diagnostic threshold), and CUD. Analysis was conducted from January to May 2022.

Exposures CUD, NDCU, or cannabis nonuse. NDCU was defined as endorsing recent cannabis use but not meeting the *Diagnostic and Statistical Manual of Mental Disorders* (*Fifth Edition*) (*DSM-5*) CUD criteria. CUD was defined using *DSM-5* criteria.

Main Outcomes and Measures The main outcomes were prevalence of adolescents meeting criteria for NDCU and associations between adverse psychosocial events and NDCU, adjusted for sociodemographic characteristics.

Results The 68 263 respondents (mean [SD] age, 14.5 [1.7] years; 34 773 [50.9%] males) included in the analysis represented an estimated yearly mean of 25 million US adolescents during 2015 to 2019. Among respondents, 1675 adolescents (2.5%) had CUD, 6971 adolescents (10.2%) had NDCU, and 59 617 adolescents (87.3%) reported nonuse. Compared with nonusers, individuals with NDCU had approximately 2 to 4 times greater odds of all adverse psychosocial events examined, including major depression (adjusted odds ratio [aOR], 1.86; 95% CI, 1.67-2.08), suicidal ideation (aOR, 2.08; 95% CI, 1.88-2.29), slower thoughts (aOR, 1.76; 95% CI, 1.58-1.96), difficulty concentrating (aOR, 1.81; 95% CI, 1.65-2.00), truancy (aOR, 1.90; 95% CI, 1.67-2.16), low grade point average (aOR, 1.80; 95% CI, 1.62-2.00), arrest (aOR, 4.15; 95% CI, 3.17-5.43), fighting (aOR, 2.04; 95% CI, 1.80-2.31), and aggression (aOR, 2.16; 95% CI, 1.79-2.62). Prevalence of adverse psychosocial events was greatest for adolescents with CUD (range, 12.6% to 41.9%), followed by NDCU (range, 5.2% to 30.4%), then nonuse (range, 0.8% to 17.3%).

Conclusions and Relevance In this cross-sectional study of US adolescents, past-year NDCU was approximately 4 times as prevalent as past-year CUD. A stepwise gradient association was observed for odds of adverse psychosocial events between adolescent NDCU and CUD. In the context of US normalization of cannabis use, prospective research into NDCU is necessary.

Cannabis Use (Marijuana Use) Disorders According to DSM V

Consequence	Definition/Symptoms
Cannabis Use Disorder	A problematic pattern of cannabis use leading to clinically significant impairment or distress as manifested by at least two of the following occurring in a 12 month period:
	1. Cannabis is often taken in larger amounts over a longer period than was intended.
	2. There is a persistent desire or insignificant effort to cut down or control cannabis use.
	3. A great deal of time is spent in activities necessary to obtain cannabis, use cannabis or recover from its effects.
	4. Craving or a strong desire or urge to use cannabis.
	5. Recurrent cannabis use resulting in failure to fulfill major role obligations at work, school or home.
	6. Continued cannabis use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of cannabis.
	7. Important social, occupational or recreational activities are given up or reduced because of cannabis use.
	8. Recurrent cannabis use in situations which is physically hazardous.
	9. Cannabis use is continued despite knowledge of having persistent or recurrent physical or psychological problems that are unlikely to have been caused or exacerbated by cannabis.
	10. Tolerance, as defined by either:
	1) A need for markedly increased amounts of cannabis to achieve intoxication and desired effect, or
	2) A markedly diminished effect with continued use of the same amount of cannabis.
	11. Withdrawal, as manifested by either:
	1) The characteristic withdrawal symptoms for cannabis, or
	2) A closer related substance is taken to relieve or avoid withdrawal symptoms.
Cannabis Intoxication	1. Recent use of cannabis.
	2. Clinically significant problematic behavior or psychological changes (e.g. impaired motor coordination, euphoria, anxiety, sensation of slowed time, impaired judgment, social withdrawal) that develop during, or shortly after, cannabis use.
	3. Two or more of the following signs or symptoms developing within two hours of cannabis use:
	1) Conjunctival injection
	2) Increased appetite
	3) Dry mouth
	4) Tachycardia
	4. The signs or symptoms are not attributable to another medical condition and are not better explained by another mental disorder, including intoxication with another substance.
Cannabis Withdrawal	1. Cessation of cannabis use that has been heavy and prolonged (i.e., usually daily or almost daily over a period of at least a few months)
	2. Three or more of the following signs and symptoms develop within approximately one week after cessation of heavy, prolonged use:
	1) Irritability, anger or aggression
	2) Nervousness or anxiety
	3) Sleep difficulty (e.g. insomnia, disturbing dreams)
	4) Decreased appetite or weight loss
	5) Restlessness
	6) Depressed mood
	7) At least one of the following physical symptoms causing significant discomfort:
	i. Abdominal pain,
	ii. Shakiness/tremors,
	iii. Sweating,
	iv. Fever,
	v. Chills, or
	vi. Headache
	3. The signs or symptoms cause clinically significant distress or impairment in social, occupational or other important areas of functioning.
	4. The signs and symptoms are not attributable to another medical condition and are not better explained by another mental disorder, including intoxication or withdrawal from another substance.
Cannabis-Induced Mental Disorder	1. Affective Disorders
	a. Anxiety Disorders
	b. Depression
	c. Bipolar Disorder
	2. Schizophrenia
	3. Amotivational Syndrome
	4. Disruptive Cognitive Function
	5. Neuropsychological decline
	6. Psychotic Disorders
Cannabis-Induced Physical Disorder	1. Lung Damage
	2. Heart Disease
	3. Cancer
	4. Pregnancy Complications

DSM-5 Criteria for Cannabis Use Disorder

Table 1: DSM-5 cannabis use and addictive disorders.

Cannabis use and cannabis use disorder

Jason P Connor [1] [2], Daniel Stjepanović [3], Bernard Le Foll [4] [5], Eva Hoch [6] [7], Alan J Budney [8], Wayne D Hall [3] [9]

Affiliations + expand

Using more to maintain desired effects

Failing to stop using

Abandoning hobbies and taking risks

Craving marijuana

Spending excessive amounts of time searching for, using, or recovering from use

verywell

Cannabis use and cannabis use disorder

Jason P. Connor ✉, Daniel Stjepanović, Bernard Le Foll, Eva Hoch, Alan J. Budney & Wayne D. Hall

Abstract

Cannabis use disorder (CUD) is an underappreciated risk of using cannabis that affects ~10% of the 193 million cannabis users worldwide. The individual and public health burdens are less than those of other forms of drug use, but CUD accounts for a substantial proportion of persons seeking treatment for drug use disorders owing to the high global prevalence of cannabis use. Cognitive behavioural therapy, motivational enhancement therapy and contingency management can substantially reduce cannabis use and cannabis-related problems, but enduring abstinence is not a common outcome. No pharmacotherapies have been approved for cannabis use or CUD, although a number of drug classes (such as cannabinoid agonists) have shown promise and require more rigorous evaluation. Treatment of cannabis use and CUD is often complicated by comorbid mental health and other substance use disorders. The legalization of non-medical cannabis use in some high-income countries may increase the prevalence of CUD by making more potent cannabis products more readily available at a lower price. States that legalize medical and non-medical cannabis use should inform users about the risks of CUD and provide information on how to obtain assistance if they develop cannabis-related mental and/or physical health problems.
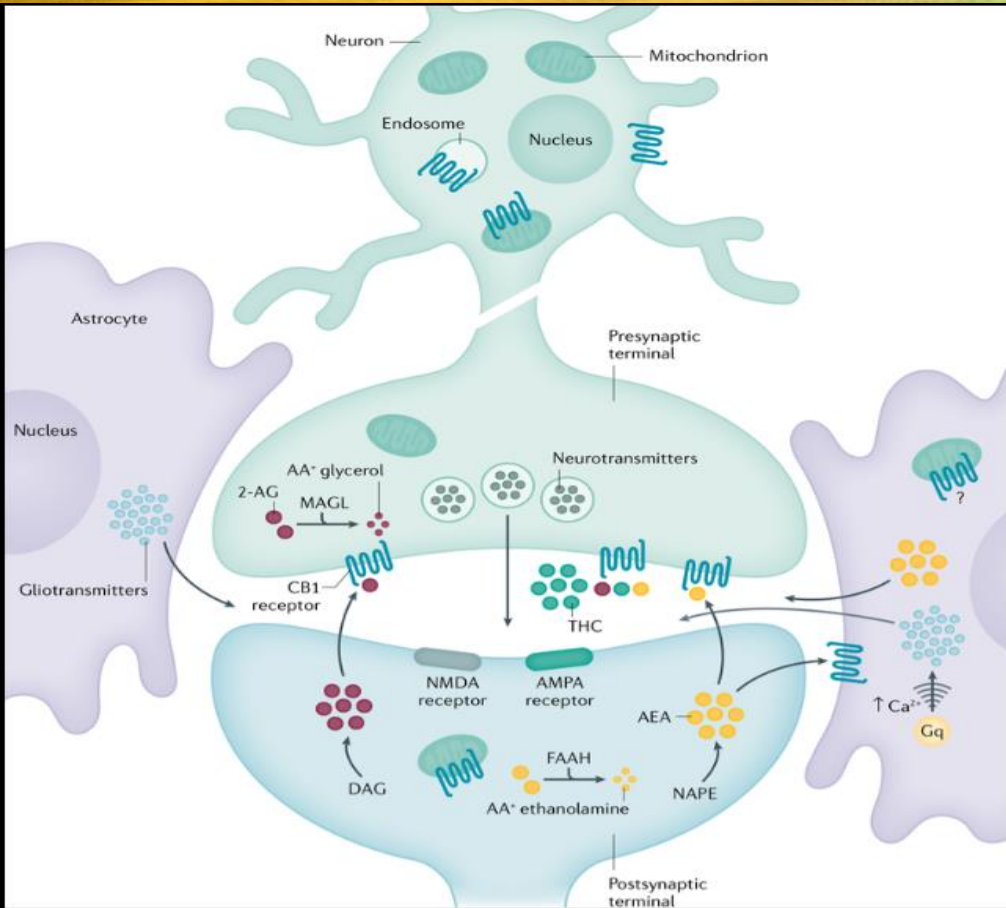
Fig. 2 |. CB1 receptor signalling. The endocannabinoid neurotransmitters anandamide (AEA) and 2-arachidonoylglycerol (2-AG) activate cannabinoid CB1 and CB2 receptors. 2-AG and AEA are synthesized from diacylglycerol (DAG) and N-arachidonoyl phosphatidylethanolamine (NAPE), respectively. Plant-derived exogenous cannabinoids such as Δ^9-tetrahydrocannabinol

Cannabis use and cannabis use disorder

Jason P. Connor ✉, Daniel Stjepanović, Bernard Le Foll, Eva Hoch, Alan J. Budney & Wayne D. Hall
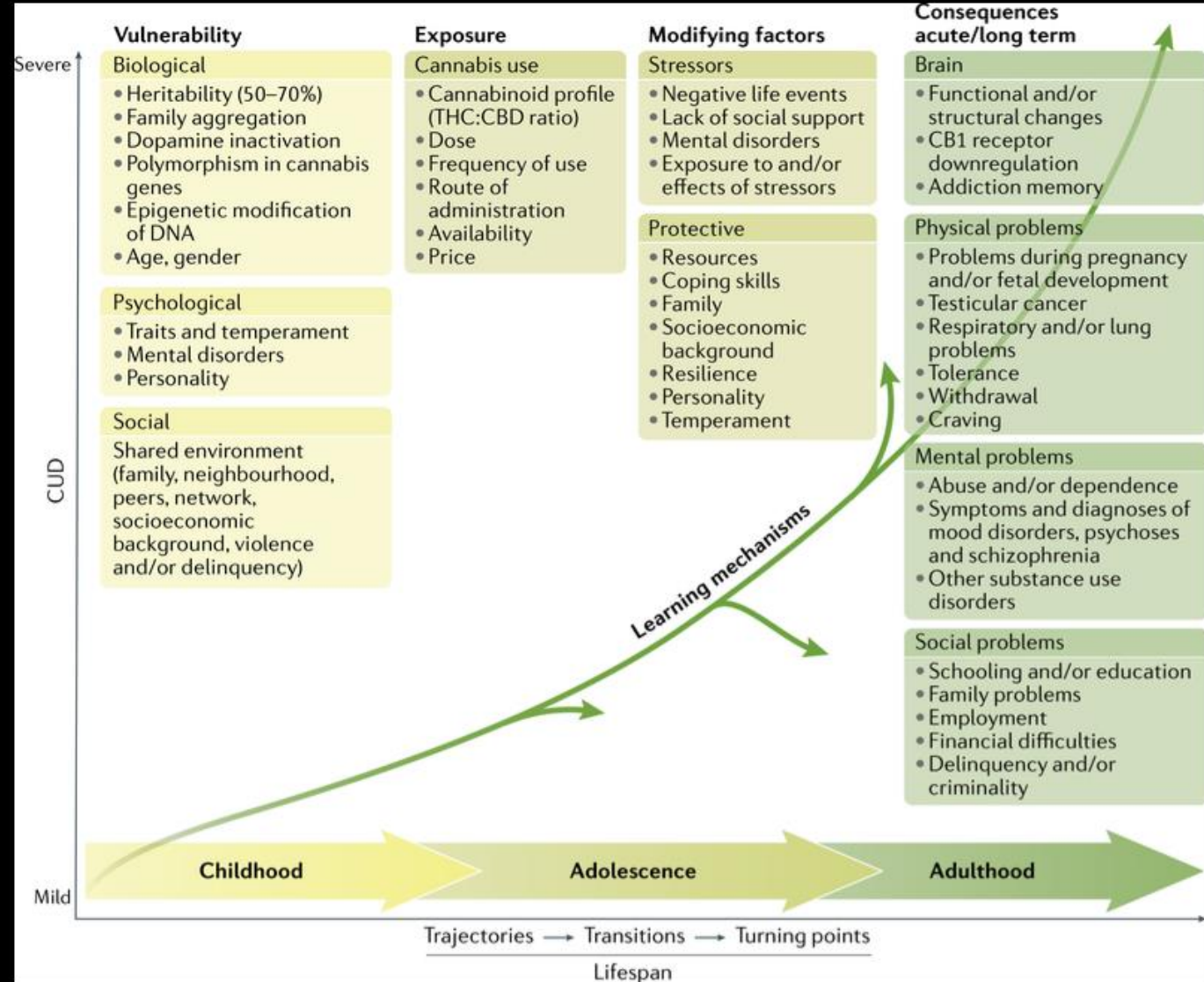
Fig. 5 |. A multifactorial model for cannabis use disorders. A range of biological factors, psychological factors and social factors shape an individual's vulnerability. Repeated exposure to sufficiently high doses of Δ^9-tetrahydrocannabinol (THC) for an extended period (months to years) can result in adverse acute and long-term mental, physical and social consequences.
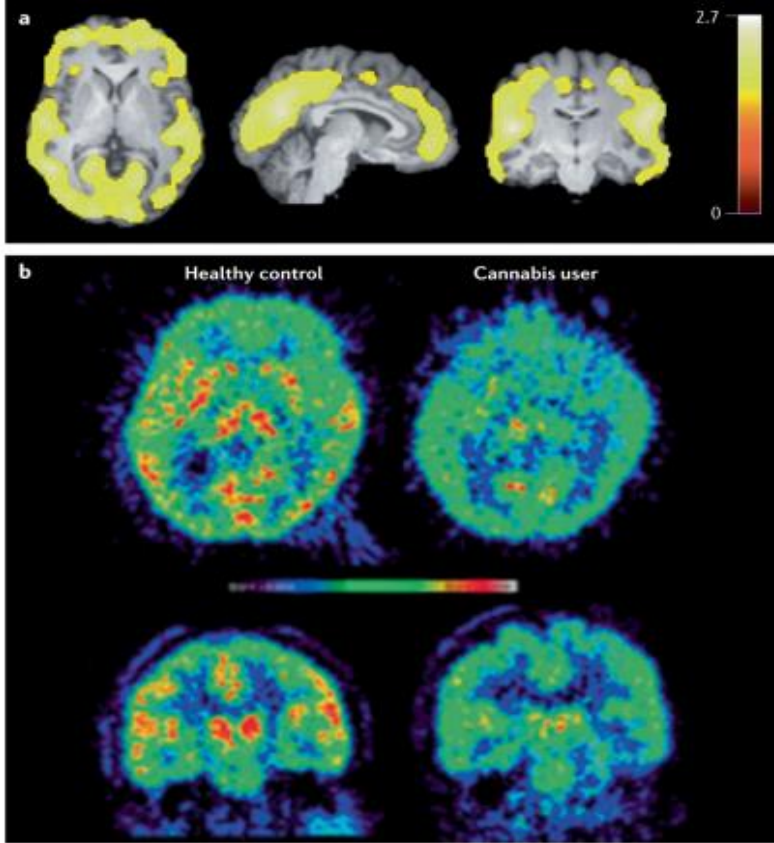
Fig. 4 |. PET imaging of CB1 receptors and FAAH.
a | PET imaging of CB1 receptors using $[^{18}F]$FMPEP-d_2. Statistical parametric mapping (SPM) analysis showed lower distribution volume V_T (a measure of receptor density) in chronic daily cannabis smokers ($n = 30$) than in control subjects ($n = 28$) at baseline as a large single cluster that includes cortical regions. Bar represents t-values in each voxel within the significant cluster. **b** | PET imaging of fatty acid amide hydrolase (FAAH) using $[^{11}C]$CURB in transaxial (top) and coronal (bottom) views of an individual used as control (left) and a subject with cannabis use disorder (CUD) (right) following overnight abstinence. The subject with CUD had lower uptake of PET tracer in striatum, thalamus and cortical regions. Panel **a** reprinted from REF.[99], Springer Nature Limited. Panel **b** reprinted with permission from REF.[293], American Chemical Society.

Cannabis use and cannabis use disorder

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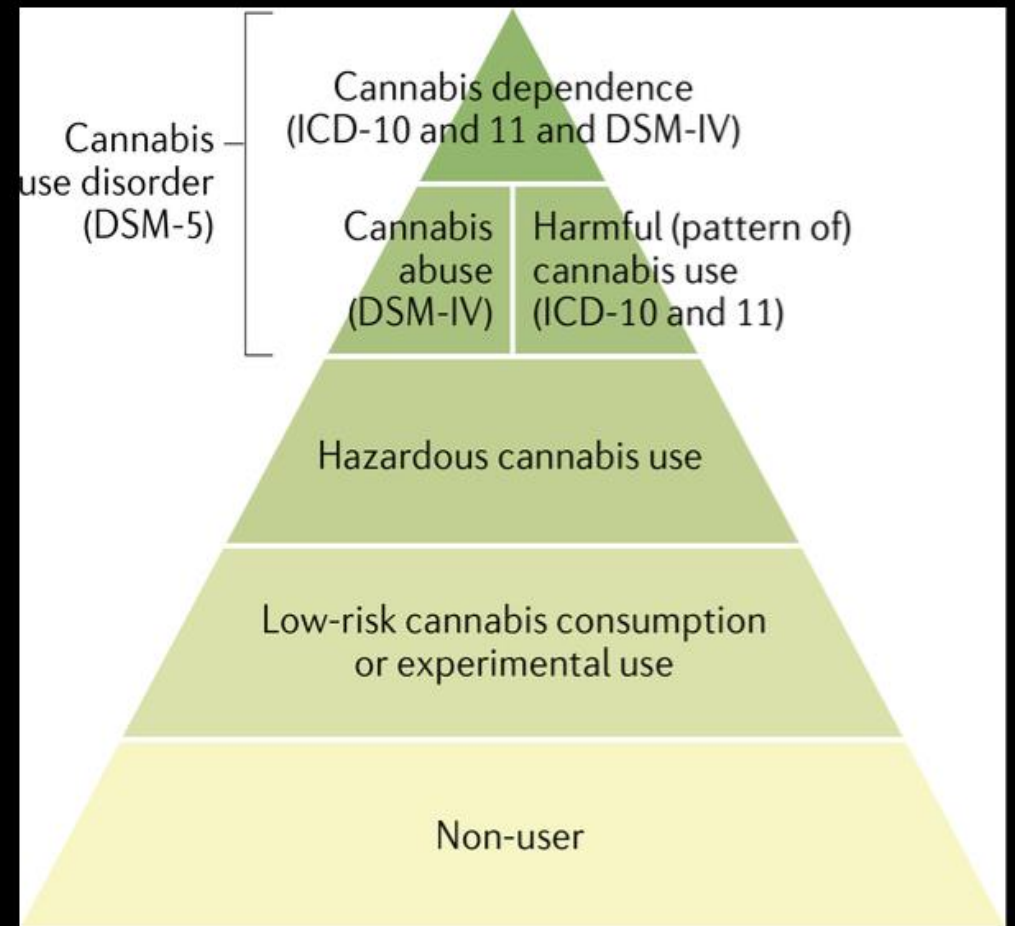
Fig. 6 |. The hierarchy of substance use disorders across diagnostic systems. Cannabis use and misuse form a spectrum of severity. Most individuals do not use cannabis. Individuals who do use cannabis typically use infrequently. However, in a smaller percentage of cannabis users, frequent use increases risk of harm (that is, hazardous cannabis use according to the

Toxic Tetrahydrocannabinol (THC) Dose in Pediatric Cannabis Edible Ingestions ⊘

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WHAT IS THE RISK/BENEFIT OF CANNABIS? NO ONE REALLY KNOWS

WHAT DO WE KNOW?

- Physicians and Researchers still know very little
- C1
- Quality, Consistency, Purity, and Standardardization
- Accepted THC Unit
- Limited Access to Research-grade cannabis
- State initiatives lists hundreds of conditions for which the drug(s) can be used
- Inhalation vs oral, topical
- Politics vs Medicine
- $$$$$$$$/Industry/Legislatures

- Use during pregnancy/fetal development
- Endocannabinoid System
- Avoid in Adolescence and neuro-development
- Under the Influence/Impairment
- Not a Homogeneous Product
- Increasing Use in US
- 2018 US Farm Bill: Hemp <0.3% THC
- Health Records and med. Rec.
- Research: (poor or moderate quality) case reports, small cohorts
- Use Disorders
- Efficacy

CANNABIS CONFUSION

START LOW. TAKE IT SLOW.

STAY SAFE
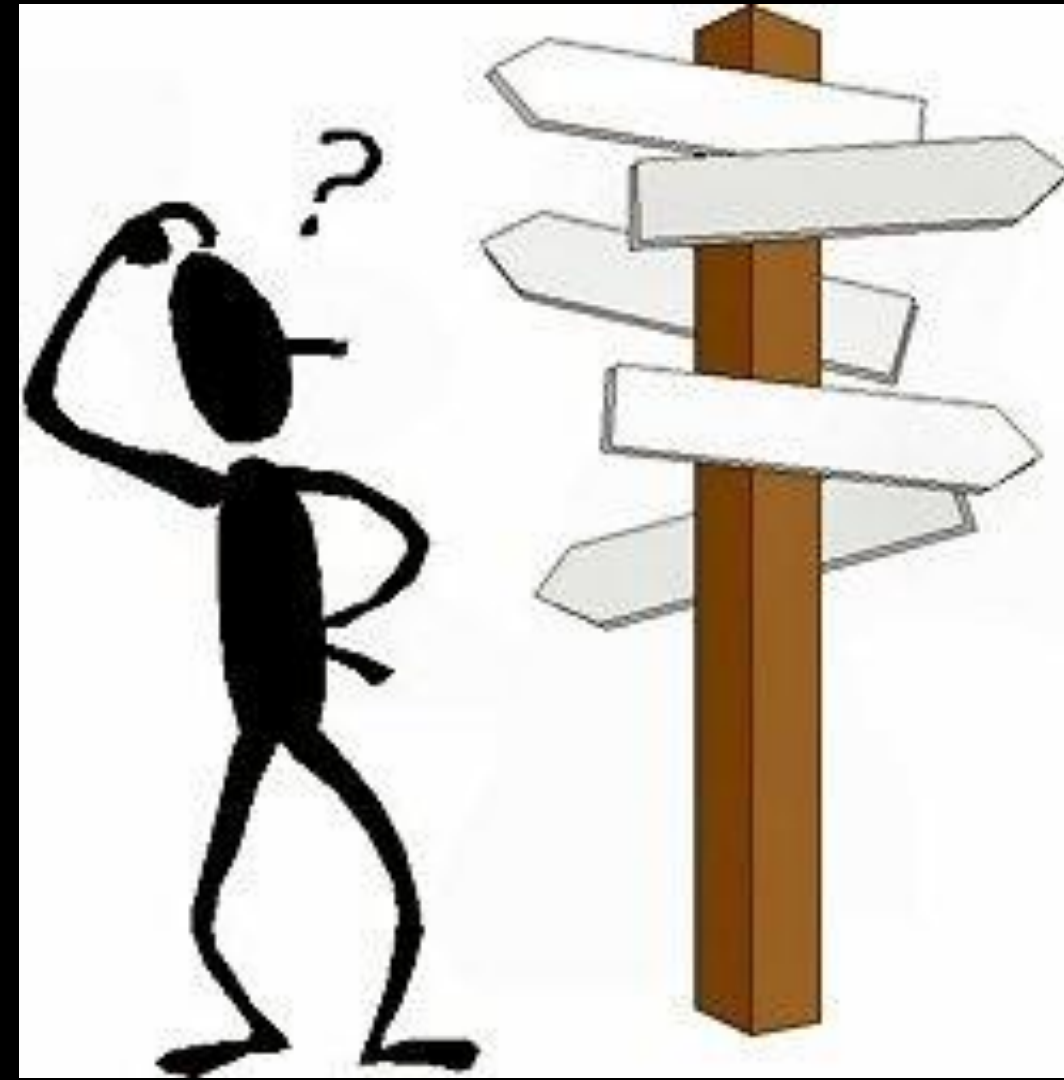
Medicalization of Botanical Cannabis: Is the "Cart Before the Horse"?
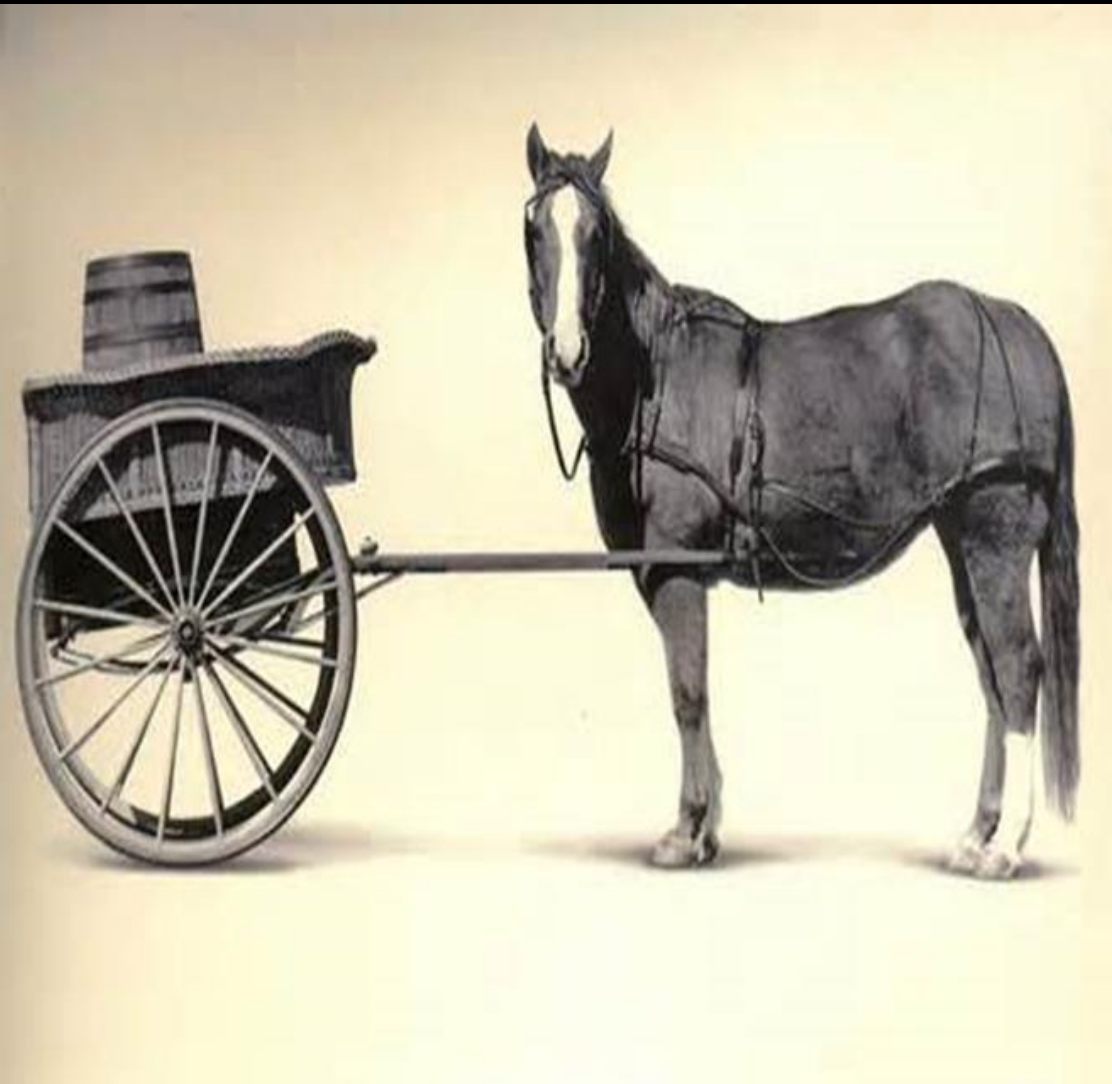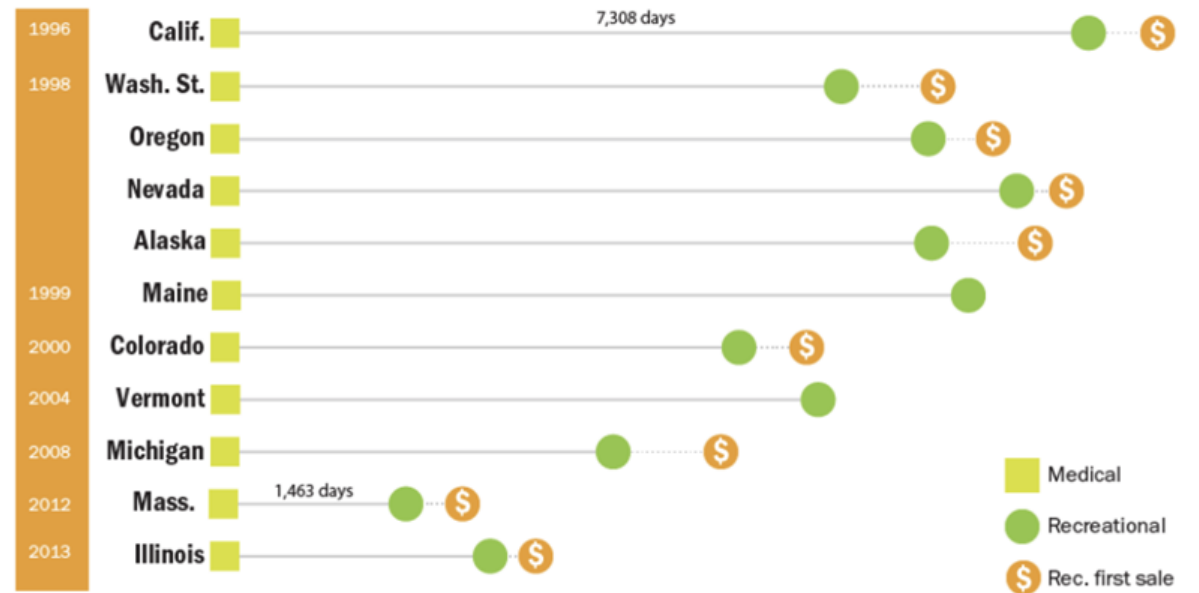
"Share Your Knowledge, It Is a Way to Achieve Immortality"