Medical Cannabis Update

November 2015

Charlie Reznikoff

Published: June 2015

Science Seeks to Unlock Marijuana's Secrets

As the once-vilified drug becomes more accepted, researchers around the world are trying to understand how it works and how it might fight disease.

JAMA June 23/30 2015 p2456

Original Investigation

Cannabinoids for Medical Use
A Systematic Review and Meta-analysis

Penny F. Whiting, PhD; Robert F. Wolff, MD; Sohan Deshpande, MSc; Marcello Di Nisio, PhD; Steven Duffy, PgD; Adrian V. Hernandez, MD, PhD; J. Christiaan Keurentjes, MD, PhD; Shona Lang, PhD; Kate Misso, MSc; Steve Ryder, MSc; Simone Schmidlkofer, MSc; Marie Westwood, PhD; Jos Kleijnen, MD, PhD

IMPORTANCE Cannabis and cannabinoid drugs are widely used to treat disease or alleviate symptoms, but their efficacy for specific indications is not clear.

OBJECTIVE To conduct a systematic review of the benefits and adverse events (AEs) of cannabinoids.

DATA SOURCES Twenty-eight databases from inception to April 2015.

STUDY SELECTION Randomized clinical trials of cannabinoids for the following indications: nausea and vomiting due to chemotherapy, appetite stimulation in HIV/AIDS, chronic pain, spasticity due to multiple sclerosis or paraplegia, depression, anxiety disorder, sleep disorder, psychosis, glaucoma, or Tourette syndrome.

DATA EXTRACTION AND SYNTHESIS Study quality was assessed using the Cochrane risk of bias tool. All review stages were conducted independently by 2 reviewers. Where possible, data were pooled using random-effects meta-analysis.

MAIN OUTCOMES AND MEASURES Patient-relevant/disease-specific outcomes, activities of daily living, quality of life, global impression of change, and AEs.

RESULTS A total of 79 trials (6462 participants) were included; 4 were judged at low risk of bias. Most trials showed improvement in symptoms associated with cannabinoids but these associations did not reach statistical significance in all trials. Compared with placebo, cannabinoids were associated with a greater average number of patients showing a complete nausea and vomiting response (47% vs 20%; odds ratio [OR], 3.82 [95% CI, 1.55-9.42];

Editorial page 2431

Related article page 2474

Supplemental content at jama.com

Medical Marijuana for Treatment of Chronic Pain and Other Medical and Psychiatric Problems
A Clinical Review

Kevin P. Hill, MD, MHS

IMPORTANCE As of March 2015, 23 states and the District of Columbia had medical marijuana laws in place. Physicians should know both the scientific rationale and the practical implications for medical marijuana laws.

OBJECTIVE To review the pharmacology, indications, and laws related to medical marijuana use.

EVIDENCE REVIEW The medical literature on medical marijuana was reviewed from 1948 to March 2015 via MEDLINE with an emphasis on 28 randomized clinical trials of cannabinoids as pharmacotherapy for indications other than those for which there are 2 US Food and Drug Administration–approved cannabinoids (dronabinol and nabilone), which include nausea and vomiting associated with chemotherapy and appetite stimulation in wasting illnesses.

FINDINGS Use of marijuana for chronic pain, neuropathic pain, and spasticity due to multiple sclerosis is supported by high-quality evidence. Six trials that included 325 patients examined chronic pain, 6 trials that included 396 patients investigated neuropathic pain, and 12 trials that included 1600 patients focused on multiple sclerosis. Several of these trials had positive results, suggesting that marijuana or cannabinoids may be efficacious for these indications.

CONCLUSIONS AND RELEVANCE Medical marijuana is used to treat a host of indications, a few of which have evidence to support treatment with marijuana and many that do not. Physicians should educate patients about medical marijuana to ensure that it is used appropriately and that patients will benefit from its use.

JAMA. 2015;313(24):2474-2483. doi:10.1001/jama.2015.6199

Editorial page 2431

Related articles page 2456 and page 2491 and **JAMA Patient Page** page 2508

Supplemental content at jama.com

CME Quiz at jamanetworkcme.com and **CME Questions** page 2489

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Section Editor: Edward H. Livingston, MD, Deputy Editor, *JAMA*.

This article is based on a conference that took place at the Medicine Grand Rounds at Beth Israel Deaconess Medical Center, Boston, Massachusetts, on May 16, 2014.

Dr Burns Mr Z is a 60-year-old man who fell at work 19 years ago and has had chronic low back pain and left leg radicular symptoms since that time. None of the numerous interventions performed in an effort to treat this pain were effective. These include an L2-3 laminectomy in 1996, multiple lumbar epidural steroid injections, selective nerve root blocks, lidocaine infusions, and a trial of a spinal cord stimulator. He has been to a pain psychologist and received physical therapy. Several medications have helped, such as gabapentin, sertraline, and nortriptyline.

His most recent magnetic resonance imaging scan showed posterior disk bulges at L2-3, L3-4, L4-5, and L5-S1, with the largest bulge at L2-3. Mild effacement of the thecal sac and narrowing of the left-sided neural foramina were seen. Mr Z was diagnosed as having failed back syndrome (chronic back pain following a laminectomy) and treated with long-term narcotics. He signed a narcotics contract with his primary care physician and has never violated the contract. Since signing his narcotics contract, Mr Z has decreased his narcotic requirements and is now taking oxycodone, 10 mg, along with ibuprofen, 600 mg, every 6 hours.

Because his overall goal remains pain relief, he has recently begun using marijuana. He received a recommendation from a cannabis clinic, a clinic whose primary function is to certify patients for the use of medical marijuana, but is now wondering if this is something his primary care physician could also agree with and therefore be responsible for the recommendation of in the future. He uses marijuana at home in the evening after returning from work. He has found marijuana to have a sedative effect, enabling him to get a good night's sleep and to have less pain the next day.

Mr Z's medical history is notable for hyperlipidemia, prediabetes, basal cell carcinoma, and anxiety. His other medications include bupropion, 150-mg sustained-release tablet twice daily; clonazepam, 0.5 mg twice daily as needed; and simvastatin, 20 mg once daily. Previously he was received disability benefits but currently works as an arborist. He drinks alcohol socially and continues to smoke cigarettes, although he has been able to cut down from 1½

Medical Cannabis:

-Scant medical evidence base
-Unconventional process of approval
-Regulated and monitored by local authorities

Prescribe outside the evidence base?

- Palliation, in accordance with patient wish
- No alternative evidence-based treatment
- All alternative evidence-based treatments tried and ineffective
- Experimental therapy
- Very low risk to the patient

Medical Cannabis Topics

1. Minnesota Medical Cannabis: Law, enrollment, products, community practices, social effects

2. Cannabinoid physiology and pharmacology

3. Medicinal effects of medical cannabis

4. Adverse effects of and contraindications to medical cannabis

1. Nonmedical issues of Minnesota Medical Cannabis

Legal Qualifying conditions

- HIV/AIDS
- Cancer (pain, nausea, cachexia)
- Severe muscle spasm (typical of MS)
- ALS
- End of life, <1 year expectancy (pain, nausea, cachexia)
- Crohn's
- Seizure disorder
- Glaucoma
- Tourette's syndrome

To Certify a Patient (1):

- You must register with the state *(very easy)*
- Determine that the patient has a qualifying condition
- ***You*** must be treating the patient for their qualifying condition
- Review one year of the medical history of the qualifying condition
- Do a medical interview and approrpiate exam

To Certify a Patient (2):

- Determine that medical cannabis is appropriate
  - You can say “no” at this point!
- Certify through the state website that this patient has a qualifying condition *(very easy)*
- Follow up: Poorly defined, provider judgment,
- Document you visit

Common incorrect concerns….

“Only subspecialists treat these conditions so only they can certify them, by law.”

Common incorrect concerns….

“Only subspecialists treat these conditions so only they can certify them, by law.”

Primary providers who might treat nausea associated with chemo or neuropathy associated with HIV, for example, can certify medical cannabis for those conditions

Common incorrect concerns….

“My job is only to certify the condition. It Is not my job to weigh risks and benefits.”

Common incorrect concerns….

"My job is only to certify the condition. It Is not my job to weigh risks and benefits."

Certifying docs have a confusingly defined role. But there are clear legal requirements that require proper medical decision making documentation and follow up, not just rubber-stamping conditions.

It is true that a lot of the work will be done for you by the state and the manufacturers

Common incorrect concerns….

“I am obligated by law to certify conditions if I am a registered doctor, and if the patient I’m seeing has the condition…. Therefore I will not register with the state”

Common incorrect concerns….

“I am obligated by law to certify conditions if I am a registered doctor, and the patient I’m seeing has the condition…. Therefore I will not register with the state”

The law explicitly states you can say “no” if you believe that the patient would not benefit despite having a qualifying condition

When you certify a patient

-You certify the patient for one year

-Once you certify, you cannot “revoke” the certification

-You can log in to the state database and see the products and quantities dispensed

Medical cannabis will not be on the prescription monitoring program

Reporting Requirements

- Life threatening and serious adverse events* need to be reported to the state within 24 hours after it is known to the certifying doctor
  - *Death, hospital admission, medical treatment beyond first aid or mental health care
- This requirements are under review

Designated Providers=Cannabis Consultants

- A large practice with a shared computer system, and regular communications, may have one or a few “designated providers” to certify patients for the entire practice EVEN THOUGH that provider does not have an ongoing relationship with the patient
- This provider must notify the state, *their high volume of medical cannabis will be caught by the state monitoring of registered docs*
- All other rules/laws apply to the process

Designated Caregivers

- If the patient is unable to self administer or possess medical cannabis (spinal cord injury or minor)
- A disabling condition is verified by provider
- A designated caregiver can be vetted and authorized by the state

- ***Possession by an "undesignated caregiver" is treated like marijuana possession***

MDH website: helpful

MDH Minnesota Department of Health

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Medical Cannabis

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For Patients
Find out which conditions qualify, how to get certified, where to get medical cannabis and the costs.

For Parents/Legal Guardians and Caregivers
Find out how you can assist the patient to get medical cannabis.

For Health Care Practitioners
Register yourself and certify your patients.

For Public Safety
Information for law enforcement.

Laws and Rules
Information about laws, rules and policies related to Minnesota medical cannabis.

Registry Login/Create Account
For health care practitioners, certified patients and certified caregivers.

News
News releases about the Medical Cannabis program.

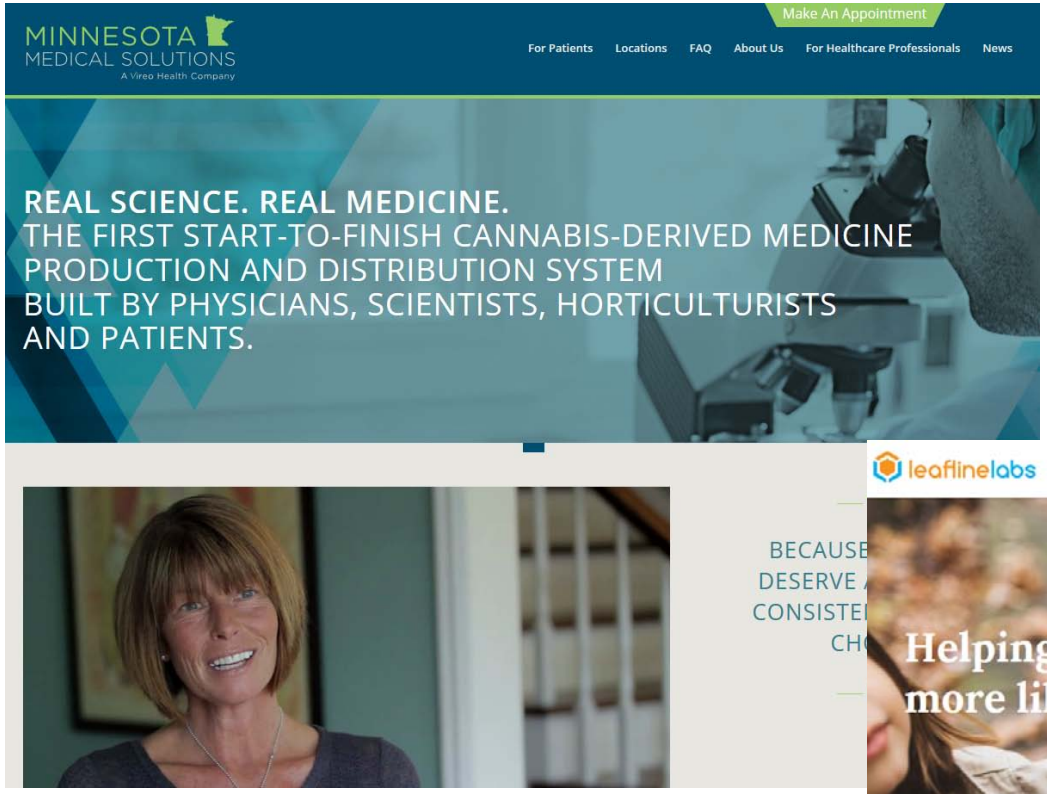
Print Materials and Forms
Repository for forms and documents.

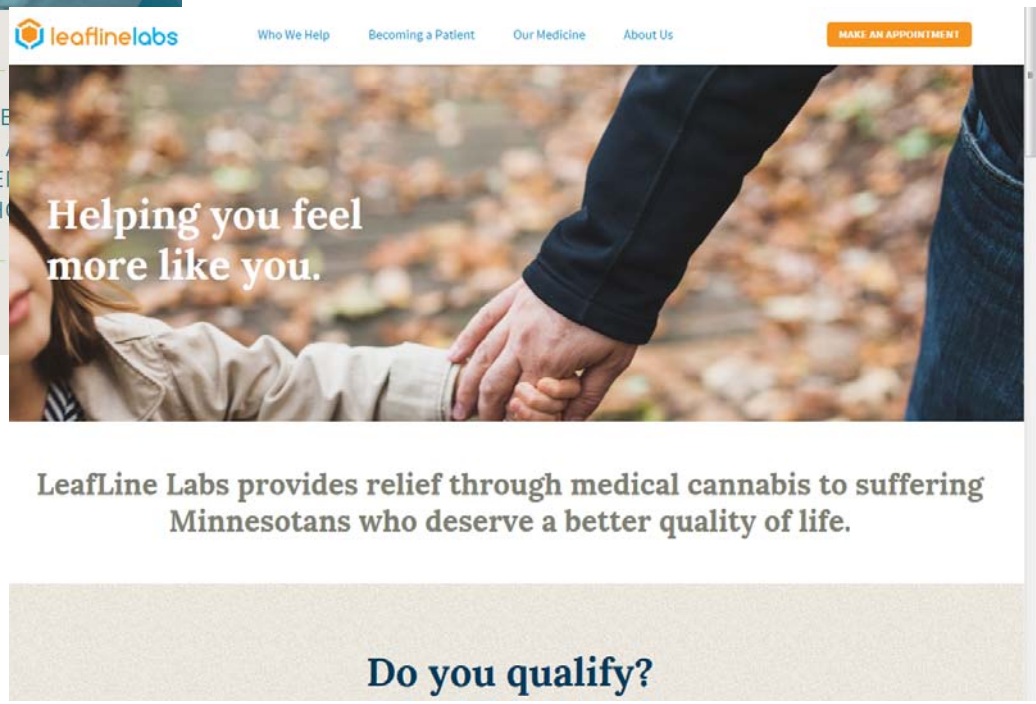
About the Medical Cannabis Program
Manufacturer and laboratory selection, rulemaking, task force, and other details about Minnesota's unique medical cannabis program.

Spotlight

- Medical Cannabis Registry
- Statistics
- Intractable Pain - Including Opportunities for Public Comment
- MDH Office of Medical Cannabis to hold community sessions around state

Two medical cannabis manufacturers: Law prohibits recommending one





Medicine made with you in mind

All three medicines (Tangerine, Heather and Cobalt) come in a variety of formats. Our pharmacists will work with you to choose the format that's right for you.

Capsules

Easy-to-swallow format.

Syrups + Suspensions

Medication homogenized in healthy coconut oil (other options for those with coconut allergy). Ideal for children or adults who cannot swallow capsules.

Oils for Vaporization

Medication in extract oil form is turned into a mist-like vapor and is able to be inhaled. Medication absorption is generally rapid and the effects can be seen more quickly than with other forms. Some side effects seen with the oral medications are not experienced with this route of administration. Some vaporizers come with prepackaged oil cartridges and others use oils that patients load into a vaporizer themselves.

Tinctures and Sublingual Sprays

Drops are placed under the tongue for quick absorption without swallowing. Best for patients who need certain medication effects experienced only when absorbed directly without passing into the stomach. Sometimes an alternative to vaporization.

labeled with directions and important information. All of our medicines are smoke free.

Tangerine

THC > CBD

THC in appropriate amounts has many therapeutic effects such as appetite stimulation and pain relief. This benefit comes without the risk of respiratory depression and narcotic addiction that current prescription pain pills do.

Available in:

- Oral suspension, *unflavored and flavored (creamsicle)*
- Oils for vaporization
- Sublingual spray, *flavored (vanilla mint)*
- Tincture, *flavored (vanilla)*

Heather

THC = CBD

Commonly used for painful muscle spasm disorders. Combining THC and CBD in similar amounts diminishes the sedating effect possible with higher THC concentrations while increasing the overall targeted therapeutic effect of the medication.

Available in:

- Oral suspension, *unflavored and flavored (cherry vanilla)*
- Oils for vaporization
- Sublingual spray, *flavored (vanilla mint)*

Cobalt

THC < CBD

CBD is generally accepted as less sedating and is often utilized to treat epilepsy and other seizure disorders. It also has potent anti-inflammatory properties as well.

Available in:

- Oral suspension, *unflavored*

Tinctures & Oils

Tinctures and oils are liquids made of cannabis-derived medicine that can be placed in the mouth and either swallowed or absorbed to some degree in the mouth itself. It can take up to 2-3 hours for these medicines to take full effect, so you should wait three hours before taking another dose. Too often, patients do not believe the first dose is working due to the delay in effect. Be aware that these doses add up over time so please wait the recommended amount so as not to over dose.

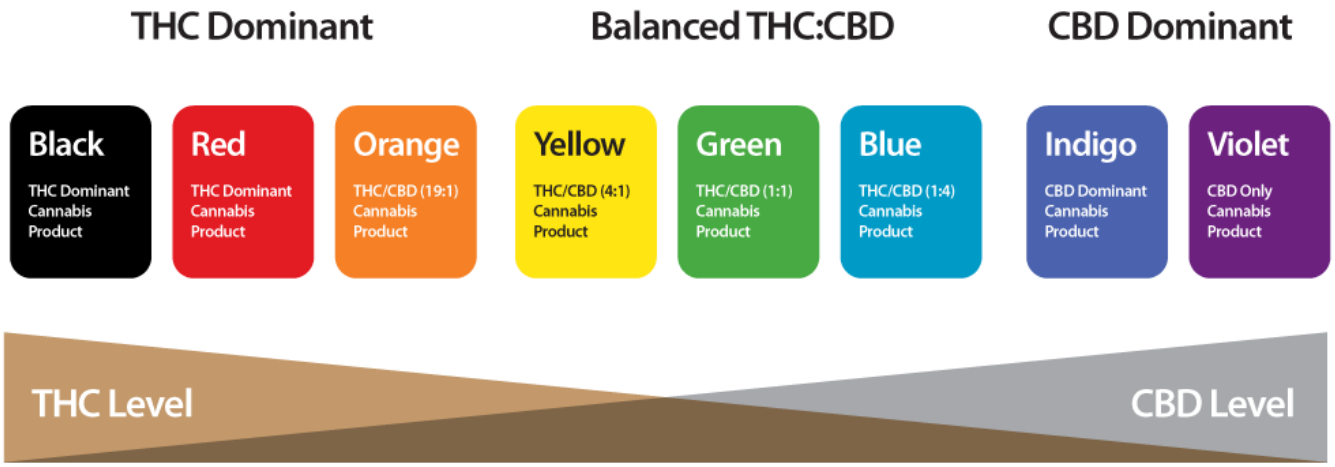
Vaporizers

Vaporizers gently heat the oils in the cannabis-derived medicine until they evaporate and can be inhaled. It is important with your first use that you take a very short "puff" from the vaporizer. You should then wait at least 10 minutes to feel the effects. At that point you can again take another slightly longer "puff". Remember to wait a sufficient time after each inhalation to be certain you do not take too much.

Capsules

These types of medicine, like the liquids, take a long time to enter your system and take effect. They also last for a long time. As a general rule, patients should wait at least 3 hours before taking another dose.

commonly experienced by users of THC. In our spectrum of cannabis derivatives, a small CBD percentage will be incorporated into the THC-dominate products to minimize side effects.



THC = Δ9-tetrahydrocannabinol

This chemical produces the mental effects of cannabis, commonly referredto as “high”. In the past, THC was the most desired chemical within the cannabis plant, and strains have been bred to maximize THC content ranging from 4-35%.

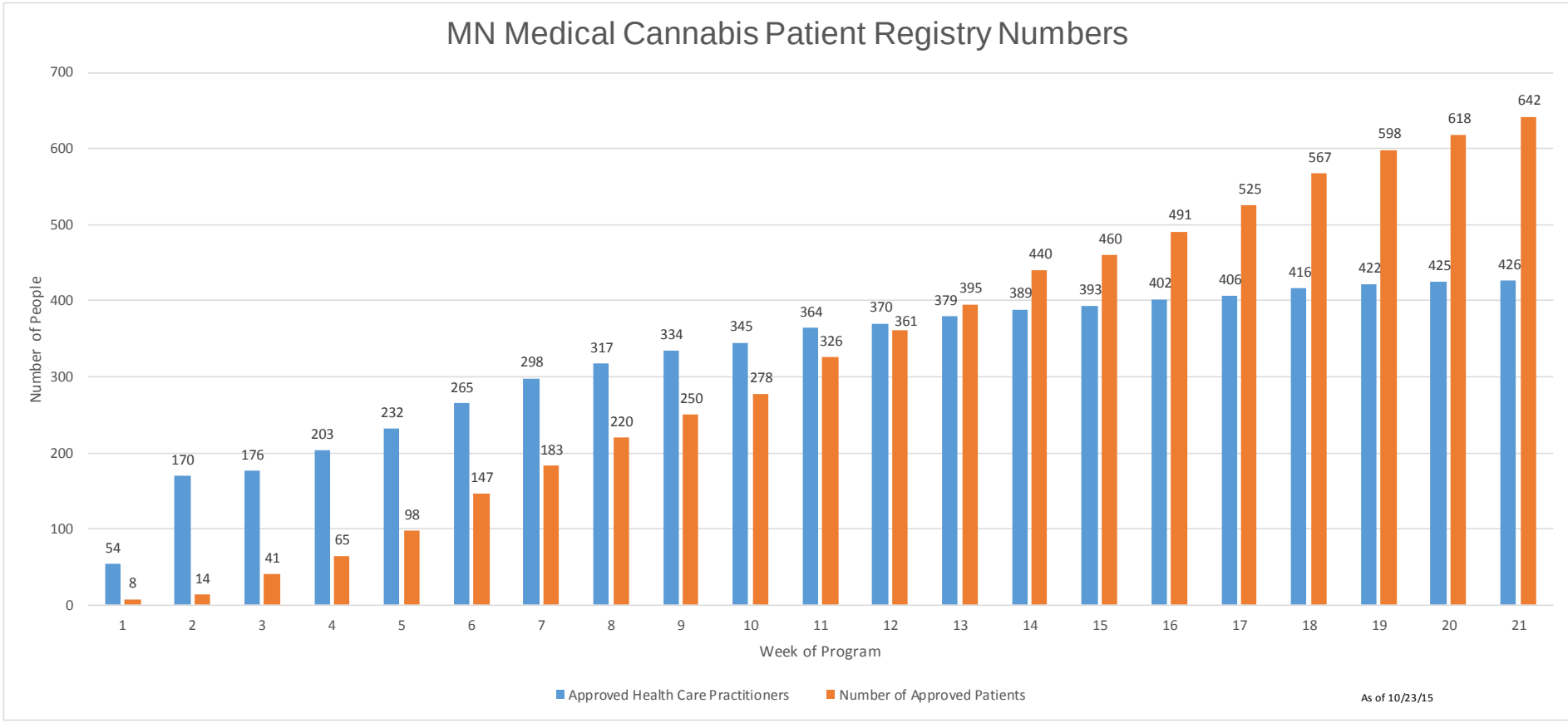
CBD = cannabidiol

This compound produces medicinal effects without psychoactivity. Historically, this less-desired chemical was nearly nonexistent within popular cannabis strains, but more recently its medical potential has brought CBD to the forefront of cannabis research.

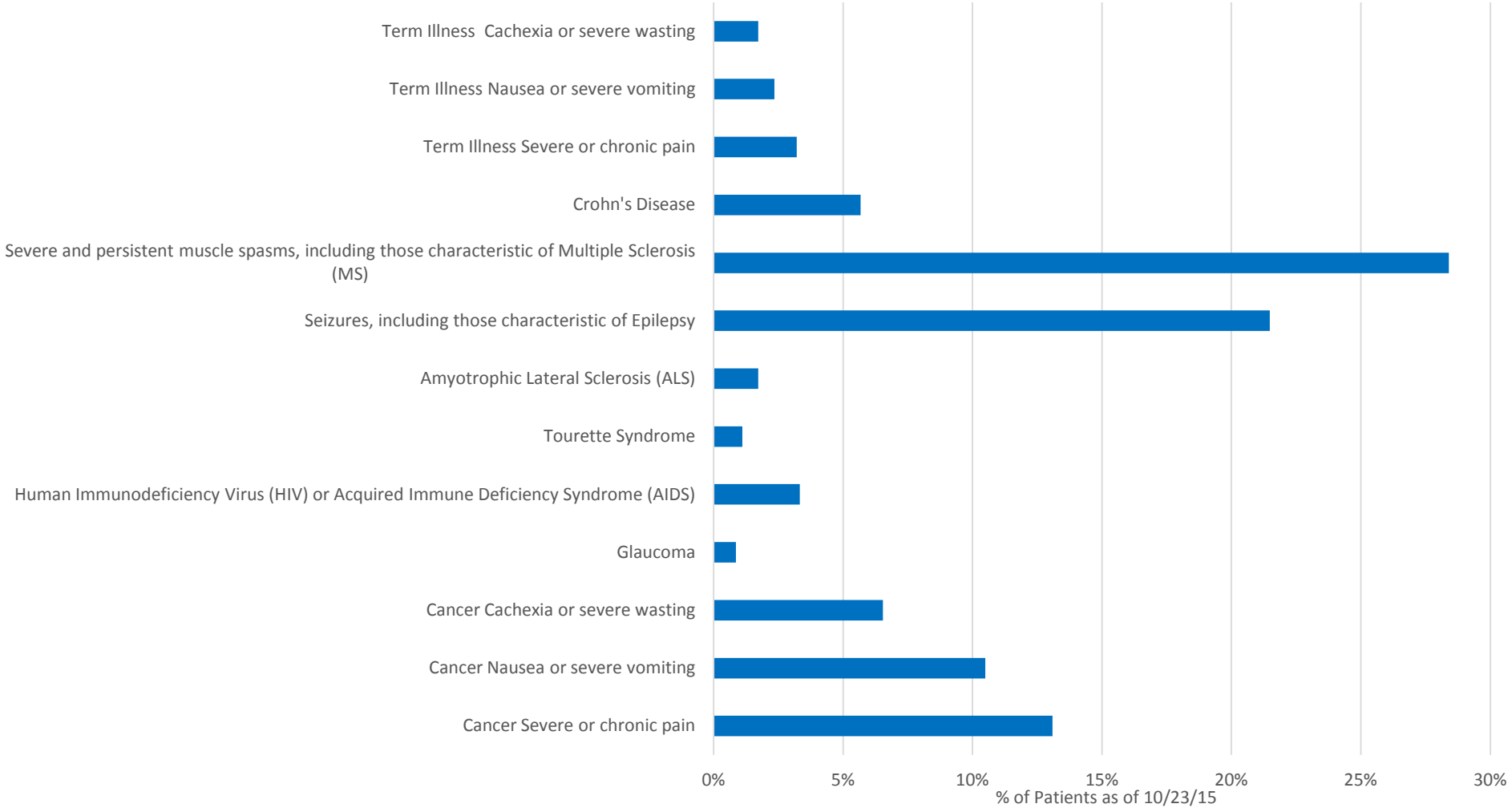
Cost is High

- Insurance does not cover medical cannabis
- Patient state registration fee $50-$200
  - Medical assistance patients get a discount
- Monthly cost of medication is variable
  - $100 to $500 per month depending on product and dose

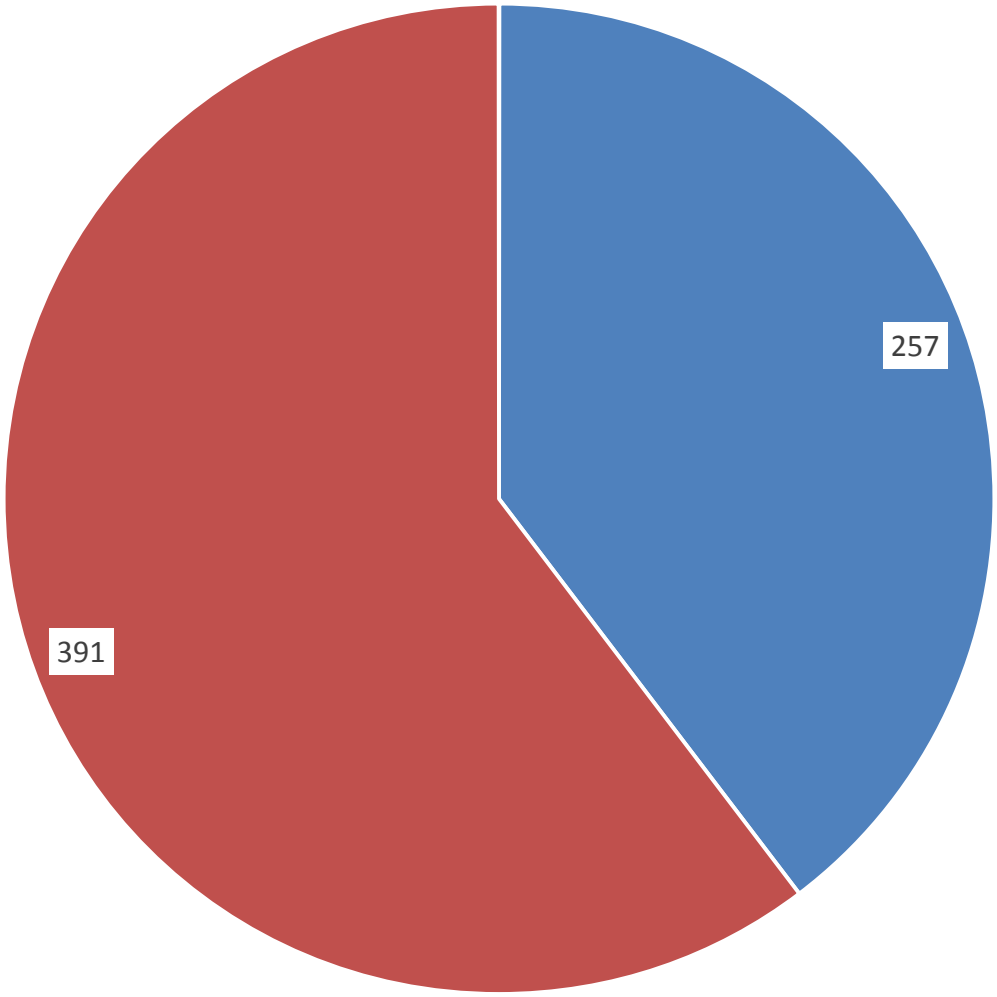
October 25, 2015:
642 approved patients, 426 providers



Patients Qualifying Medical Conditions

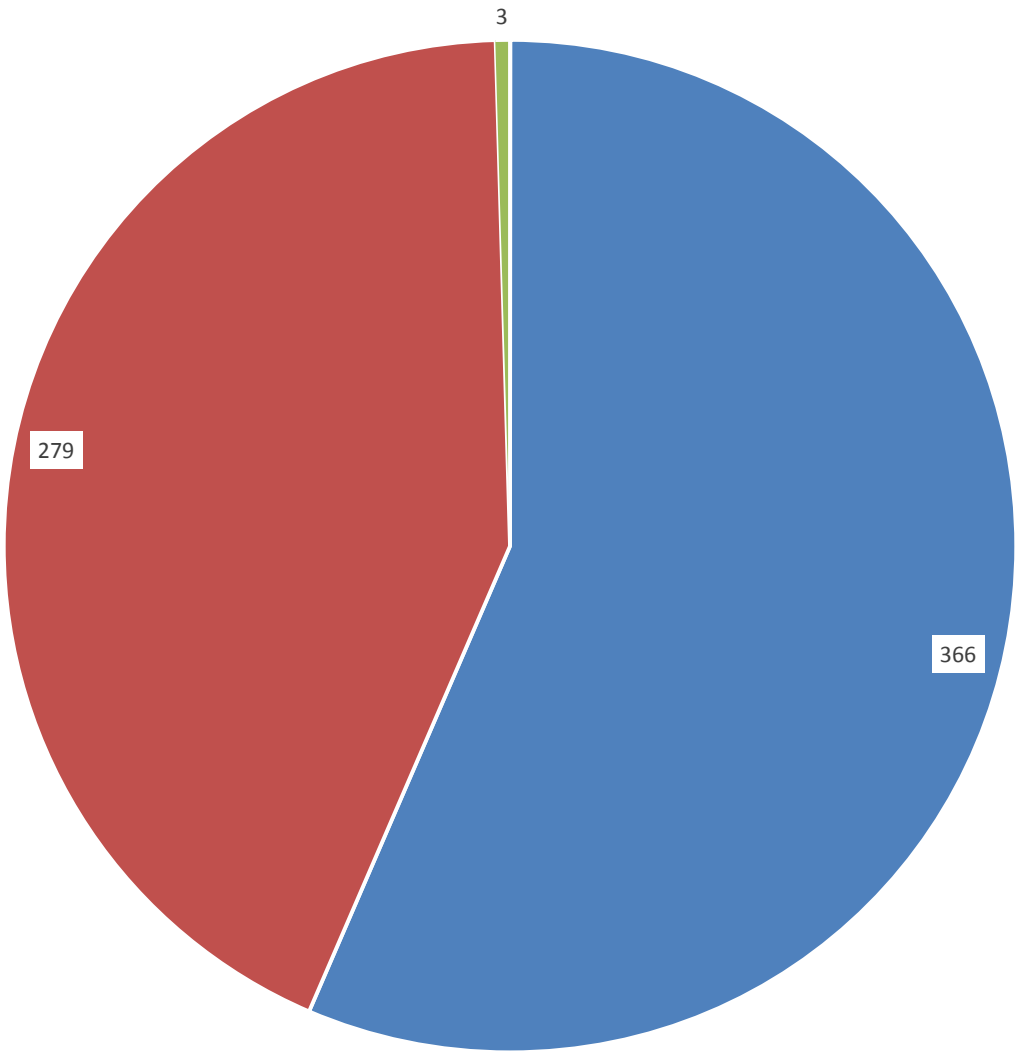


MN Medical Cannabis Program
Patient Medical Condition Count



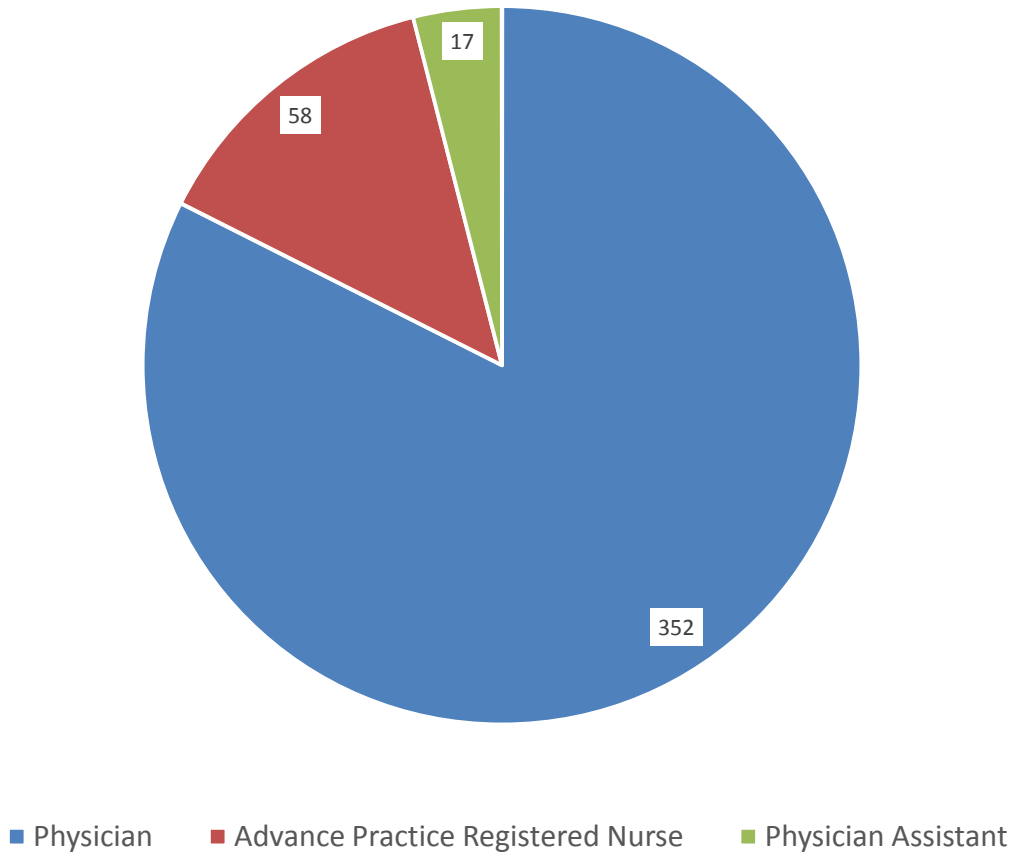
As of 10/23/2015

MN Medical Cannabis Program Patient Gender Breakdown



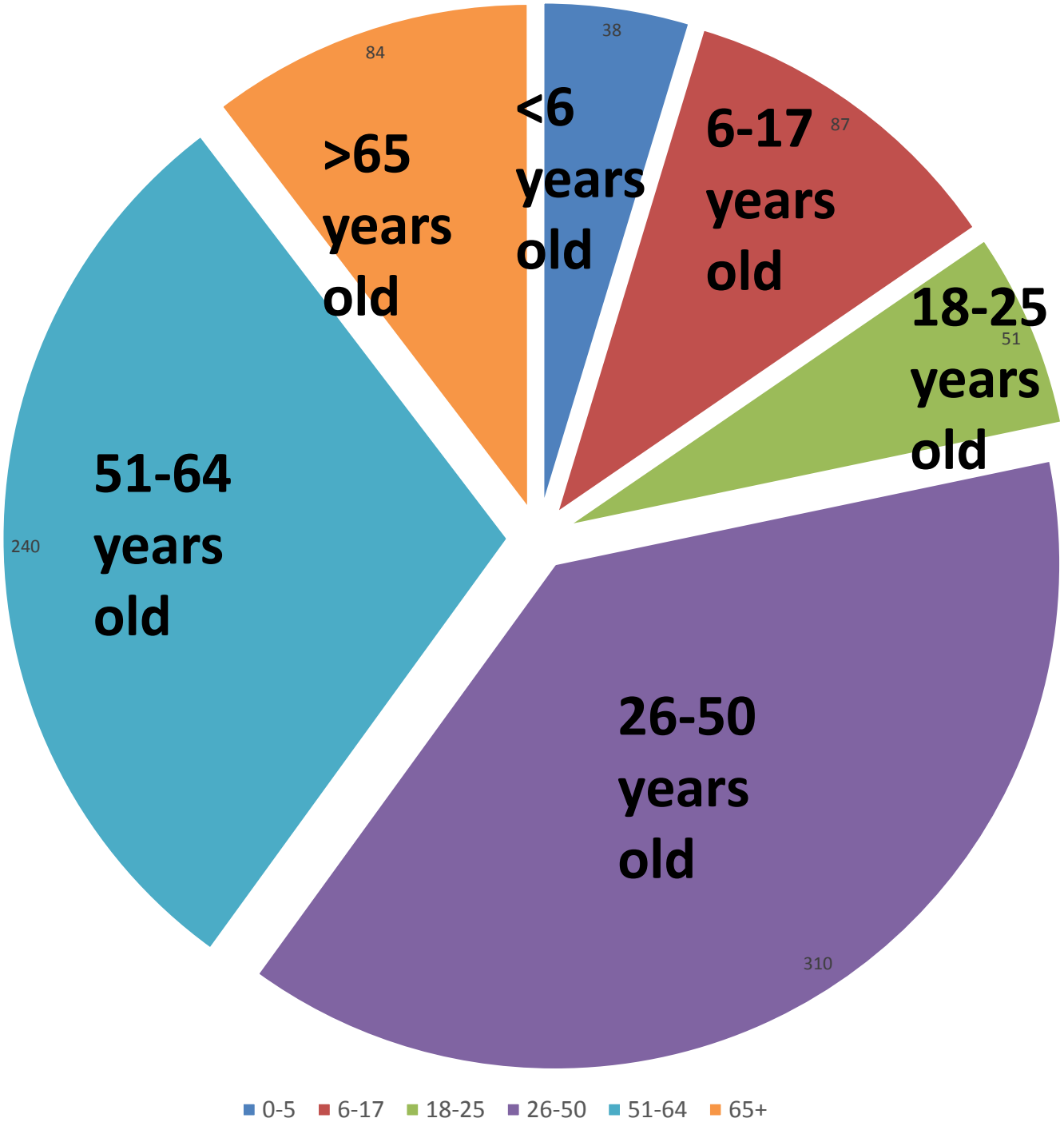
As of 10/23/2015

MN Medical Cannabis Program
Health Care Practitioner Breakdown



Type	Status	Total
Physician	Approved	352
Advance Practice Registered Nurse	Approved	58
Physician Assistant	Approved	17

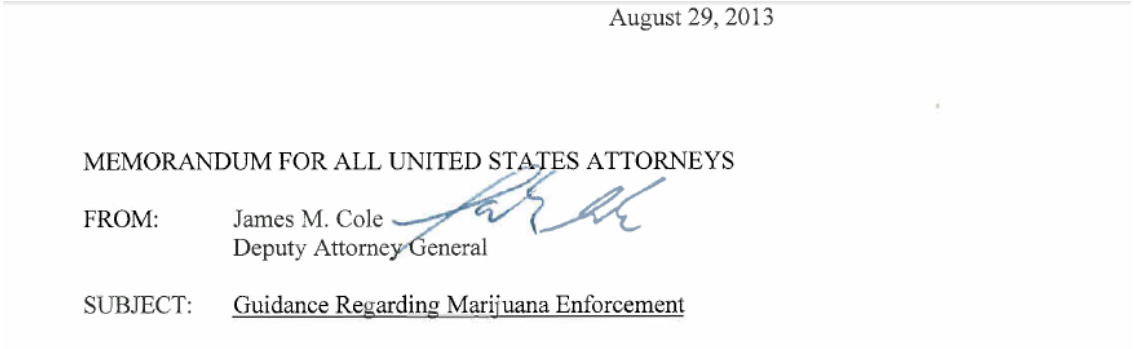
As of 10/23/2015



As of 10/23/2015

Legal issues

Federal prosecution priorities



August 29, 2013

MEMORANDUM FOR ALL UNITED STATES ATTORNEYS

FROM: James M. Cole
Deputy Attorney General

SUBJECT: Guidance Regarding Marijuana Enforcement

- Minors
- Driving
- Gangs, criminal enterprises, violence
- Possession on federal property
- Transit across state lines
- Using public properties to grow or use marijuana


Matt Ramos Become a fan
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Matt Ferner Become a fan
Matt.Ferner@huffingtonpost.com

House Votes In Favor Of Medical Marijuana Protections

Posted: 06/03/2015 4:26 pm EDT | Updated: 06/03/2015 4:59 pm EDT

WASHINGTON -- The House of Representatives voted Wednesday to reauthorize an amendment that would protect medical marijuana operations from federal interference in states where the drug is legal, siding with a majority of Americans who say that medical marijuana is an issue best left to the states.

Inpatient use of medical cannabis

- *Minnesota is the first state to do this*
- CMS, JCAHO, pharmDs, nursing unions, security guards all need to be appeased
- Multiple approaches to “threading the needle” appeasing everyone
- Patient self administered vs stored and administered by hospital staff
- <1/2 local hospitals are allowing inpatient medical cannabis

Will my malpractice insurance cover me?

Will my malpractice insurance cover me?

If you are otherwise practicing professionally in regards to medical cannabis, you are probably covered, but it is best to ask

“Intractable pain” as a qualifying condition.
Recommendation due January 1st, 2016

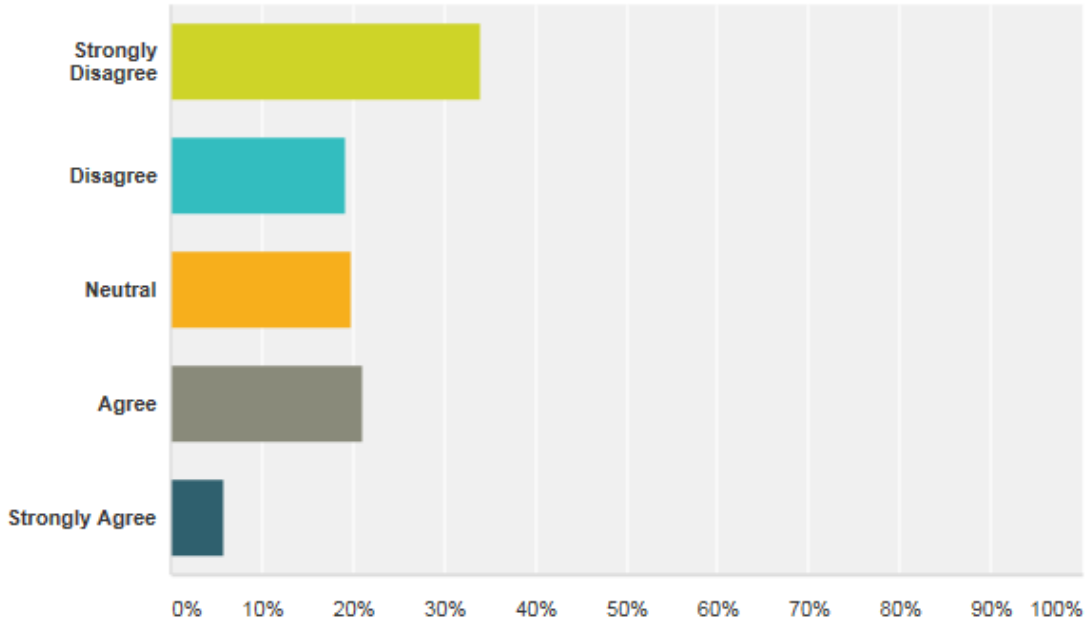
Years lived with disability 1990-2010

Table 2. YLD Numbers in 1990 and 2010 for Both Sexes Combined for the 30 Leading Diseases and Injuries Contributing to YLDs in 2010 in the United States and Percentage Change From 1990 to 2010, Ranked by the Magnitude of YLDs in 2010[a]

	YLD Rank		No. of YLDs (in Thousands)		Median Change, %	
Diseases and Injuries	1990	2010	1990	2010	YLDs	Age-Standardized YLD Rate
Low back pain	1 (1-3)	1 (1-3)	2538.00 (1771.4-3427.2)	3180.60 (2179.5-4318.6)	24.9 (13.8 to 38.4)	−3 (−11.6 to 7.3)
Major depressive disorder	2 (1-5)	2 (1-4)	2142.50 (1525.2-2843.7)	3048.90 (2151.3-4122.3)	42.7 (9.2 to 83.3)	13.4 (−12.9 to 46.3)
Other musculoskeletal disorders	3 (1-4)	3 (2-4)	2024.40 (1664.7-2311.9)	2602.50 (2138.0-2986.8)	28.5 (18.9 to 38.9)	−0.2 (−8.0 to 7.8)
Neck pain	4 (2-6)	4 (2-6)	1652.70 (1151.0-2296.4)	2134.40 (1482.6-2934.4)	29.1 (17.4 to 41.1)	0.2 (−9.1 to 9.5)
Anxiety disorders	5 (2-6)	5 (3-6)	1541.00 (1078.5-2172.8)	1866.10 (1310.2-2569.3)	21.3 (4.7 to 39.5)	−1.5 (−15.2 to 13.1)
Chronic obstructive pulmonary disease	6 (4-9)	6 (3-10)	1304.10 (761.3-2007.2)	1745.40 (1011.9-2601.4)	34.1 (4.6 to 70.9)	−1.5 (−23.2 to 25.0)
Drug use disorders	7 (6-10)	7 (6-10)	996.9 (722.3-1337.9)	1295.50 (921.6-1725.1)	29.8 (6.5 to 58.6)	20.1 (−1.4 to 47.1)
Diabetes	8 (7-15)	8 (6-11)	747.7 (506.1-1059.3)	1164.90 (789.1-1648.6)	56.2 (38.4 to 74.8)	11.2 (−1.4 to 24.5)
Osteoarthritis	12 (8-19)	9 (7-17)	637.6 (393.1-972.0)	994 (611.5-1471.0)	56.1 (28.3 to 88.3)	5.5 (−13.7 to 27.8)
Asthma	9 (7-19)	10 (7-19)	769.3 (418.1-1229.5)	932 (504.7-1469.3)	21.2 (11.5 to 31.6)	−0.8 (−9.4 to 8.2)

Intractable pain should be a qualifying condition for medical cannabis.

Answered: 156 Skipped: 0

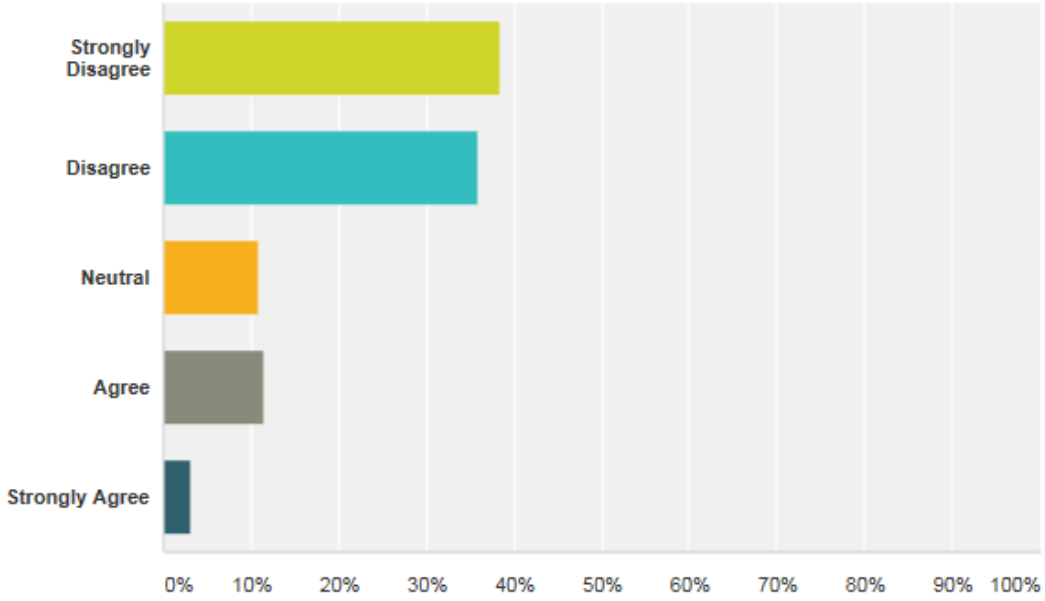


Answer Choices	Responses	
Strongly Disagree	33.97%	53
Disagree	19.23%	30
Neutral	19.87%	31
Agree	21.15%	33
Strongly Agree	5.77%	9
Total		156

Comments (33)

I have the knowledge to discuss the risks and benefits of medical cannabis with a patient seeking certification for a qualifying condition.

Answered: 156 Skipped: 0

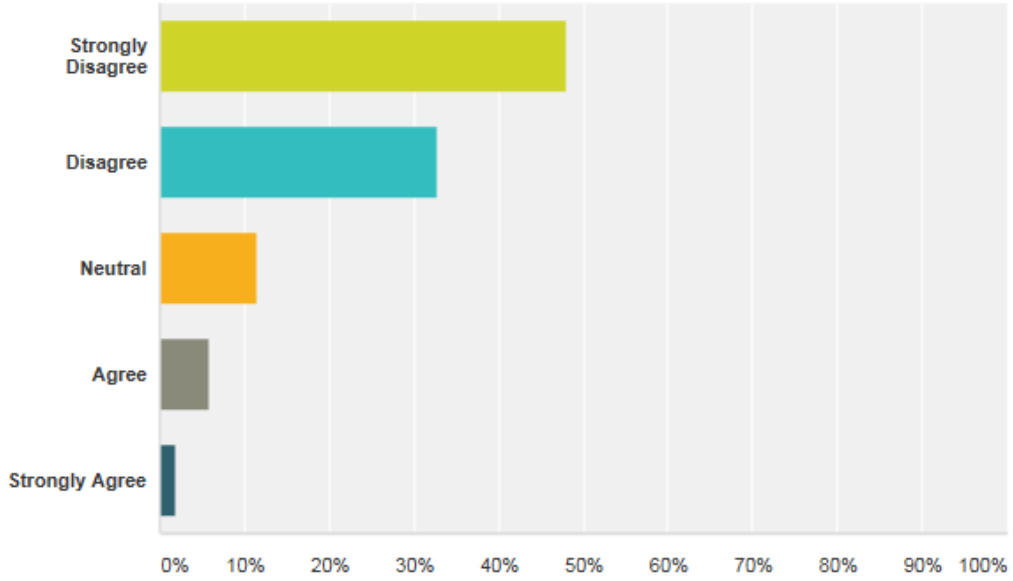


Answer Choices	Responses	
Strongly Disagree	**38.46%**	60
Disagree	**35.90%**	56
Neutral	**10.90%**	17
Agree	**11.54%**	18
Strongly Agree	**3.21%**	5
Total		156

Comments (17)

If I believe medical cannabis to be appropriate for my patient, I have the facilities, time, and know-how to go about certifying the patient for medical cannabis, and managing their response to treatment.

Answered: 156 Skipped: 0



Answer Choices	Responses	
Strongly Disagree	48.08%	75
Disagree	32.69%	51
Neutral	11.54%	18
Agree	5.77%	9
Strongly Agree	1.92%	3
Total		156

Comments (19)

Physician concerns

- Practicing medicine outside the evidence base norms
- Unconventional production, regulation, dispensing
- Recreating the opioid-for-pain epidemic
- Challenging conversations, demanding patients
- Paperwork and red tap
- Time and energy to learn something new
- Personal opinions about marijuana

JAMA Internal Medicine
Formerly *Archives of Internal Medicine*

Invited Commentary | August 25, 2014

Legalization of Medical Marijuana and Incidence of Opioid Mortality ONLINE FIRST

Marie J. Hayes, PhD[1,2]; Mark S. Brown, MD[2]

[+] Author Affiliations

JAMA Intern Med. Published online August 25, 2014. doi:10.1001/jamainternmed.2014.2716

The rapid acceleration of prescription opioid–related overdose deaths in the United States is correlated with the availability of stronger opioid medications, as well as a change in medical practice from withholding opioid medication because of dependence risk[1] to treating patients with chronic pain with opioids. Subsequently, the pendulum of concern has swung again, driven by the public health crisis of rising opioid analgesic addiction, overdose, and death. Opioid medications are problematic as a treatment for chronic pain. Opioid pharmaceuticals cause other adverse effects when used for long periods, such as tolerance, hyperalgesia, and gastrointestinal complications, making this class of drugs a poor choice for long-term use. As is well known, prescription opioids also have great abuse potential due to their influence on stress and reward circuits in the brain, promoting nonmedical use and abuse and diversion of prescription medications.

In this issue, Bachhuber et al[2] examine the link between medical marijuana laws and unintentional overdose mortality in which an opioid analgesic was identified. Using Centers for Disease Control and Prevention data, states with and without medical marijuana laws were contrasted for age-adjusted, opioid-related mortality. Overall, the incidence of opioid analgesic–associated mortality rose dramatically across the study period (1999-2010). States with medical marijuana laws had higher overdose rates than did those without such laws when population-adjusted mortality was analyzed across years, although the rise in deaths over the study period was similar for both groups. In contrast, a convincing protective effect of medical marijuana laws was found in a covariate-adjusted, time-series model in which opioid analgesic mortality declined steadily based on years since medical marijuana laws were enacted, termed *implementation*. The model included an analysis of the impact of critical policies for prescription opioid regulatory efforts: prescription monitoring programs, pharmacist collection of patient information, state and oversight of pain management clinics, as well as state unemployment rates. In states with medical marijuana laws, age-

Are medical cannabis laws bad public policy that will increase adolescent marijuana use?

Percentage of U.S. Students (Grades 9 to 12) Reporting Past Year Alcohol and Other Drug Use, 2012

(N=3,884)

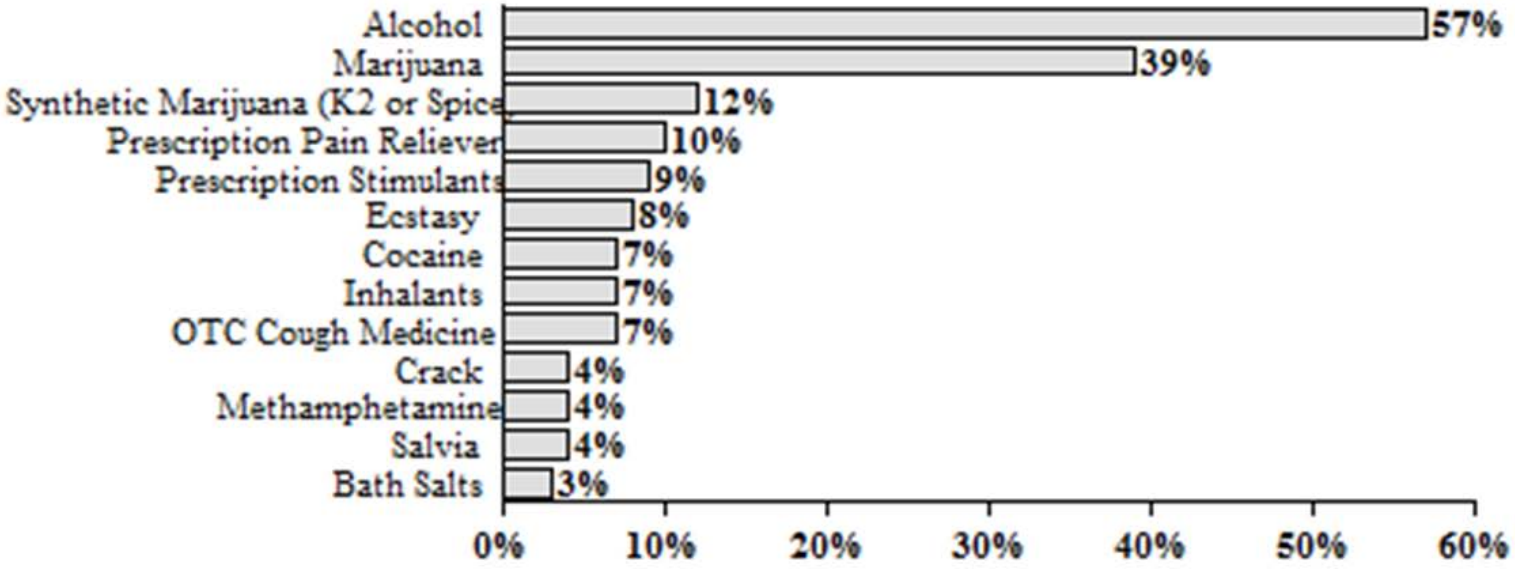
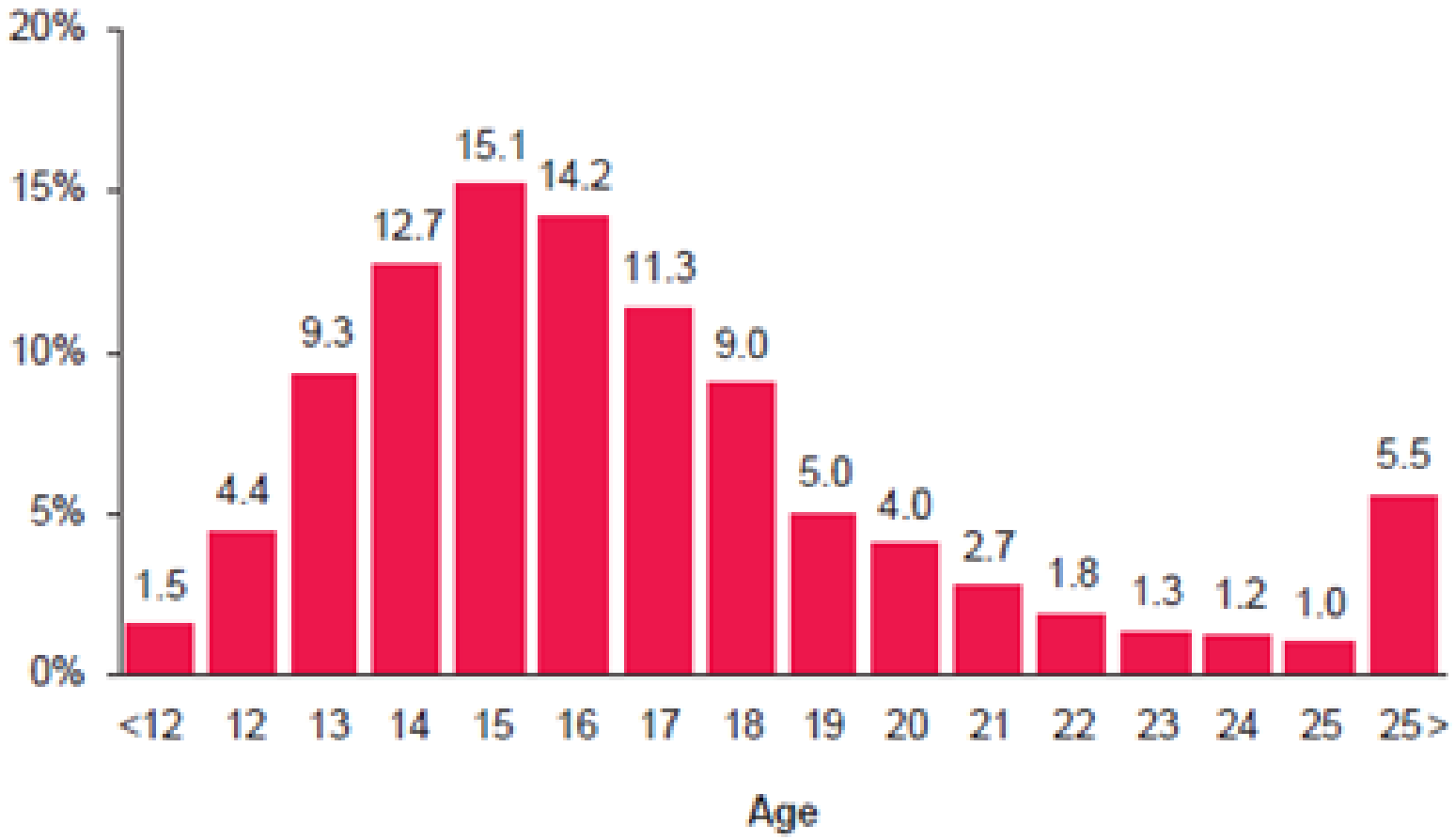


Figure 2. Percentages of Recent Marijuana Initiates By Age of First Marijuana Use

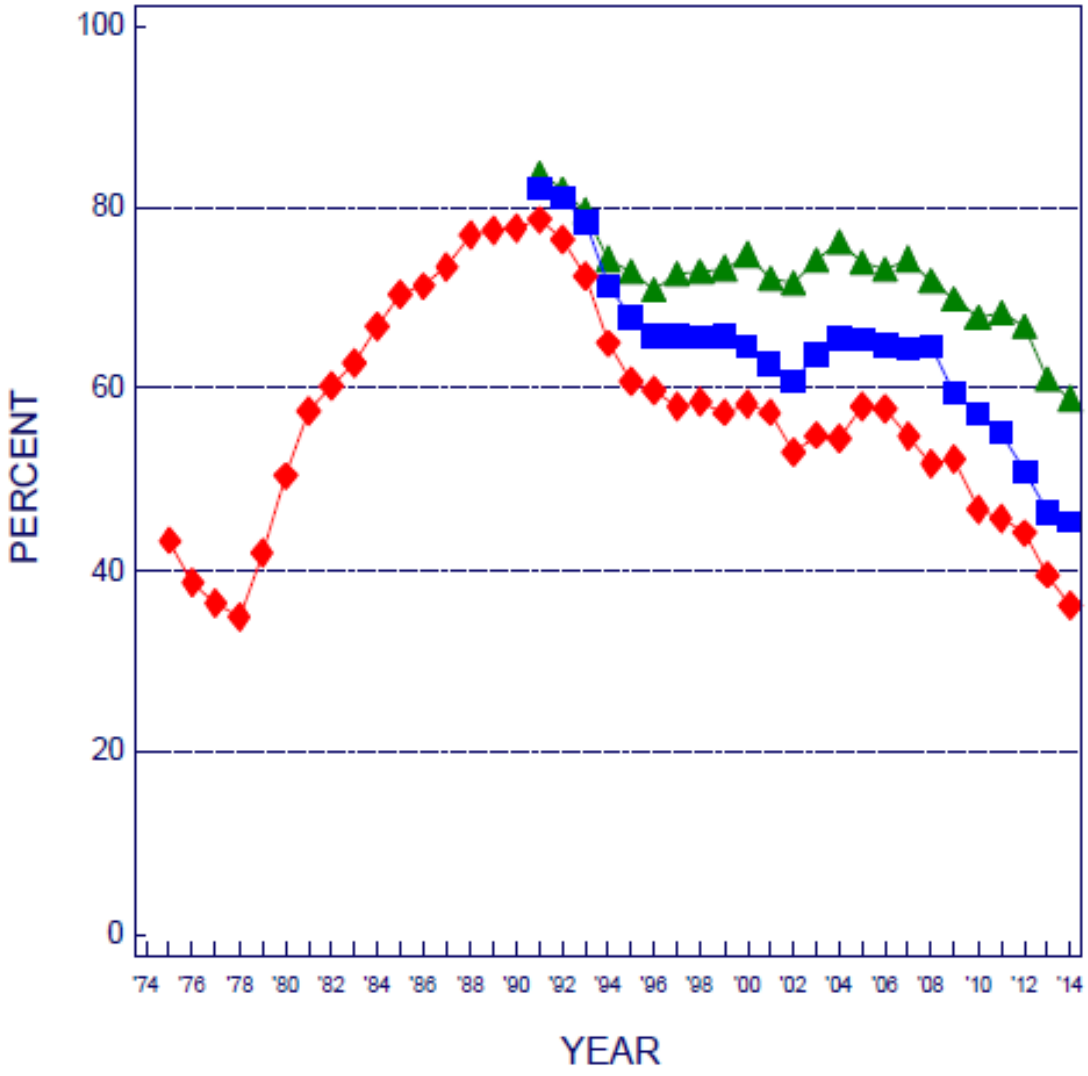


Why would a young person try something new?

- Acceptability
- Availability
- Perceived safety

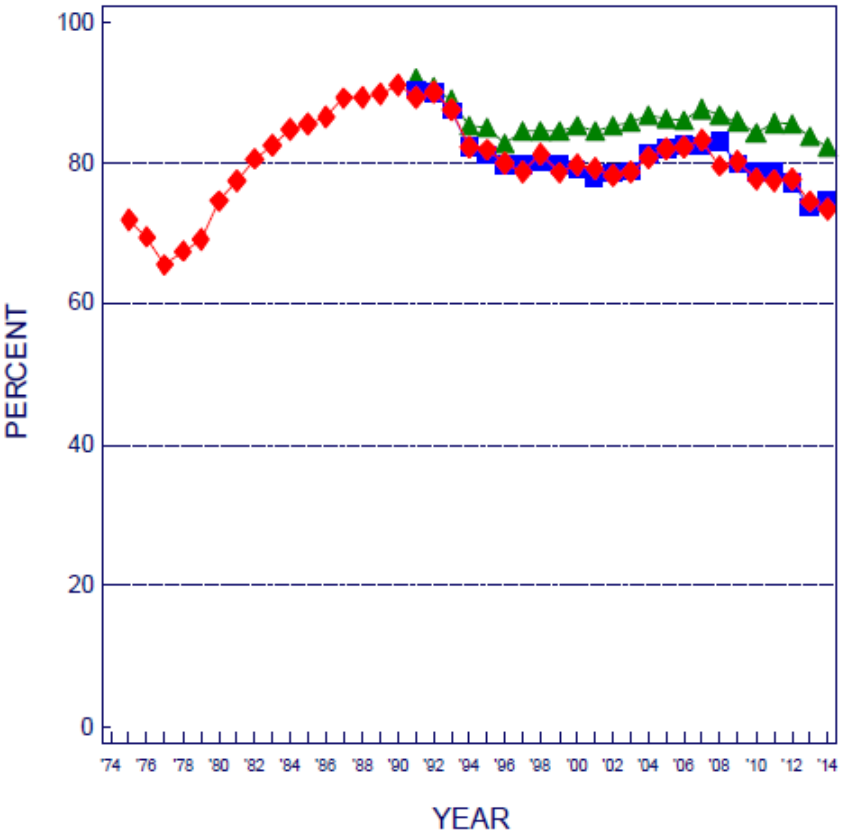
Risk

% seeing "great risk" in using regularly



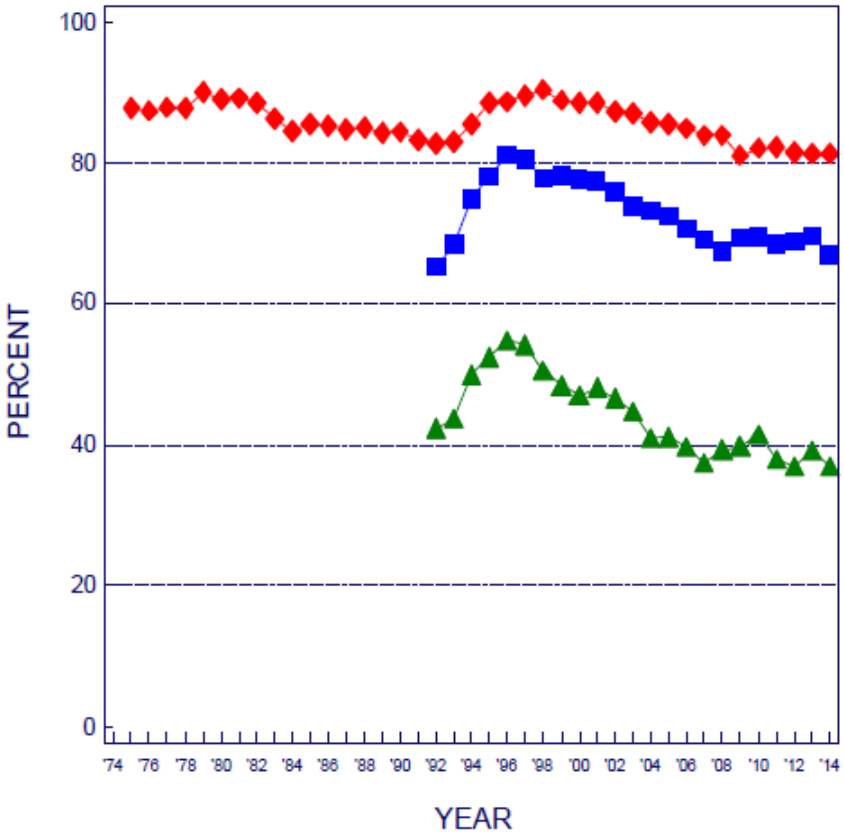
Disapproval

% disapproving of using regularly



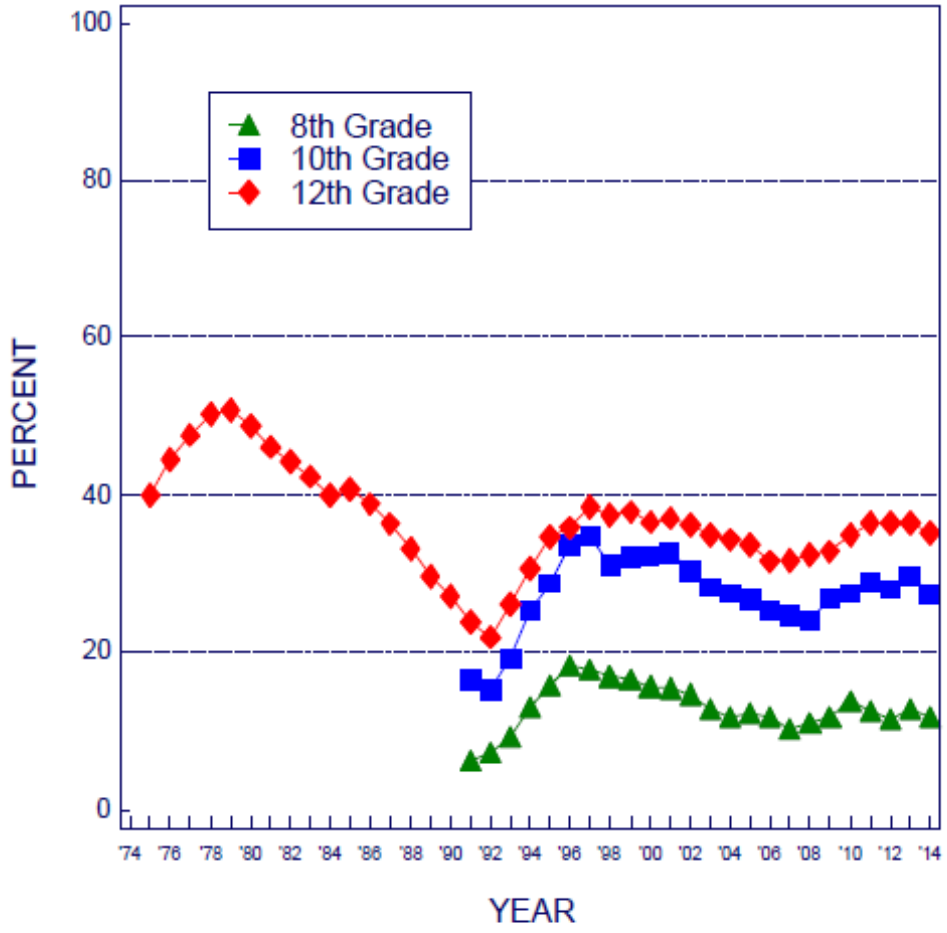
Availability

% saying "fairly easy" or "very easy" to get

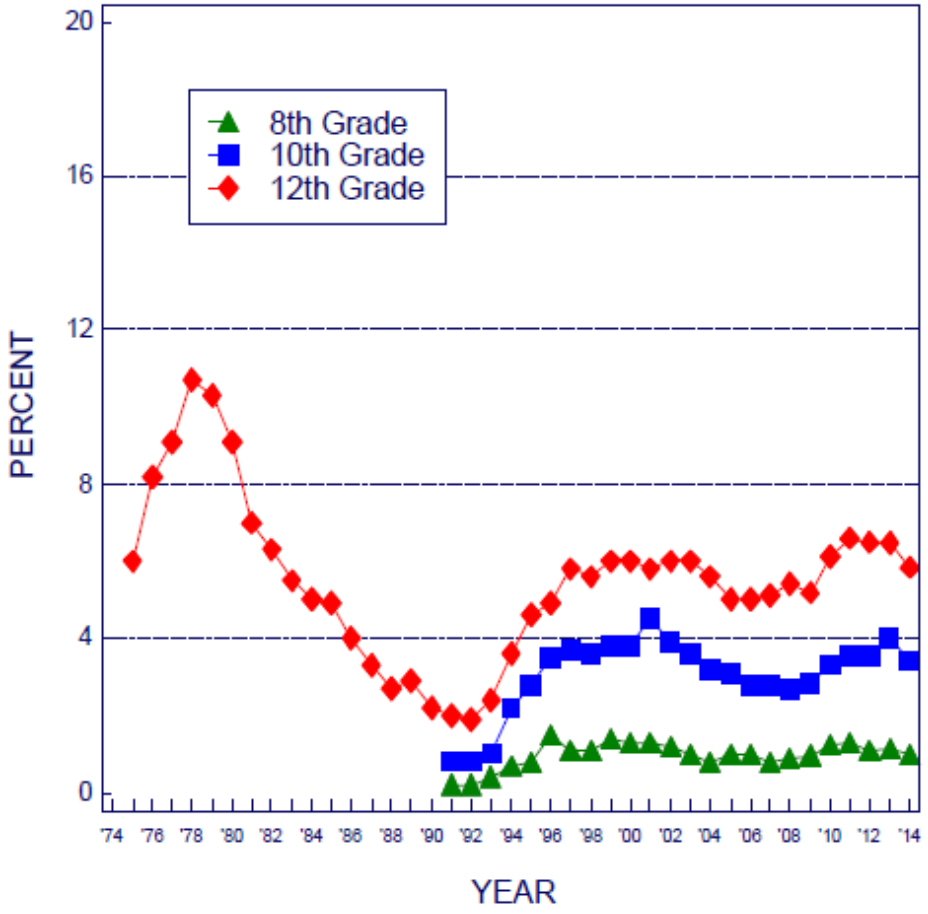


Use

% who used in last 12 months



% who used daily



Legalizing medical marijuana does not increase use among adolescents

Date: June 15, 2015

Source: The Lancet

Summary: A nationwide study analyzing 24 years of data (1991 to 2014) from over one million American adolescents in the 48 contiguous states has found no evidence that legalizing the use of marijuana for medical purposes leads to increased use among teenagers.

RELATED TOPICS

Health & Medicine

- Controlled Substances
- Medical Education and Training

Mind & Brain

- Marijuana
- Illegal Drugs

Plants & Animals

- Mice
- Biology

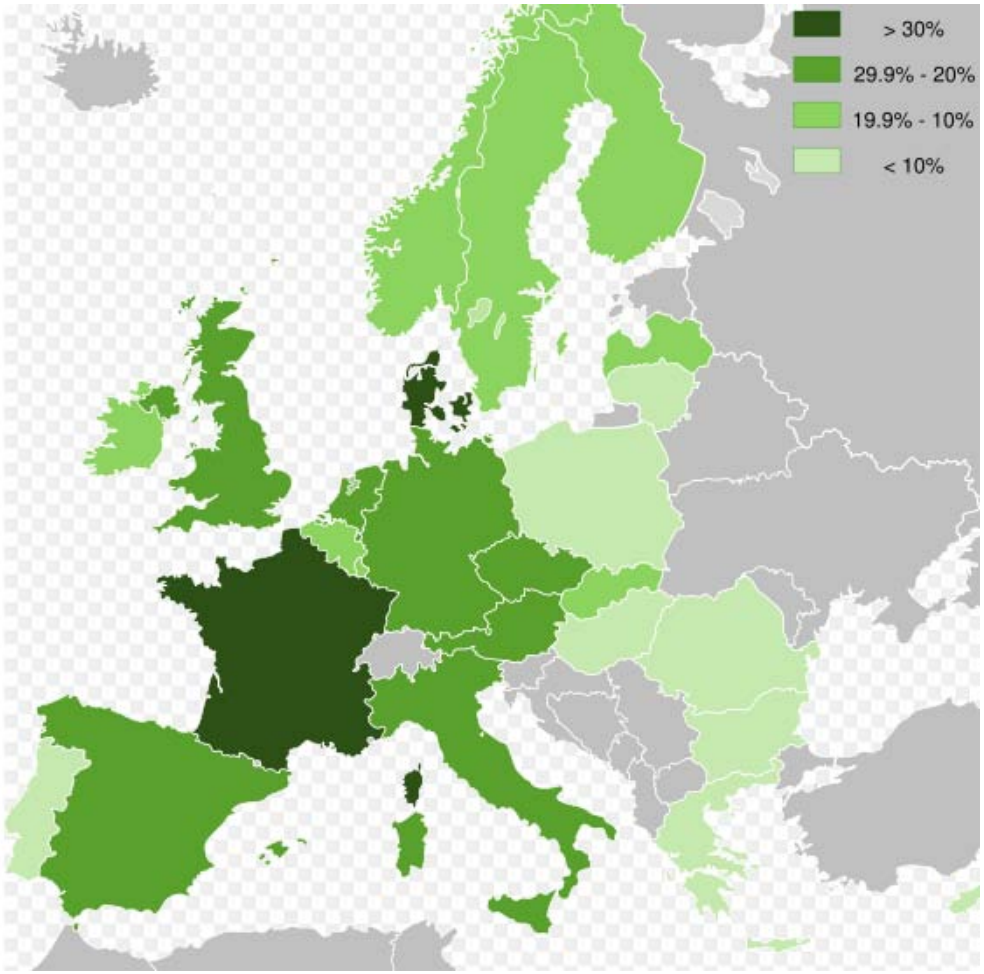
Science & Society

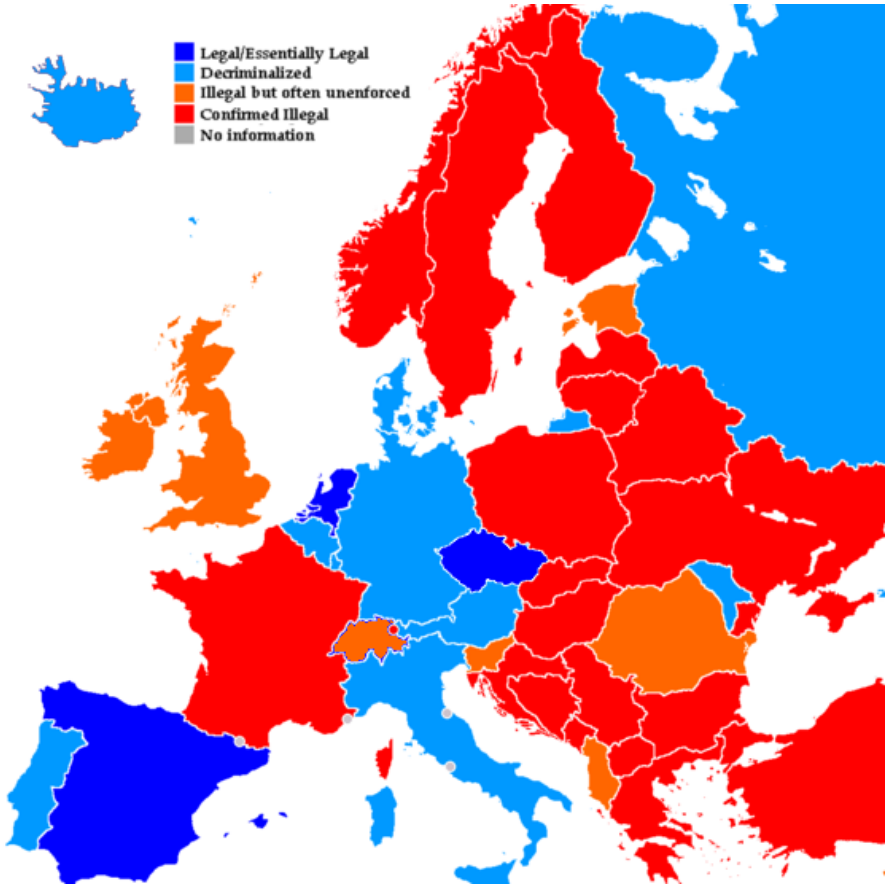
- Public Health
- Educational Policy

FULL STORY

A new study showed no significant difference in adolescent marijuana use in 21 states with medical marijuana laws before or after implementation of these laws.

Strict laws do not align with low use





Prevalence of Marijuana Use Disorders in the United States Between 2001-2002 and 2012-2013 FREE

ONLINE FIRST

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JAMA Psychiatry. Published online October 21, 2015. doi:10.1001/jamapsychiatry.2015.1858 Text Size: A A A

ABSTRACT

Importance Laws and attitudes toward marijuana in the United States are becoming more permissive but little is known about whether the prevalence rates of marijuana use and marijuana use disorders have changed in the 21st century.

Objective To present nationally representative information on the past-year prevalence rates of marijuana use, marijuana use disorder, and marijuana use disorder among marijuana users in the US adult general population and whether this has changed between 2001-2002 and 2012-2013.

Design, Setting, and Participants Face-to-face interviews conducted in surveys of 2 nationally representative samples of US adults: the National Epidemiologic Survey on Alcohol and Related Conditions (data collected April 2001-April 2002; N = 43 093) and the National Epidemiologic Survey on Alcohol and Related Conditions–III (data collected April 2012-June 2013; N = 36 309). Data were analyzed March through May 2015.

Main Outcomes and Measures Past-year marijuana use and *DSM-IV* marijuana use disorder (abuse or dependence).

Results The past-year prevalence of marijuana use was 4.1% (SE, 0.15) in 2001-2002 and 9.5% (SE, 0.27) in 2012-2013, a significant increase ($P < .05$). Significant increases were also found across demographic subgroups (sex, age, race/ethnicity, education, marital status, income, urban/rural, and region). The past-year prevalence of *DSM-IV* marijuana use disorder was 1.5% (0.08) in 2001-2002 and 2.9% (SE, 0.13) in 2012-2013 ($P < .05$). With few exceptions, increases in the prevalence of marijuana use disorder between 2001-2002 and 2012-2013 were also statistically significant ($P < .05$) across demographic subgroups. However, the prevalence of marijuana use disorder among marijuana users decreased significantly from 2001-2002 (35.6%; SE, 1.37) to 2012-2013 (30.6%; SE, 1.04).

Conclusions and Relevance The prevalence of marijuana use more than doubled between 2001-2002 and 2012-2013, and there was a large increase in marijuana use disorders during that time. While not all marijuana users experience problems, nearly 3 of 10 marijuana users manifested a marijuana use disorder

Table 1. Past-Year Prevalence of Marijuana Use by Sociodemographic Characteristics, 2001-2013[a]

Sociodemographic Characteristics	% (SE)	
	NESARC Wave 1, 2001-2002	NESARC-III, 2012-2013
Total	4.1 (0.15)	9.5 (0.27)
Sex		
Male	5.6 (0.24)	12.3 (0.40)
Female	2.6 (0.15)	6.9 (0.29)
Age, y		
18-29	10.5 (0.47)	21.2 (0.67)
30-34	4.1 (0.24)	10.1 (0.41)
45-64	1.6 (0.15)	5.9 (0.28)
≥65	0.0 (0.02)	1.3 (0.22)
Race/ethnicity		
White	4.1 (0.17)	9.4 (0.34)
Black	4.7 (0.35)	12.7 (0.64)
Native American	7.0 (1.15)	17.1 (2.32)
Asian	3.1 (0.54)	5.0 (0.59)
Hispanic	3.3 (0.31)	8.4 (0.50)
Education		
<High school	4.5 (0.38)	9.7 (0.51)
High school	4.0 (0.26)	10.4 (0.43)
Some college	4.0 (0.17)	9.1 (0.32)
Marital status		
Married	2.1 (0.13)	5.5 (0.24)
Widowed/separated	3.4 (0.30)	8.3 (0.40)
Not married	10.5 (0.41)	21.0 (0.65)
Income, $		
0-19 999	6.3 (0.34)	15.6 (0.61)
20 000-34 999	4.2 (0.28)	9.8 (0.47)
35 000-69 999	3.4 (0.23)	8.4 (0.33)

Table 2. Past-Year Prevalence of *DSM-IV* Marijuana Use Disorder (Abuse or Dependence) by Sociodemographic Characteristics, 2001-2013

Sociodemographic Characteristics	% (SE)	
	NESARC Wave 1, 2001-2002	NESARC-III, 2012-2013
Total	1.5 (0.08)	2.9 (0.13)[a]
Sex		
Male	2.2 (0.14)	4.2 (0.21)[a]
Female	0.8 (0.07)	1.7 (0.13)[a]
Age, y		
18-29	4.4 (0.30)	7.5 (0.45)[a]
30-34	1.2 (0.12)	2.9 (0.21)[a]
45-64	0.4 (0.08)	1.3 (0.15)[a]
≥65	0.0 (0.01)	0.3 (0.10)
Race/ethnicity		
White	1.4 (0.10)	2.7 (0.16)[a]
Black	1.8 (0.22)	4.6 (0.39)[a]
Native American	3.4 (0.78)	5.5 (1.46)
Asian	1.0 (0.37)	1.3 (0.28)[a]
Hispanic	1.2 (0.17)	2.8 (0.23)[a]
Education		
<High school	1.8 (0.23)	3.3 (0.34)[a]
High school	1.7 (0.15)	3.7 (0.27)[a]
Some college	1.2 (0.09)	2.5 (0.15)[a]
Marital status		
Married	0.6 (0.07)	1.4 (0.12)[a]
Widowed/separated	1.1 (0.17)	2.3 (0.25)[a]
Not married	4.2 (0.27)	7.3 (0.38)[a]
Income, $		
0-19 999	2.3 (0.18)	5.4 (0.35)[a]
20 000-34 999	1.4 (0.16)	2.8 (0.26)[a]

Poll says marijuana legalization support nears 60%

Trevor Hughes, USA TODAY 7:25 p.m. EDT October 21, 2015

(Photo: Trevor Hughes/USA TODAY)

DENVER – More Americans than ever are smoking, eating and drinking marijuana, and they now overwhelmingly support full legalization of the long-banned plant, a new study and poll show.

A Gallup poll released Wednesday shows 58% of American adults think marijuana should be legal, up from 51% a year ago, with just 40% believing it should remain illegal.

And the number of adults who said they've used marijuana sometime in the past year has doubled in the past decade, with 9.5% of adults in 2013 saying they'd used marijuana sometime in the past year, compared to 4.1% in 2001. Notable increases came among women, African-Americans, the middle-aged, and those living in the South, the study published in *JAMA Psychiatry* found.

The trends appear to be reinforcing each other, say experts who caution that broader marijuana use brings the potential for abuse. Young people in particular are

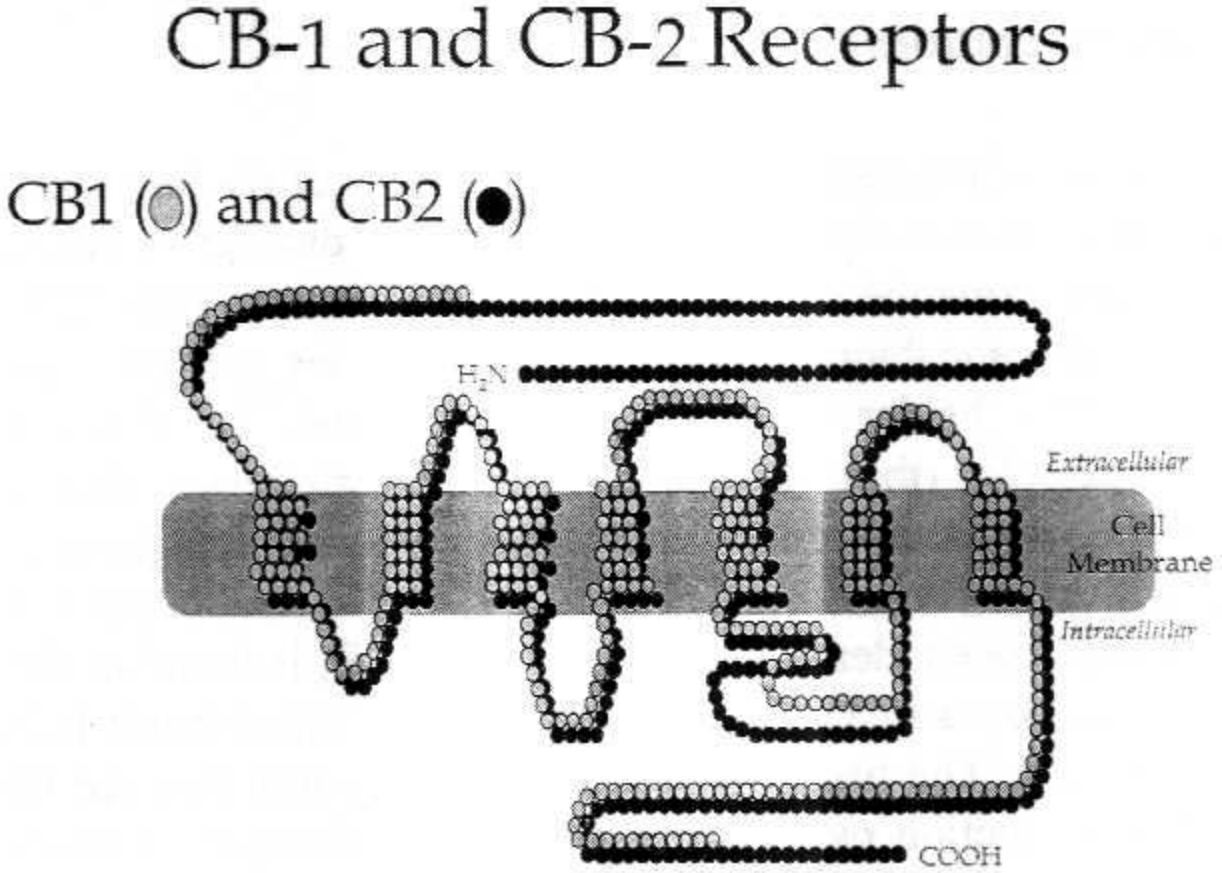
Is Medical Marijuana part of a bigger, organized plan to legalize marijuana for recreational use?

Conclusions

- It is easy to register as a provider and certify patients for medical cannabis
- There is scant evidence for medical cannabis
- It is best to treat this process medically
- The list of qualifying conditions may add pain shortly
- Medical cannabis has unclear public health effects

2. Marijuana Physiology and Pharmacology

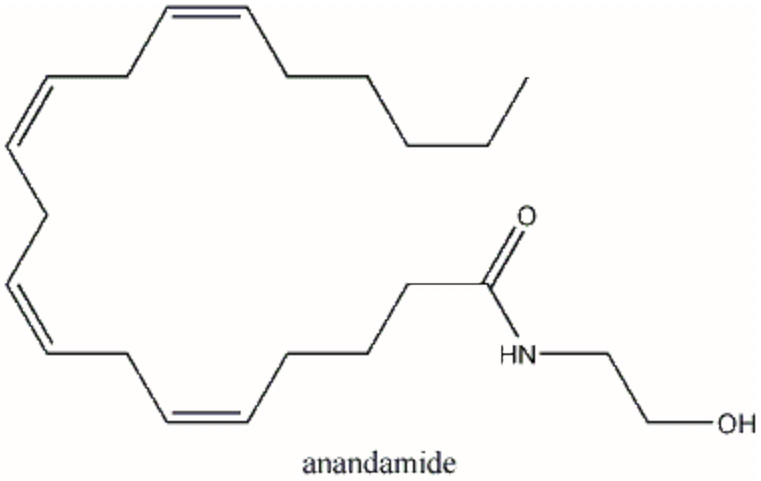
Endocannabinoids and cannabis receptors



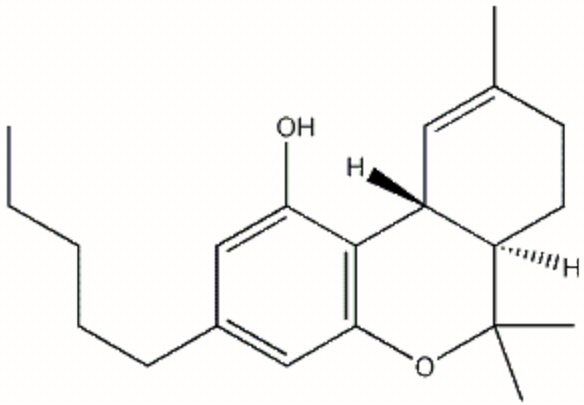
Cannabis receptor ligands

- Endocannabinoids
  - Anandamide
- Phytocannabinoids
  - THC, CBD
- Synthetic cannabinoids
  - K2, spice

THC and anandamide have little similarity



anandamide

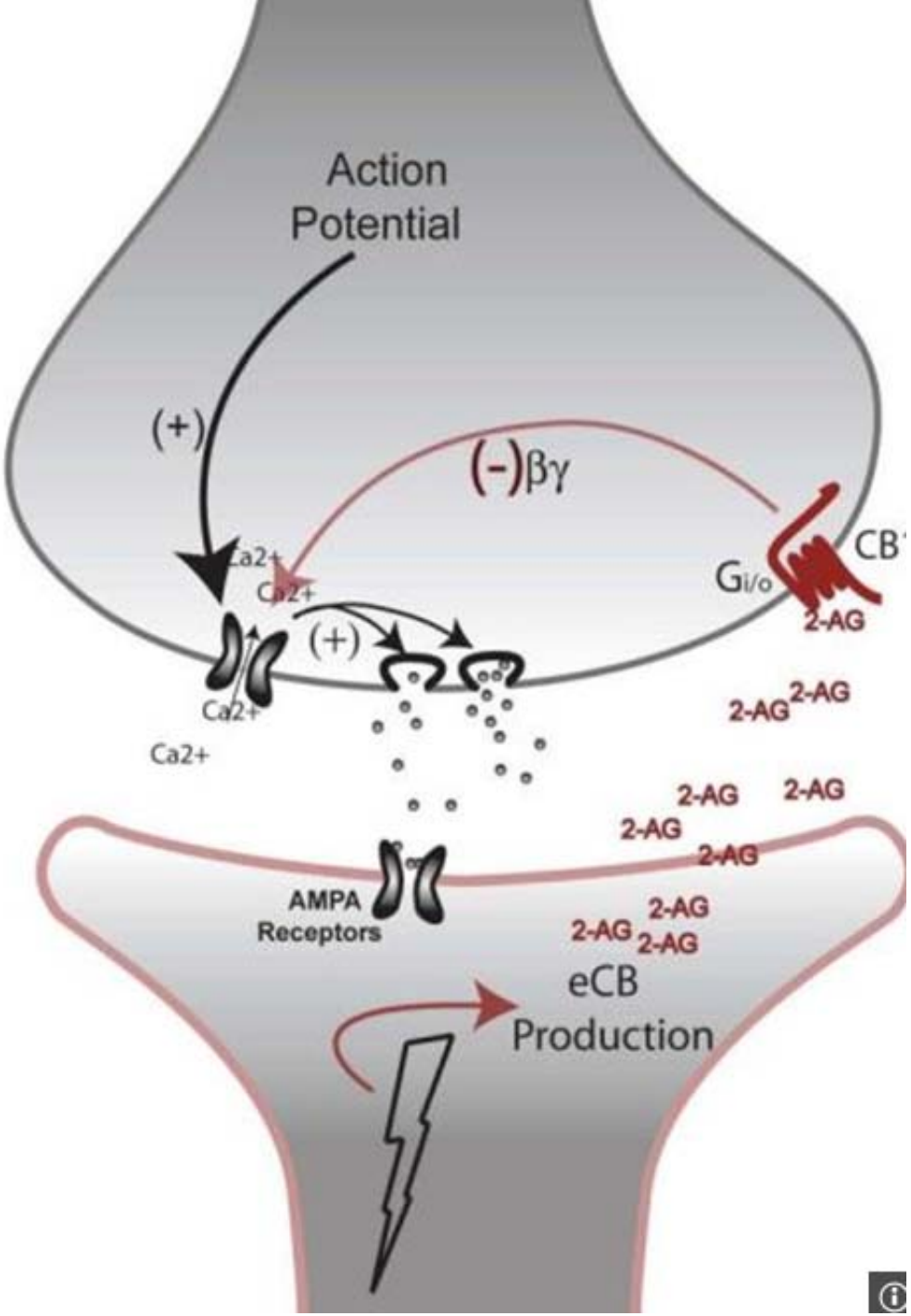


tetrahydrocannabinol

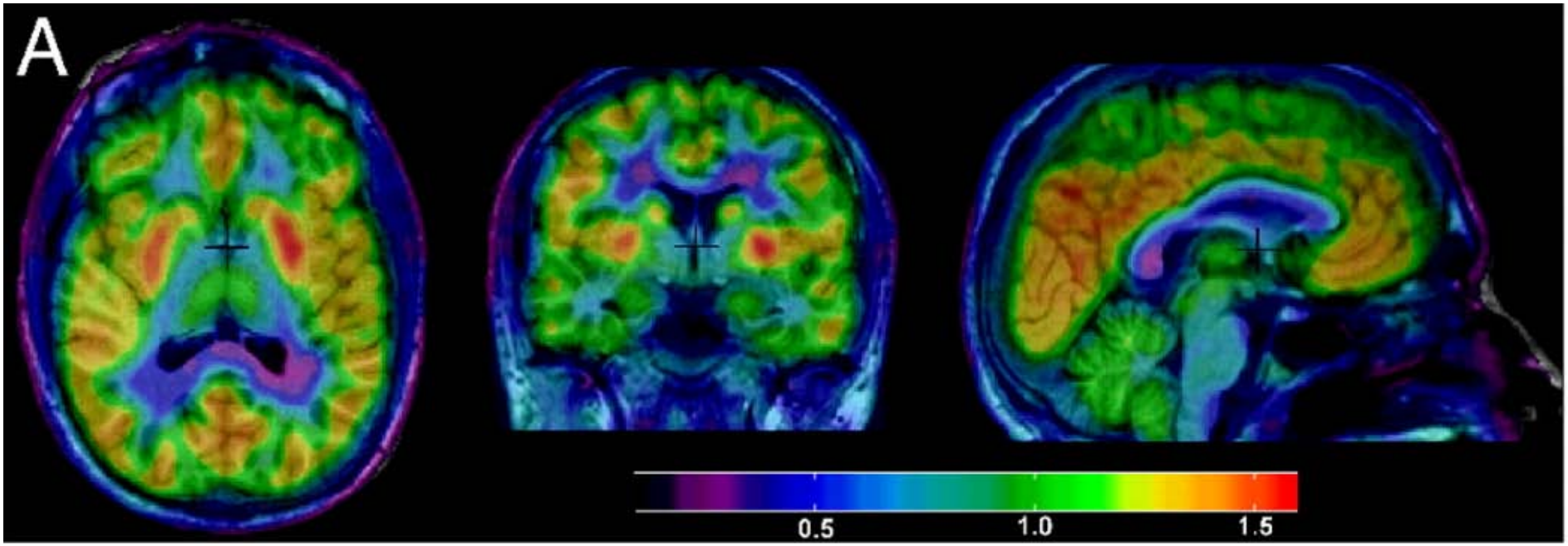
Cannabinoids are metabolized by p450 enzymes in the liver (2C9, 3A4)

Endocannabinoids are metabolized at the site of action by COX and FAAH– ubiquitous enzymes

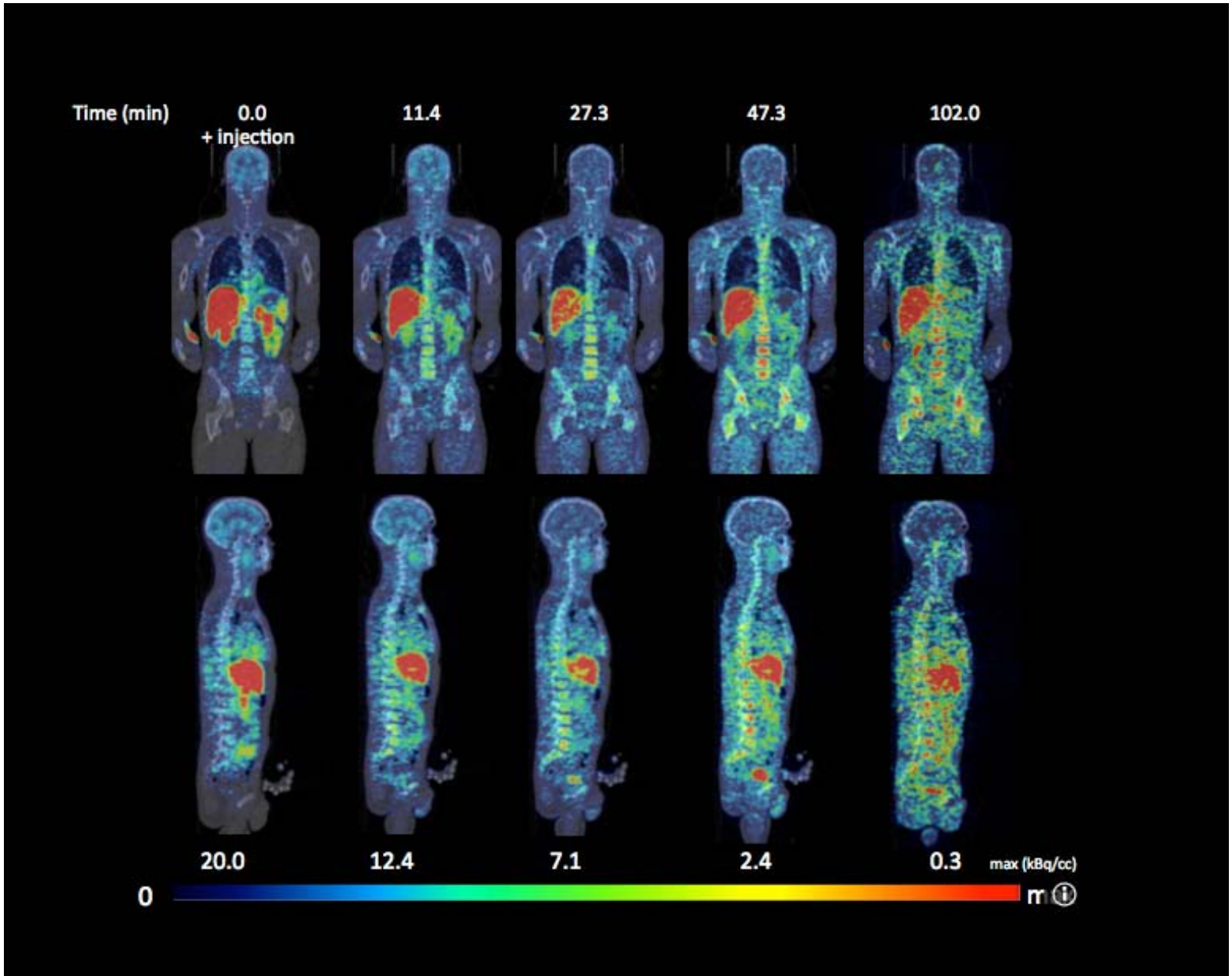
Cannabinoids are inhibitory retrograde inhibitors



CB1 receptor distribution: limbic system, hippocampus, cerebellum



CB2 receptor distribution: Immune cells, bone marrow



Endocannabinoid System

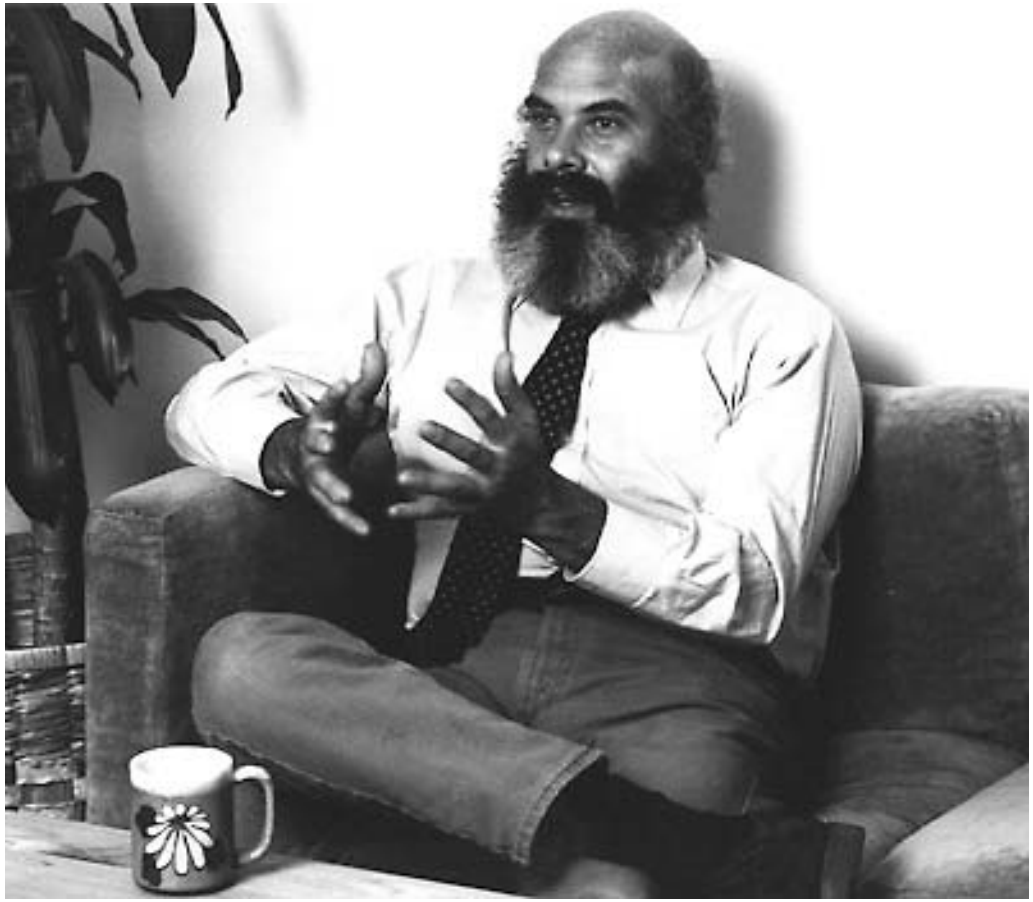
Endocannabinoids

- Dampen tonic nerve and immune signals
- Rapidly broken down in the body at the site of action by enzymes (FAAH, COX)
- Endocannabinoid signals are quick and localized

Cannabinoids

- Same
- Metabolized by the liver, not the site of action. Large volume of distribution
- Cannabinoids have sustained and global

“Active Placebo”
Set & Setting



THC vs CBD

both naturally occurring phytocannabinoids

THC- agonist for CB1 And CB2 receptors

CBD- nonagonist for CB receptors

Cannabidiol (CBD)

- Indirect antagonist of CB receptor ligands
- Not impairing or intoxicating
- Not much is known clinically:
  - Antiseizure
  - Antipsychotic
  - Anti-addictive

MN Medical Cannabis products

- High THC
- Mixed THC/CBD
- High CBD

- All are derived from plant extracts
- 85+ phytocannabinoids present
- “entourage effect”

Fig. 1

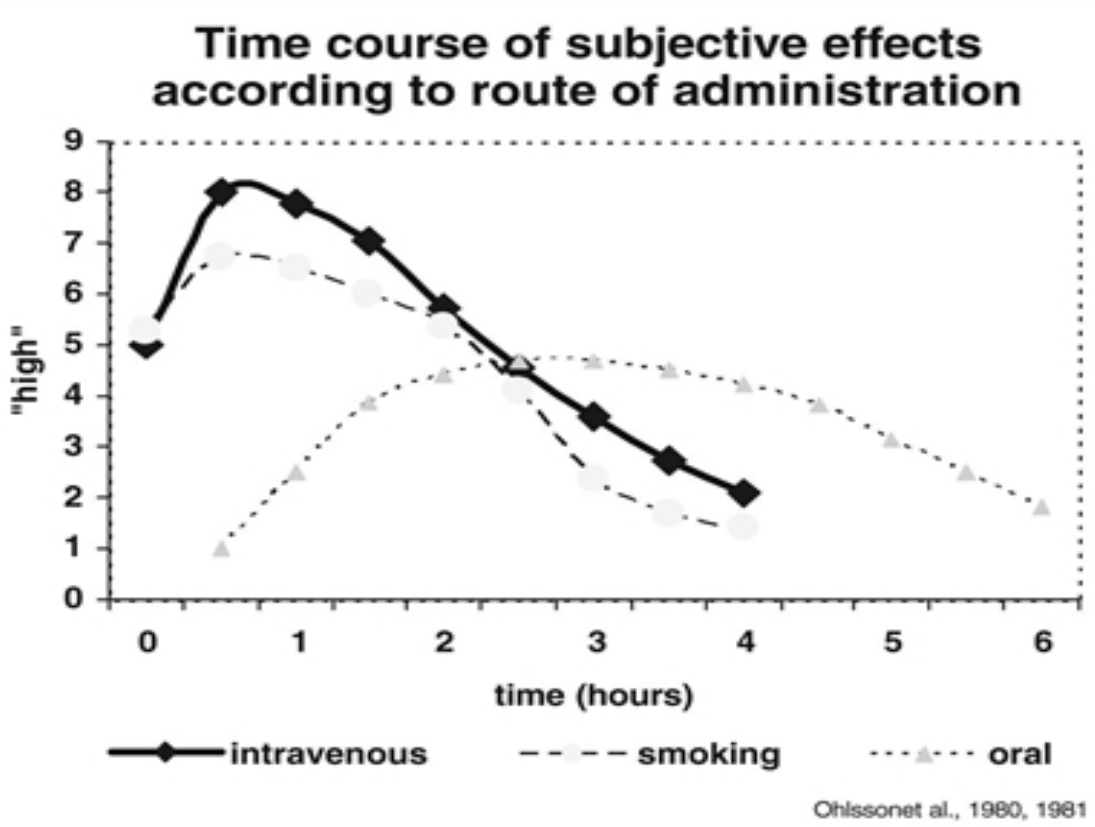


Fig. 1 Figure shows the time course of the acute behavioral effects of Δ-9-THC (feeling high) as a function of route of administration (intravenous, inhaled and oral)

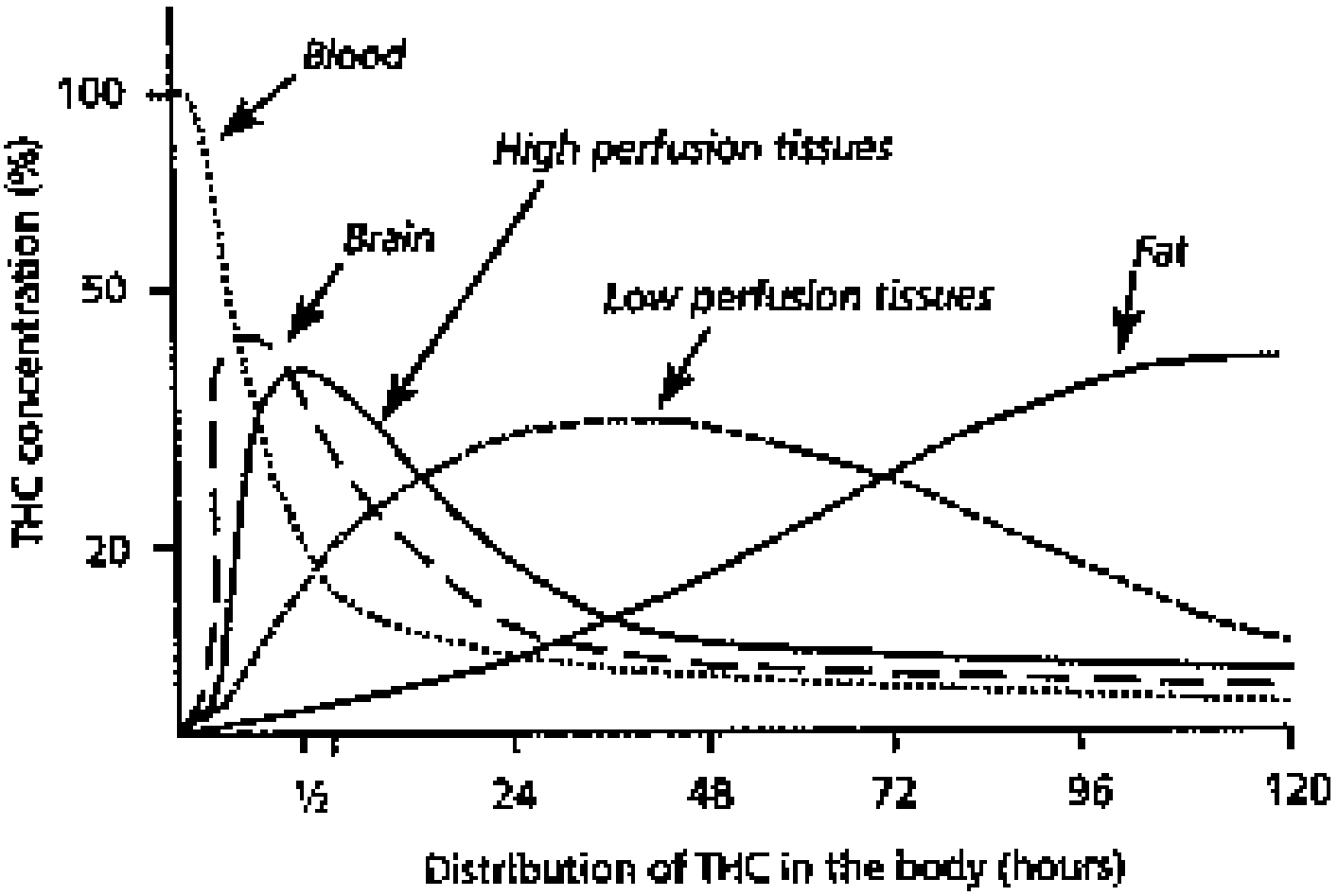
Figure shows the time course of the acute behavioral effects of Δ-9-THC (feeling high) as a function of route of administration (intravenous, inhaled and oral)

The acute effects of cannabinoids on memory in humans: a review.

Psychopharmacology, Nov2006, Vol. 188 Issue 4, p425-444, 20p, 1 chart, 3

Distribution of THC in the Body (lipid soluble)

Kreutz & Axelrod (1973)



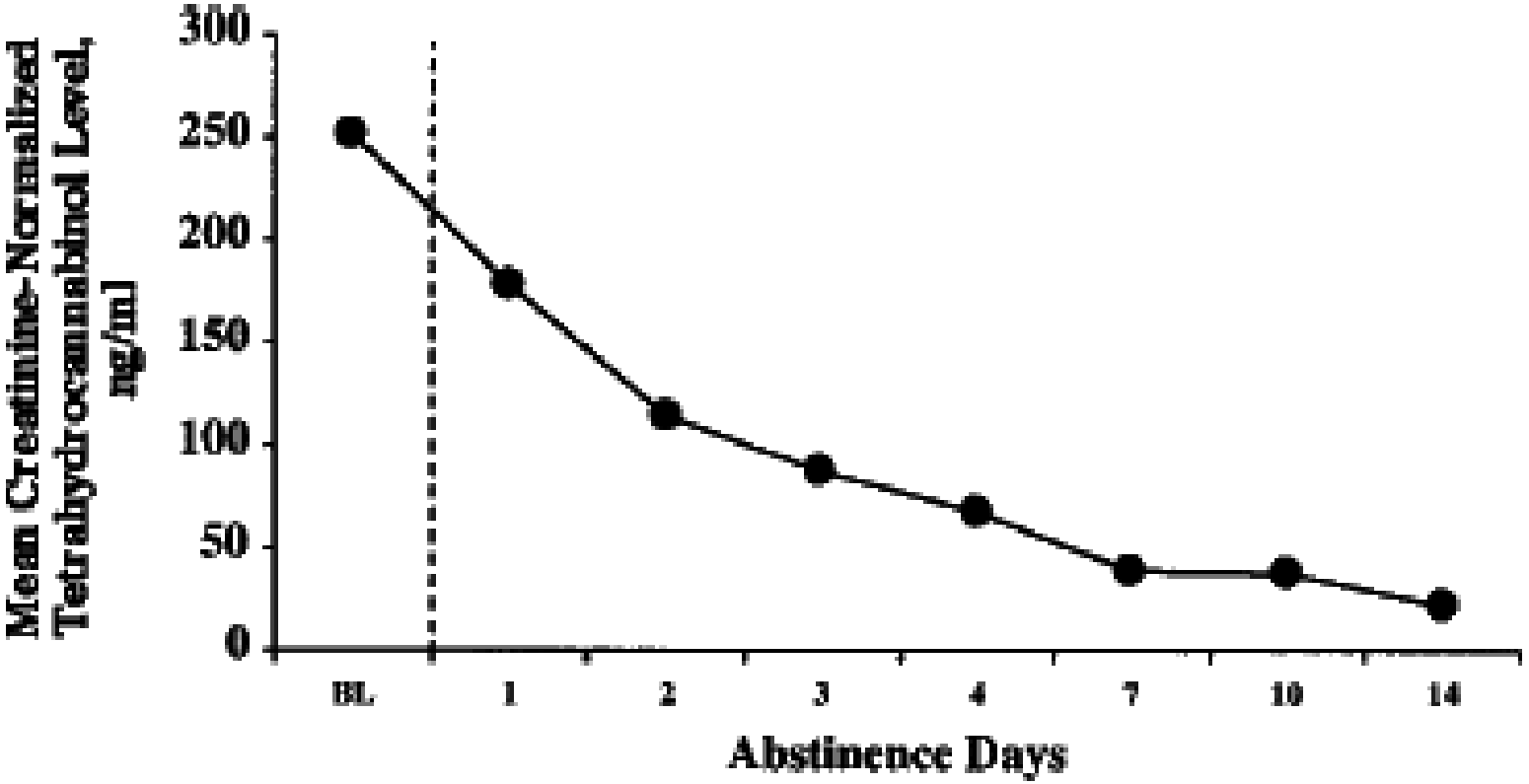


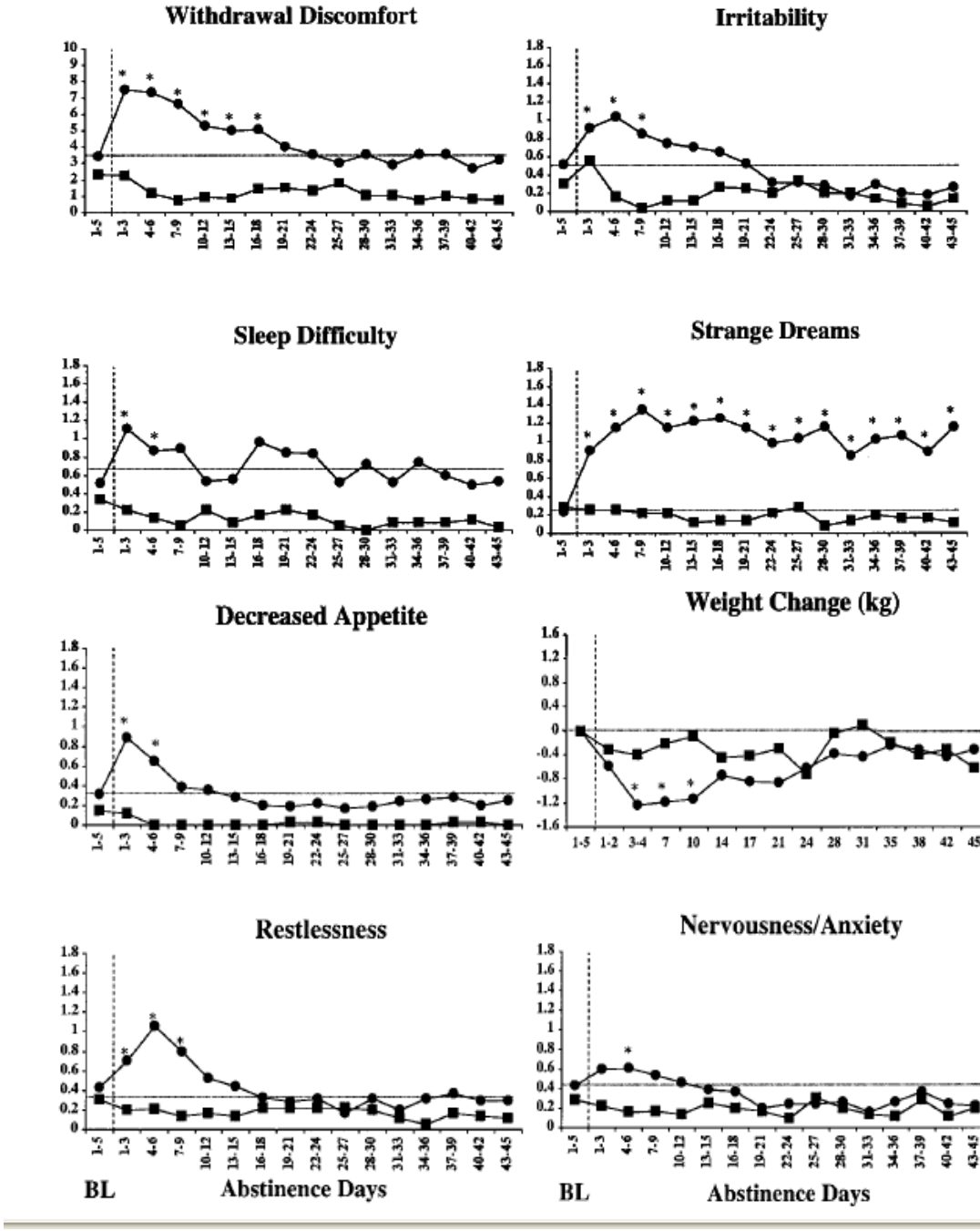
Figure 1. Mean creatinine-normalized tetrahydrocannabinol levels are presented across the first 2 weeks of the abstinence phase ($n = 18$). The value of the baseline (BL) data point reflects the mean of Days 1, 3, and 5.

Pharmacology

- Two known receptors, thc agonist to both
- Cbd interacts with both receptors uniquely
- Inhaled cannabinoids are easy to titrate
- Oral-- delayed peak, first pass metabolism
- P450 2C9, 3A4 metabolism
- Lipophilic, huge volume of distribution
- Detectable presence in urine days to weeks

Self reported symptoms newly sober users compared to former users.

Budney et al, J of Abnl Psyche 2003 vol 112 #3 p393



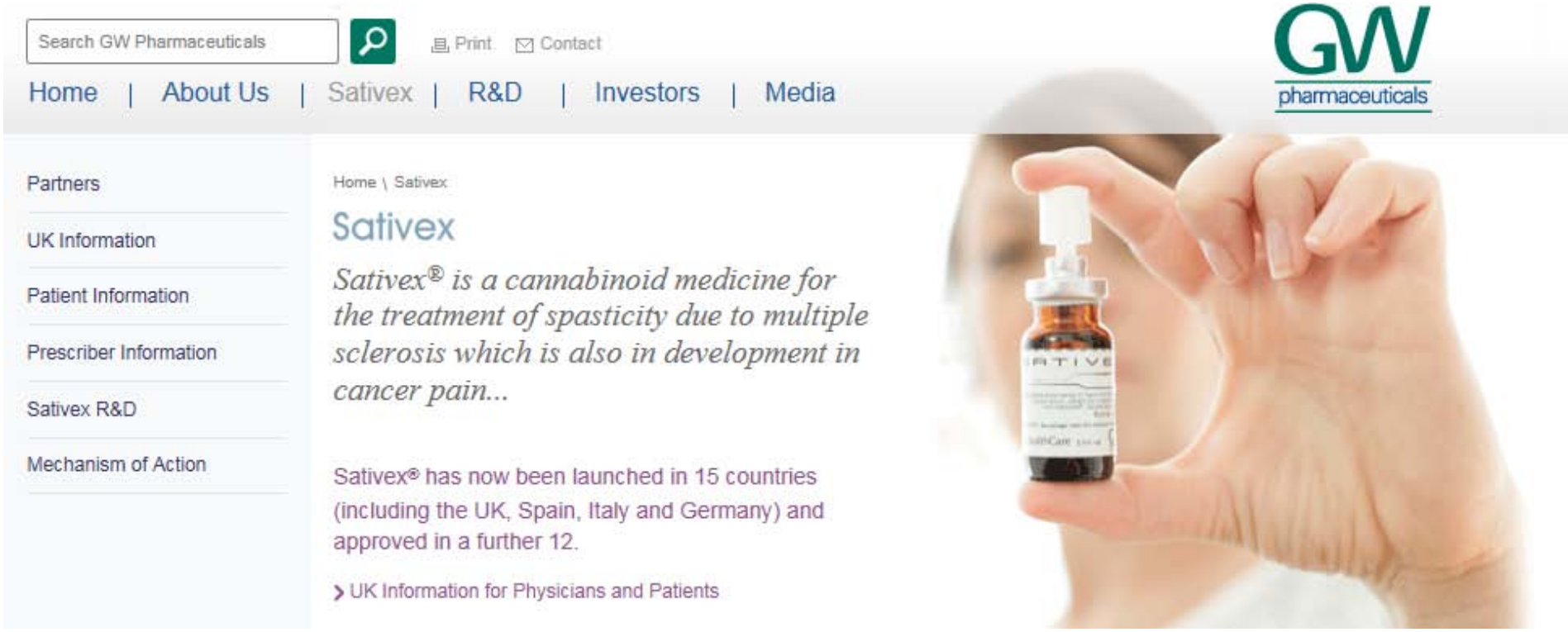
Cannabis withdrawal:
Mild, not life threatening, irritability, poor sleep, poor appetite, restlessness

Requires no treatment, only education and reassurance

3. Medicinal effects of Medical Cannabis

Dronabinol (marinol)
synthetic thc
DEA schedule 3
AIDS cachexia and Cancer/chemo nausea

Nabiximols (sativex)
1:1 thc:cbd ratio
Not FDA approved in USA
Fast track for approval 2016



Insys Therapeutics' Cannabidiol Receives FDA Orphan Drug Designation

Mon, 09/29/2014 - 3:23pm

Get today's drug discovery & development headlines and news - Sign up now!

Insys Therapeutics, Inc., a specialty pharmaceutical company that is developing and commercializing innovative drugs and novel drug delivery systems, announced that the U.S. Food and Drug Administration (FDA) has granted orphan drug designation (ODD) to its pharmaceutical cannabidiol (CBD) for the treatment of glioma, which comprises approximately 80% of all malignant brain tumors. The ODD includes pontine glioma (PG), a devastating form of primary brainstem glioma.

"We are pleased to have received broad orphan drug designation for CBD to treat glioma," said Michael Babich, president and chief executive officer. "We will most likely focus initially on pontine glioma, or PG, which has multiple similarities with glioblastoma multiforme, for which our pharmaceutical CBD was granted ODD last month. We believe that this product has excellent potential as treatment for PG, and look forward to advancing its development and offering a potential efficacious treatment for patients."

Insys, which has more than seven years of research and development experience in the pharmaceutical cannabinoid space, manufactures pharmaceutical CBD and pharmaceutical dronabinol (THC), both of which are cannabinoids, at its FDA-inspected and Drug Enforcement Administration (DEA) approved facility in Round Rock, Texas. The company recently submitted a Drug Master File (DMF #28255) for its CBD active pharmaceutical ingredient and believes that it is the only U.S.-based company with the capacity to produce pharmaceutical cannabinoids in scalable quantities.

Insys was previously granted ODD to its pharmaceutical CBD for the treatment of glioblastoma multiforme (GBM), the most common and most aggressive malignant primary brain tumor in humans, and two rare forms of epilepsy, Lennox-Gastaut Syndrome and Dravet Syndrome. Insys is also evaluating the potential use of pharmaceutical CBD in several additional indications, including: adult epilepsy; chemotherapy-induced peripheral neuropathy; and addiction in cocaine, amphetamines and opioids. Insys intends to pursue orphan drug designation for other indications that may qualify.

Orphan drug designation is granted by the FDA Office of Orphan Products Development (OOPD) to novel drugs or biologics that treat rare diseases or conditions affecting fewer than 200,000 patients in the U.S. The designation provides the drug developer with a seven-year period of U.S. marketing exclusivity, as well as certain financial incentives that can help support its development.

Date: September 29, 2014

CBD only compound orphan-drug status in the USA

Table 3. Randomized Clinical Trials Beyond Current FDA Indications for Cannabinoids[a]

Source	Drug (Maximum Dose), Route	Control	Sample Size, Experimental Condition/Control	Primary Outcome	Results
Chronic pain					
Skrabek et al,[16] 2008	Nabilone (2 mg) orally	Placebo	n=20 Nabilone; n=20 placebo (fibromyalgia)	VAS	Significant decrease in VAS (−2.04; $P < .02$)
Narang et al,[17] 2008	Dronabinol (20 mg) orally	Placebo	n = 29 Placebo; n = 30 dronabinol, 10 mg; n = 29 dronabinol, 20 mg	Total pain relief at 8 h	Significant increase in Total pain relief dronabinol conditions (20 mg vs placebo at $P < .01$; 10 mg vs placebo at $P < .05$)
Frank et al,[18] 2008	Dihydrocodeine (240 mg), nabilone (2 mg) orally	Crossover	n=48 Dihydrocodeine followed by nabilone; n=48 nabilone followed by dihydrocodeine (chronic neuropathic pain)	VAS	Dihydrocodeine provided better pain relief than nabilone (6.0; 95% CI, 1.4-10.5; P=.01)
Pinsger et al,[19] 2006	Nabilone (1 mg) add-on orally	Placebo	n=30 Crossover	VAS	Significant decrease in VAS ($P < .006$)
Wissel et al,[20] 2006	Nabilone (1 mg) orally	Placebo	n=13 Crossover	11-Point box test (pain rating)	Significant decrease in pain rating ($P < .05$)
Blake et al,[21] 2006	Nabiximols: THC (15 mg)/ cannabidiol (13.5 mg) oromucosal spray	Placebo	n=31 Nabiximols; n=27 placebo	Pain on movement	Significant decrease in pain (−0.95; 95% CI, −1.85 to −0.02, P=.04)
Neuropathic pain					
Ellis et al,[22] 2009	Cannabis (1%-8% THC) smoked	Placebo	n=34 Crossover	Change in pain intensity	Significant decrease in pain ($P=.02$)
Abrams et al,[23] 2007	Cannabis (3.56% THC) smoked	Placebo	n=27 Cannabis; n=28 placebo	VAS, percent achieving >30% pain reduction	Significant decrease in pain (P=.03); 52% cannabis group vs 24% placebo reported >30% pain reduction (P=.04)
Wilsey et al,[24] 2008	Cannabis (7%, THC) smoked	Placebo	n=38 Crossover	VAS	Significant decrease in pain (−0.0035; 95% CI, −0.0063 to −0.0007 ($P=.02$)
Nurmikko et al,[25] 2007	Nabiximols: THC (30 mg)/ cannabidiol (27.5 mg) oromucosal spray	Placebo	n=63 Nabiximols; n=62 placebo	Change in pain intensity (NRS)	Significant decrease in pain ($P=.004$; 95% CI, −1.59 to −0.32)
Berman et al,[26] 2004	Nabiximols: THC (129.6 mg)/ cannabidiol (120 mg) oromucosal spray	Placebo	n=48 Crossover	Mean pain severity	Significant decrease in pain (THC/cannabidiol, −0.58, 95% CI, −0.98 to −0.18, P=.005; THC, −0.64, 95% CI, −1.05 to −0.24, P=.002)
Multiple sclerosis					
Zajicek et al,[27] 2003, and Freeman et al,[28] 2006	OCE: THC (25 mg), cannabidiol (12.5 mg); THC (25 mg) orally	Placebo	n=211 OCE; n=206 THC; n=213 placebo	Change in spasticity (Ashworth scale)[27]; incontinence episodes[28]	No effect ($P=.40$) on spasticity; decrease in episodes for both OCE and THC (P=.005 OCE; P=.04 THC)
Zajicek et al,[29] 2012	OCE (THC, 25 mg) orally	Placebo	n=144 OCE; n=135 placebo	Change in muscle stiffness	Significant decrease in muscle stiffness (odds ratio, 2.26; 95% CI, 1.24-4.13; P=.004)
Aragona et al,[30] 2009	Nabiximols: THC (27 mg)/ cannabidiol (25 mg) oromucosal spray	Placebo	n=17 Crossover	Psychopathology, cognition (Paced Auditory Serial Addition Test, Symptom Checklist 90-Revised)	No effect (Symptom Checklist 90-Revised, P=.36-.91; Paced Auditory Serial Addition Test, P=.39)
Collin et al,[31] 2007	Nabiximols: THC (129 mg)/ cannabidiol (120 mg) oromucosal spray	Placebo	n=124 nabiximols; n=65 placebo	Change in spasticity (NRS)	Significant decrease in spasticity (−0.52, 95% CI, −1.029 to −0.004, P=.048)
Kavia et al,[32] 2010	Nabiximols: THC (129 mg)/ cannabidiol (120 mg) oromucosal spray	Placebo	n=67 Nabiximols; n=68 placebo (overactive bladder)	Incontinence episodes	No difference ($P=.57$)
Vaney et al,[33] 2004	OCE: THC (30 mg) orally	Placebo	n=57 Crossover	Change in spasticity (self-report, frequency of symptoms)	No difference (frequency, P=.01; 95% CI, 1.76-4.63)
Ungerleider et al,[34] 1987	THC (7.5 mg) orally	Placebo	n=13 Crossover	Change in spasticity (self-report)	Significant decrease in spasticity ($P < .03$)
Svendsen et al,[35] 2004	Dronabinol (10 mg) orally	Placebo	n=24 Crossover (central pain)	Median spontaneous pain intensity (NRS) in last week of treatment	Significant decrease in median spontaneous pain intensity ($P=.02$)
Rog et al,[36] 2005	Nabiximols: THC (129.6 mg)/ cannabidiol (120 mg) oromucosal spray	Placebo	n=34 Nabiximols; n=32 placebo (central pain)	Pain, sleep disturbance (NRS)	Significant decrease in pain ($P=.005$), significant decrease in sleep disturbance ($P=.003$)
Fox et al,[37] 2004	OCE: THC (10 mg) orally	Placebo	n=14 Crossover (upper limb tremors)	Change in tremor index	No significant improvements ($P=.55$)

(continued)

Table 3. Randomized Clinical Trials Beyond Current FDA Indications for Cannabinoids[a] (continued)

Source	Drug (Maximum Dose), Route	Control	Sample Size, Experimental Condition/Control	Primary Outcome	Results
Wade et al,[38] 2004	Nabiximols: THC (129.6 mg)/cannabidiol (120 mg) oromucosal spray	Placebo	n=80 Nabiximols; n=80 placebo	VAS, most troublesome symptom	No significant improvements ($P=.12$); significant decrease in spasticity (−22.79; 95% CI, −35.52 to −10.07; P=.001)
Killestein et al,[39] 2002	Dronabinol (5 mg); OCE: THC (5 mg) orally	Placebo	n=16 Crossover (spasticity)	Change in spasticity (Ashworth scale)	No significant improvements
Parkinson disease					
Carroll et al,[40] 2004	OCE: THC (10 mg) orally	Placebo	n=19 Crossover (levodopa-induced dyskinesia)	Change in Unified Parkinson Disease Rating Scale dyskinesia score	No significant improvements ($P=.09$)
Crohn disease					
Naftali et al,[41] 2013	Cannabis: THC (115 mg) smoked	Placebo	n=11 Cannabis; n=10 placebo	Induction of remission (Crohn's Disease Activity Index score <150 after 8 wk)	No significant difference ($P=.43$)
Amyotrophic lateral sclerosis					
Weber et al,[42] 2010	Sesame oil: THC (10 mg) orally	Placebo	n=27 Crossover (cramps)	VAS, cramp intensity	No significant difference (0.24; 95% CI, −0.32 to 0.81; P=.38)
Neurogenic symptoms					
Wade et al,[43] 2003	Nabiximols: THC (120 mg)/cannabidiol (120 mg); THC (120 mg); cannabidiol (120 mg) oromucosal spray	Placebo	n=24 Crossover (n=18 multiple sclerosis, n=4 spinal cord injury, n=1 brachial plexus damage, n=1 limb amputation due to neurofibromatosis)	VAS	Significant decrease in pain with cannabidiol, THC; significant decrease in spasm with THC, cannabidiol, THC; significant decrease in spasticity with THC ($P < .05$)

http://www.health.state.mn.us/topics/cannabis/practitioners/clinicalinfo.html

Legal Qualifying conditions

- HIV/AIDS
- Cancer with nausea pain or cachexia
- Severe muscle spasm (typical of MS)
- ALS
- End of life (<1 year expectancy)
- Crohn’s
- Seizure disorder
- Glaucoma
- Tourette’s syndrome

Cancer

- Nausea– best data of the cancer indications
- Pain– mixed data small trials
- Cachexia– mixed data, negative trial

Glaucoma

- THC does decrease intraocular pressure
- There is no need for additional therapies for glaucoma
- No major Ophthalmology organizations support medical cannabis use in glaucoma
- Glaucoma can be completely and effectively treated using conventional medicines

HIV/AIDS

- Long record of thc use for symptoms associated with AIDS
- Best results in past recreational marijuana users, who are acclimated to the adverse effect of medical cannabis
- This is a reasonable indication for medical cannabis

Tourette's syndrome

- Two small trials showing decreased tic frequency with THC
- Adverse effects were somewhat limiting

ALS

- Two small trials failed to show benefit for symptoms in ALS

Seizures

- Ample and compelling anecdotal reports
- A few trials of CBD with mixed methodologies show mixed results
- There appears to be promise using cbd for seizure frequency
- National Neurology organizations do not endorse use of medical cannabis for seizure disorder

Muscle spasms

- MS and spinal cord injuries both fairly well studied
- About 50% of patients seem to respond to medical cannabis
- Response becomes evident in a few weeks
- Mixed thc/cbd seem most effective

Crohn’s disease

- No reliable information
- Anecdotal report of benefits

Terminal illness

- No information other than already seen for cancer

Legal Qualifying conditions

- **HIV/AIDS**
- **Cancer with nausea pain or cachexia**
- **Severe muscle spasm (typical of MS)**
- ***End of life (<1 year expectancy)***
- ***Seizure disorder***
- ***Tourette's syndrome***
- ALS
- Glaucoma
- Crohn's

4. Adverse Effects and Contraindications of Medical Cannabis

Estimates of drug-related emergency department visits in Minneapolis/St. Paul/Bloomington, MN-WI Metropolitan Statistical Area: 2004 - 2011

Drug	2004	2005	2006	2007	2008	2009	2010	2011
Cocaine	6,228	6,076	6,764	5,189	5,390	3,843	4,141	4,279
Heroin	1,189	1,023	1,312	1,691	1,651	1,855	2,256	3,493
Marijuana	4,455	4,468	4,302	5,757	5,617	5,596	6,794	6,627
Synthetic cannabinoids	*	*	*	*	*	*	170	418
Amphetamines	255	388	278	335	361	230	361	644
Methamphetamine	1,741	2,209	1,120	1,103	1,001	970	1,660	1,541
MDMA (Ecstasy)	204	254	252	433	485	475	362	397
PCP	*	69	132	*	*	80	*	*
Miscellaneous hallucinogens	123	68	*	142	134	115	138	153
Inhalants	183	128	*	80	100	92	126	*
Opiates/opioids, unspecified	162	282	495	559	1,052	826	1,150	1,619
Total Narcotic analgesics	1,940	1,872	2,491	3,391	3,905	3,890	4,697	4,836
Hydrocodone/combinations	562	506	625	985	1,016	1,019	1,092	1,044
Hydromorphone/combinations	*	87	115	142	252	256	297	284
Methadone	437	430	547	643	794	757	893	828
Morphine/combinations	108	120	193	272	265	288	334	413
Oxycodone/combinations	668	742	954	1,484	1,657	1,810	2,397	2,397

SOURCE: Drug Abuse Warning Network, Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration, accessed 9/12/2012. These weighted estimates of ED visits are based on a representative sample of non-Federal, general, short-stay hospitals with 24-hour EDs in the Minneapolis/St. Paul/ Bloomington, MN-WI Metropolitan Statistical Area.

Commonest emergency caused by marijuana ingestion?

Commonest emergency caused by marijuana ingestion?

Panic Attack

Is marijuana and/or medical cannabis addictive?

Diagnosing Marijuana use disorder

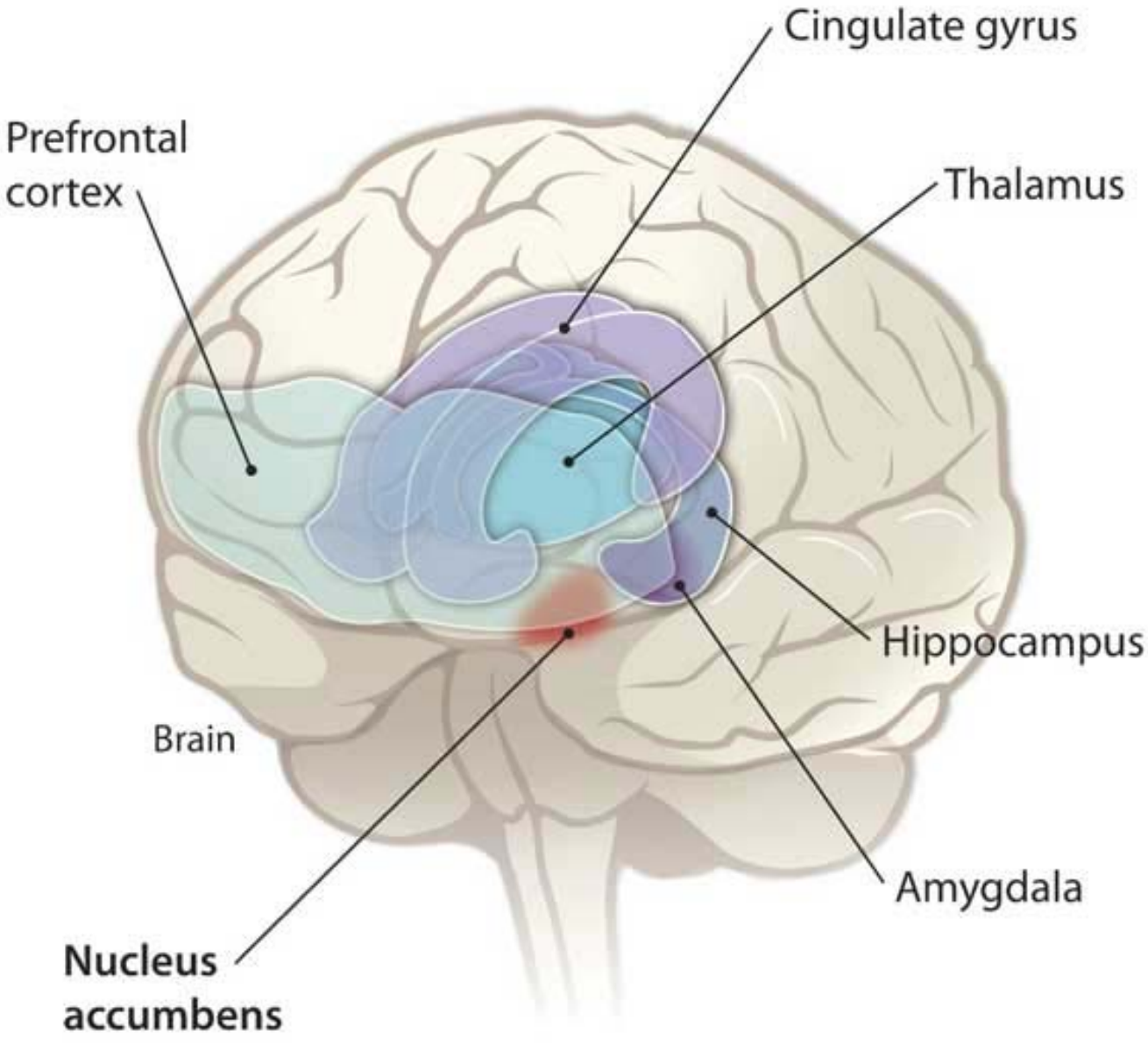
A pattern of marijuana use over 12 months

- Mild: 2-3 symptoms
- Moderate: 4-5 symptoms
- Severe: >/=6 symptoms

Diagnosing marijuana use disorder

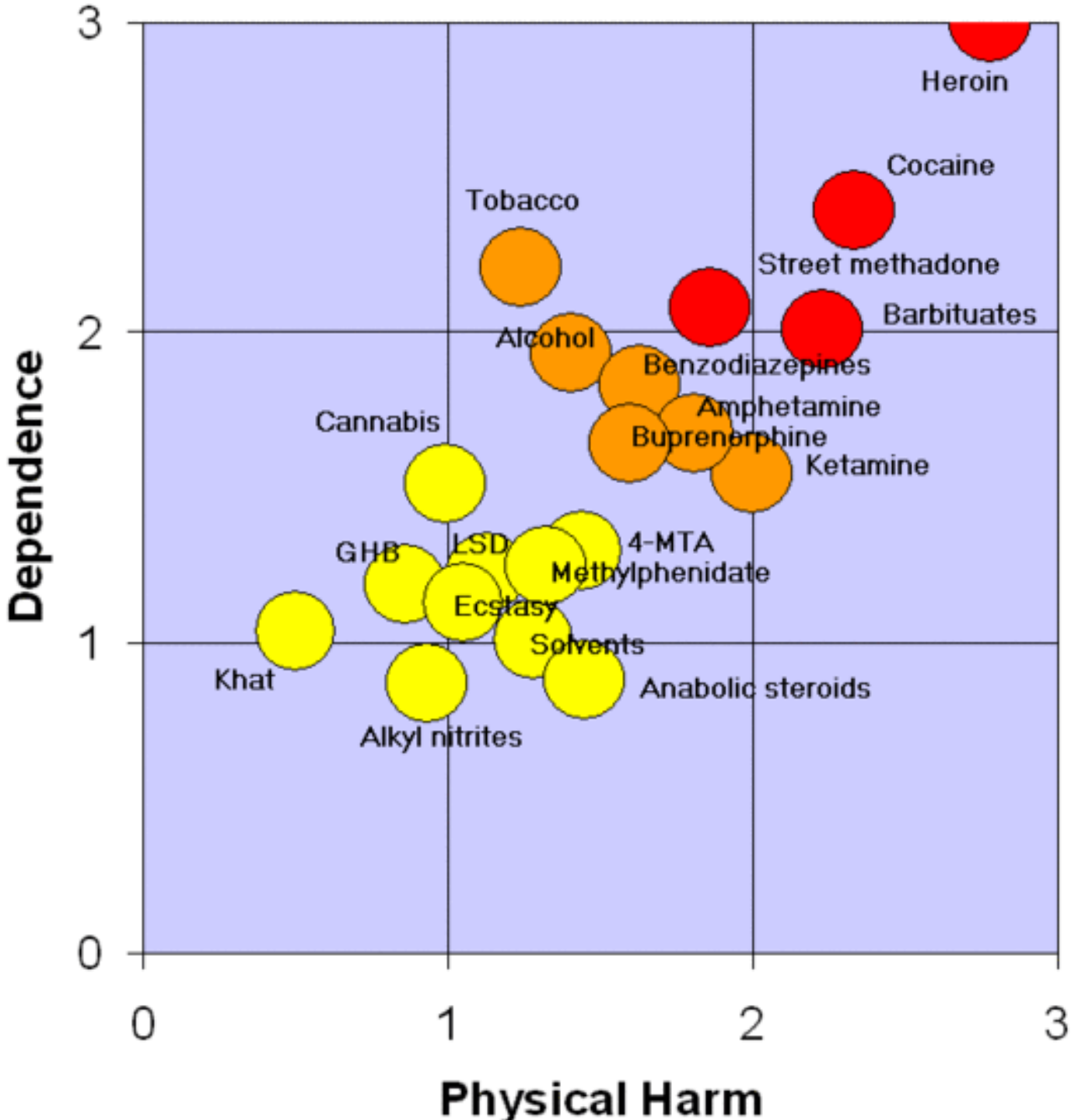
1. **Larger amounts over longer periods of time than intended**
2. **Desire or unsuccessful efforts to cut down or control use**
3. **Time is spent to obtain, use or recover from the effects**
4. **Craving**
5. **Failure to fulfill role obligations at work, home or school**
6. **Persistent or recurrent social or interpersonal problems**
7. **Social, occupational, or recreational activities are given up**
8. **Recurrent use in situations that are physically dangerous**
9. **Use despite medical or psychiatric harm**
10. ***.Tolerance**
11. ***.Withdrawal**

**If the substance in question is a prescribed substance, these criteria are eliminated*

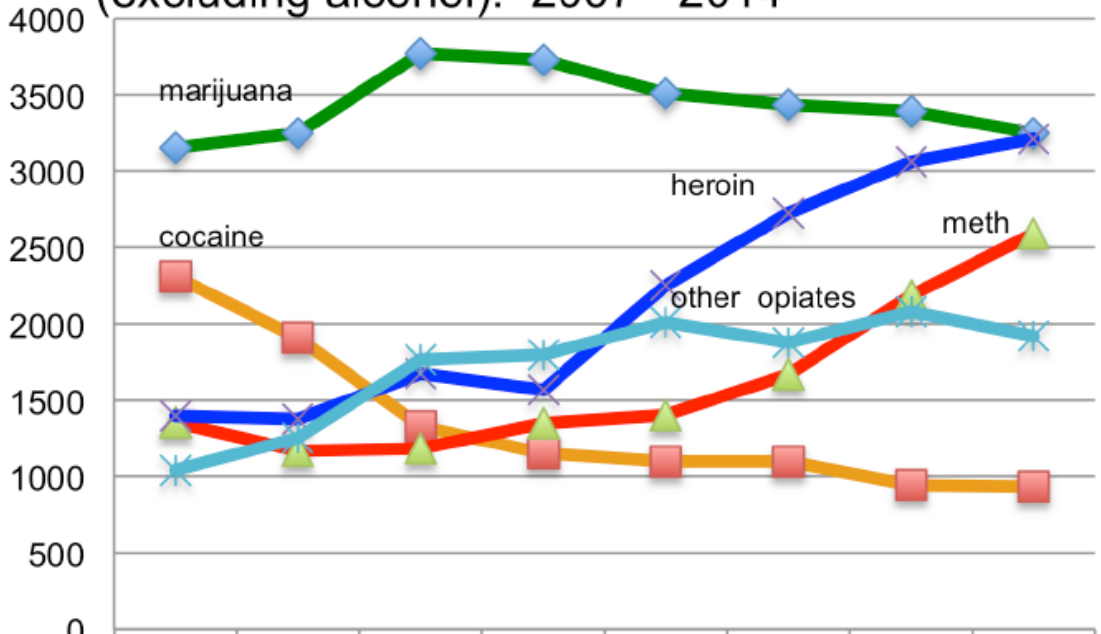

Cingulate gyrus
Prefrontal cortex
Thalamus
Hippocampus
Brain
Amygdala
Nucleus accumbens

Cannabis ranked against other drugs of abuse

Lancet 2007, 369, p1047-1053



Admissions to Minneapolis/St. Paul metro area addiction treatment programs by primary substance problem (excluding alcohol): 2007 - 2014



	2007	2008	2009	2010	2011	2012	2013	2014
marijuana	3152	3247	3772	3725	3506	3435	3390	3246
cocaine	2310	1911	1326	1153	1096	1097	944	935
methamphetamine	1355	1168	1181	1350	1403	1669	2185	2593
heroin	1396	1373	1672	1567	2252	2724	3063	3208
other opiates	1042	1254	1764	1796	2009	1879	2081	1918

SOURCE: Drug and Alcohol Abuse Normative Evaluation System, Minnesota Department of Human Services, 2015.

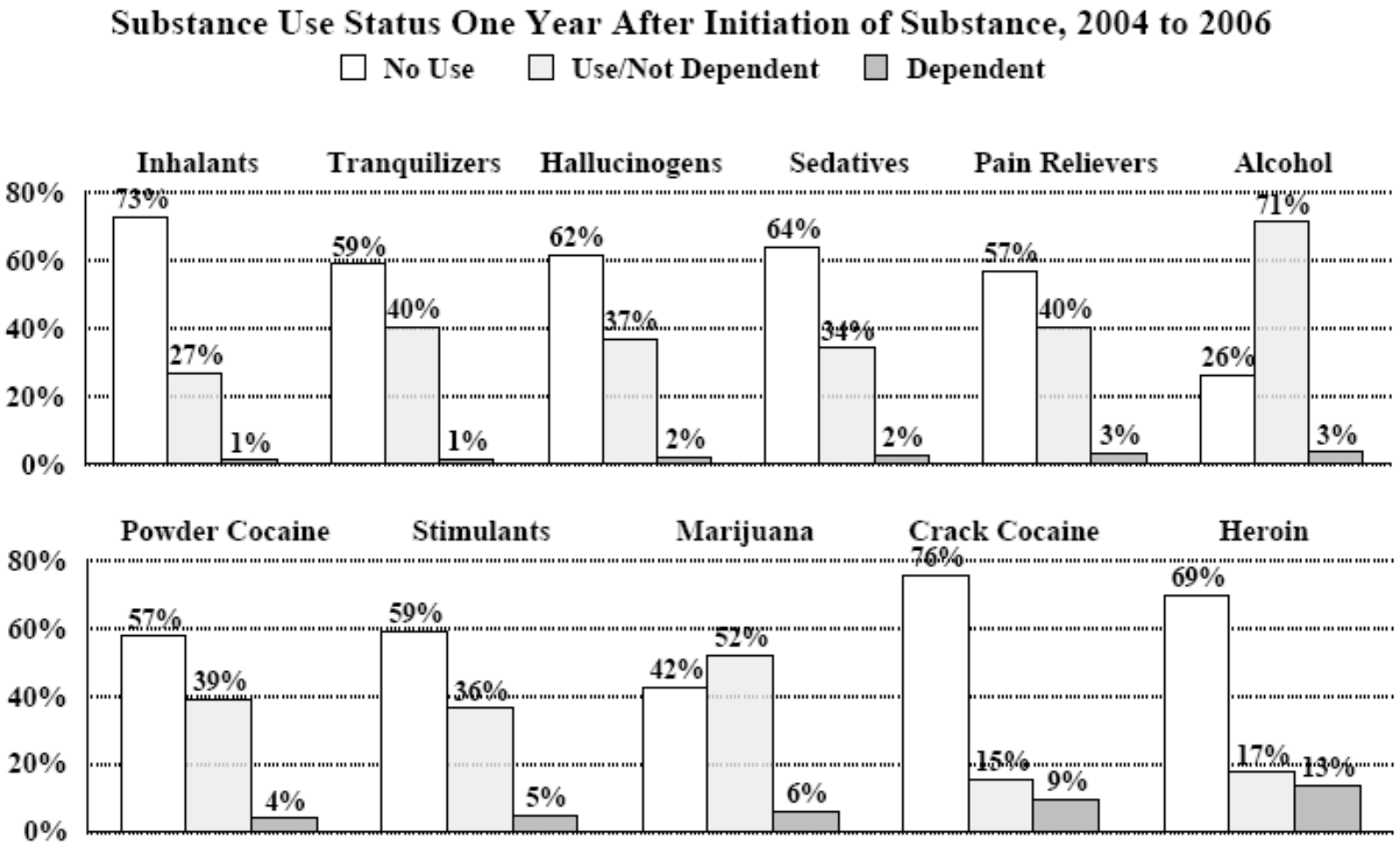
Characteristics of admissions to Minneapolis/St. Paul metro area addiction treatment programs by primary substance problem: 2014

Total Admissions	Alcohol	Marijuana	Cocaine	Meth	Heroin	Other Opiates
21,928	9,444 43.1%	3,246 14.8%	935 4.3%	2,593 11.8%	3,208 14.6%	1,918 8.7%
GENDER						
% male	67.2	77.0	65.3	62.5	63.8	50.1
% female	32.8	23.0	34.7	37.5	36.2	49.9
RACE/ETHNICITY						
% White	71.6	49.7	25.6	78.2	63.2	73.0
% African Am	15.8	29.7	60.5	2.8	19.1	6.4
% Am Indian	2.9	4.0	4.2	4.0	9.1	10.4
% Hispanic	5.0	8.0	4.3	5.7	4.4	4.3
% Asian/Pacific Isl	1.7	1.5	0.7	4.9	0.8	2.3
% Other	3.0	7.1	4.7	4.4	3.3	3.6
AGE						
% 17 and under	1.1	25.6	1.2	2.9	0.8	1.3
% 18 - 25	13.7	37.3	6.7	21.4	37.5	23.5
% 26 - 34	24.6	21.3	15.6	40.5	28.3	33.0
% 35 +	60.5	15.7	76.5	35.2	33.4	42.3
ROUTE OF ADMINISTRATION						
% oral/multiple	100	1.9	-	5.5	0.5	67.3
% smoking		98.1	73.5	65.7	9.6	5.2
% snorting		-	24.9	6.8	27.4	18.4
% injection		-	1.6	22.0	62.5	9.1
% unknown			-	-	-	-
% CURRENT SMOKERS	57.8	68.2	71.2	77.4	82.0	70.9

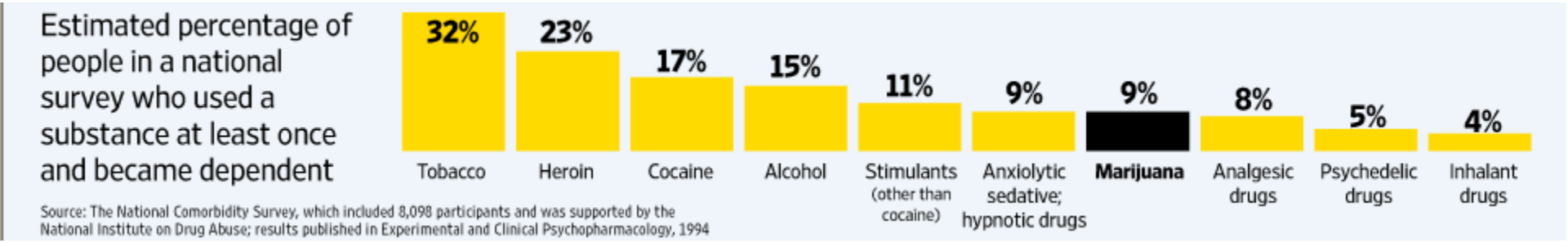
SOURCE: Drug and Alcohol Abuse Normative Evaluation System, Minnesota Department of Human Services, 2015

Likelihood of Addiction after experimentation

Center for substance abuse, university of maryland, 2008



Is Marijuana Addictive?



If <18 years, risk of addiction increased to 17%

www.drugabuse.gov/publications/research-reports/marijuana/marijuana-addictive

If medial cannabis is used, especially inhaled, cannabis addictions will result

Cannabis is a vasodilator

Cardiovascular effects of CB1 agonists

- Increased cardiac output 10%
- Decreased SVR
- Increased heart rate 50% (compensatory)
- Orthostatic hypotension

Journal of clinical pharm, 42 (11s) 2002

Orthostasis and resting tachycardia with THC use

Dose	Heart rate (bpm) Mean	SD
Placebo	26.2	11.3
Lowest	54.6*	17.2
Middle	58.4*	15.8
Highest	64.3*	17.1

* Statistically significant using paired *t*-te

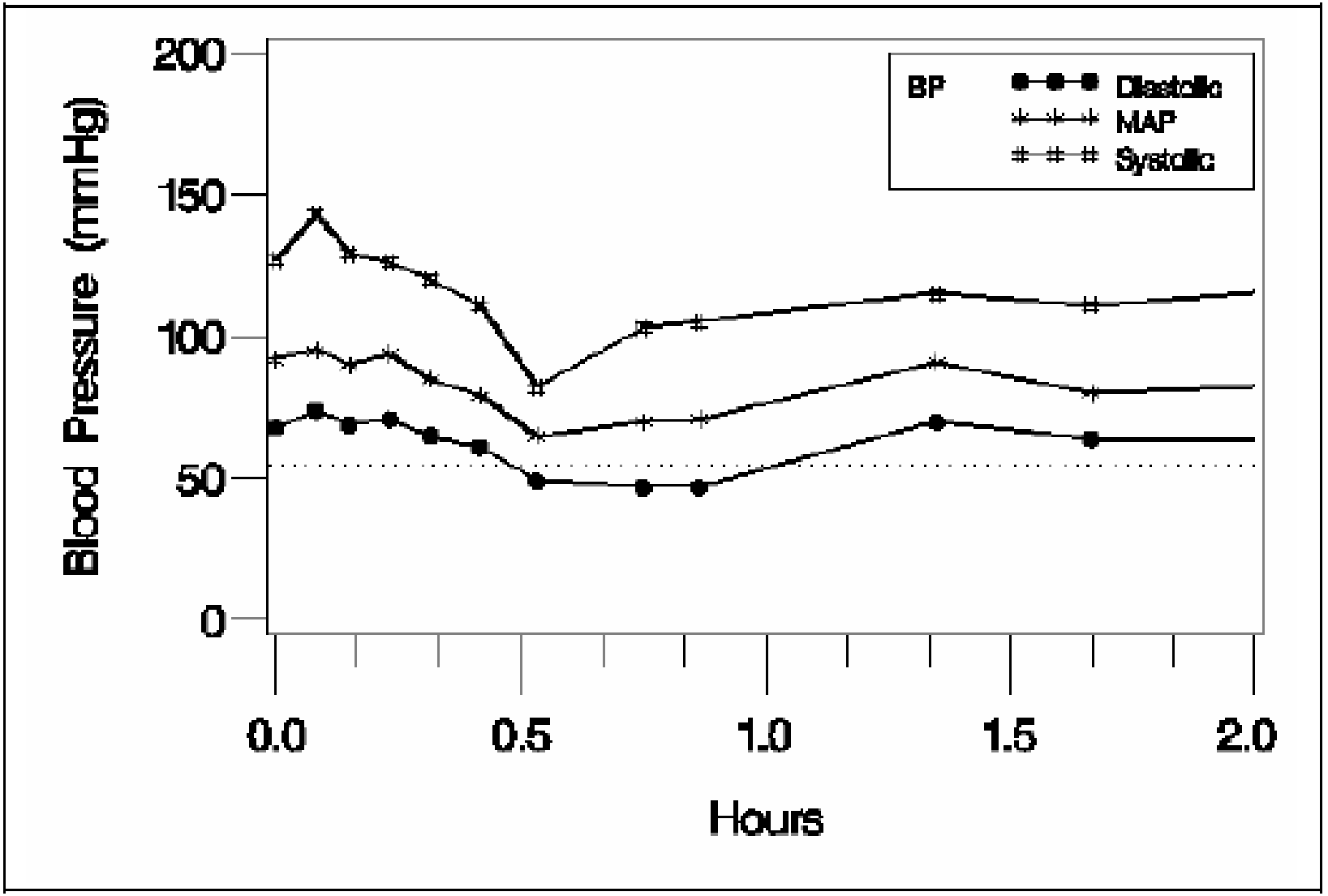


Figure 4. Change of blood pressure (systolic, diastolic, and mean arterial) after exposure to the highest dose (23.12% THC, 69.4 mg/joint), for participant 20. For this individual, the mean arterial blood pressure decreases with more than 30 mmHg during smoking.

Smoked marijuana a cardiac RF?

Table 3
Body mass index (BMI) and cardiovascular risk factors in 2000 to 2001 according to average marijuana use from 1985 to 2000 in the CARDIA study

Characteristics	Marijuana Use Over 15-Year Study Period				p Value*
	Never User (n = 2,252)	<180 Days (n = 610)	180–1,799 Days (n = 601)	≥1,800 Days (n = 154)	
Anthropometric measurements					
BMI (kg/m^2)	28.9 ± 0.1	28.5 ± 0.3	28.7 ± 0.3	28.0 ± 0.5	0.14
Waist girth (cm)	89.0 ± 0.3	89.1 ± 0.6	91.4 ± 0.6	91.0 ± 1.2	0.04
Blood pressure (mm Hg)					
Systolic	112.7 ± 0.3	112.8 ± 0.6	114.7 ± 0.6	116.5 ± 1.2	<0.001
Diastolic	74.5 ± 0.2	73.9 ± 0.5	74.8 ± 0.5	75.4 ± 0.9	0.24
Lipids					
Total cholesterol					
mg/dl	184.2 ± 0.8	184.6 ± 1.5	184.9 ± 1.5	189.6 ± 3.1	0.07
mmol/L†	4.77 ± 0.02	4.78 ± 0.04	4.79 ± 0.04	4.91 ± 0.08	
HDL cholesterol					
mg/dl	51.0 ± 0.4	51.0 ± 0.8	50.6 ± 0.8	51.0 ± 1.2	0.96
mmol/L†	1.32 ± 0.01	1.32 ± 0.02	1.31 ± 0.02	1.32 ± 0.03	
Triglycerides					
mg/dl	84.1 ± 0.9	92.0 ± 0.9	92.9 ± 0.9	100.0 ± 0.9	<0.001
mmol/L†‡	0.95 ± 0.01	1.04 ± 0.01	1.05 ± 0.01	1.13 ± 0.01	
Glucose					
mg/dl	86.7 ± 0.4	86.3 ± 0.9	86.8 ± 0.9	87.4 ± 1.6	0.57
mmol/L†	4.81 ± 0.02	4.79 ± 0.05	4.82 ± 0.05	4.85 ± 0.09	

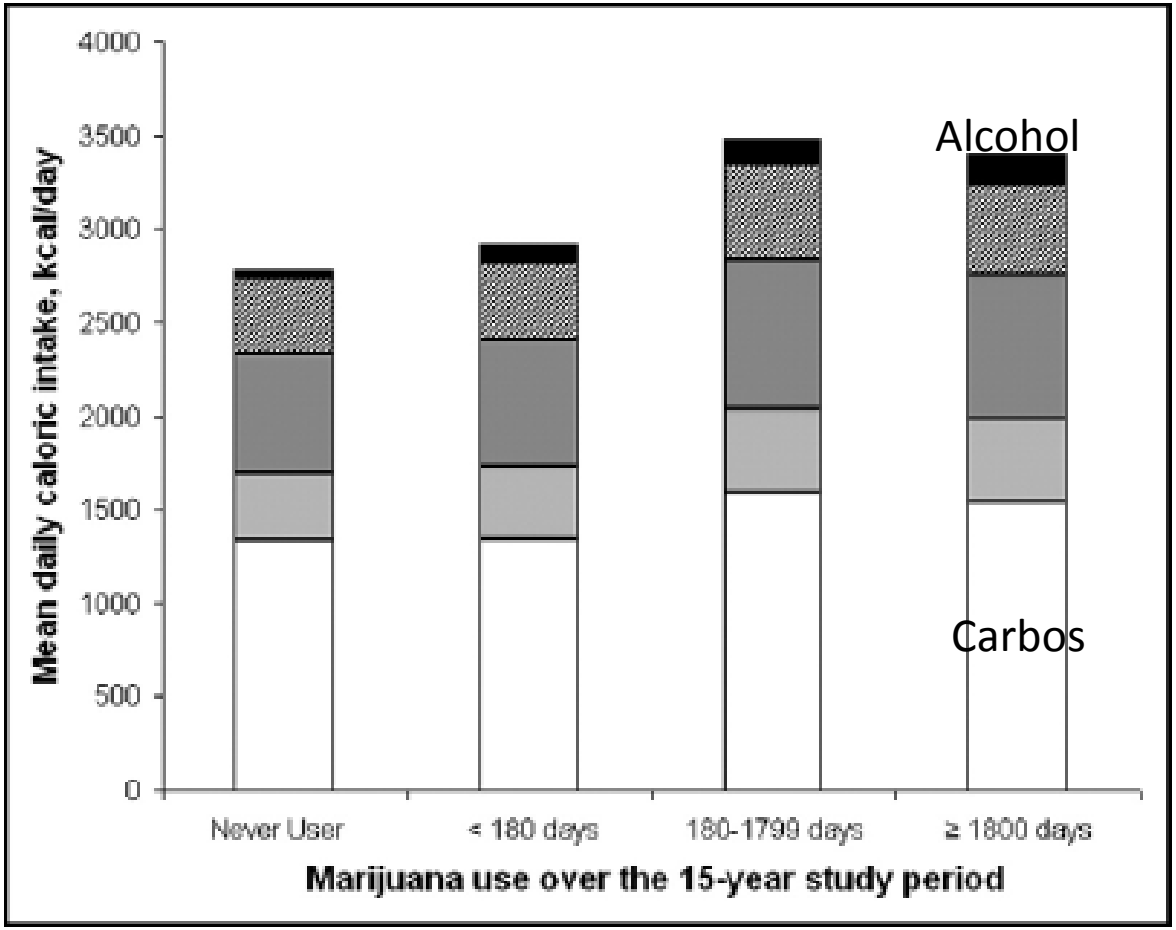
Values are means ± SE. Participants with missing values for waist girth (n = 13), lipid values (n = 42), and glucose (n = 50) were excluded from those analyses.

* Tests for trend across marijuana-use categories.

† Conversion factors: total cholesterol and HDL cholesterol, 1 mg/dl = 0.0259 mmol/L; triglycerides, 1 mg/dl = 0.0113 mmol/L; glucose, 1 mg/dl = 0.0555 mmol/L.

‡ Triglycerides levels were log-transformed for statistical analyses because the distribution was skewed.

Marijuana stimulates appetite



American Journal of Cardiology 2006 98: p478

Kaiser study: 62,000 patients no association with marijuana smoking and heart attacks or strokes

Table II Relative Risk of Cardiovascular Disease Hospitalization in Current and Former Users of Marijuana Relative to Nonusers, Kaiser Permanente Medical Care Program Members (n = 62,012), Oakland and San Francisco, June 1979 through December 1985

Marijuana Use Status	Myocardial Infarction	All Coronary Heart Disease	Stroke	All Cardiovascular Disease
Men[a]	173	329	68	593
Current user	1.1 (0.7, 1.7)	0.9 (0.7, 1.3)	1.0 (0.5, 1.9)	1.0 (0.8, 1.3)
Former user	0.9 (0.6, 1.5)	0.8 (0.5, 1.1)	0.8 (0.4, 1.8)	0.8 (0.6, 1.0)
Women[a]	36	136	62	386
Current user	1.8 (0.5, 6.3)	1.3 (0.7, 2.7)	0.7 (0.3, 2.2)	1.1 (0.7, 1.6)
Former user	1.0 (0.2, 4.5)	0.5 (0.2, 1.4)	1.5 (0.7, 3.5)	1.0 (0.7, 1.5)

Data are presented as relative risk, with the 95% confidence interval in parentheses. Relative risk is adjusted for age, race, education, body mass index, history of hypertension, smoking, and alcohol use.

a. Number of hospitalized cases.

Marijuana and heart disease

- Worsening of *preexisting* heart disease
  - Decreased exercise capacity
  - Early anginal symptoms
  - Five fold heart attacks one hour after smoking marijuana; no change 24 hours after smoking

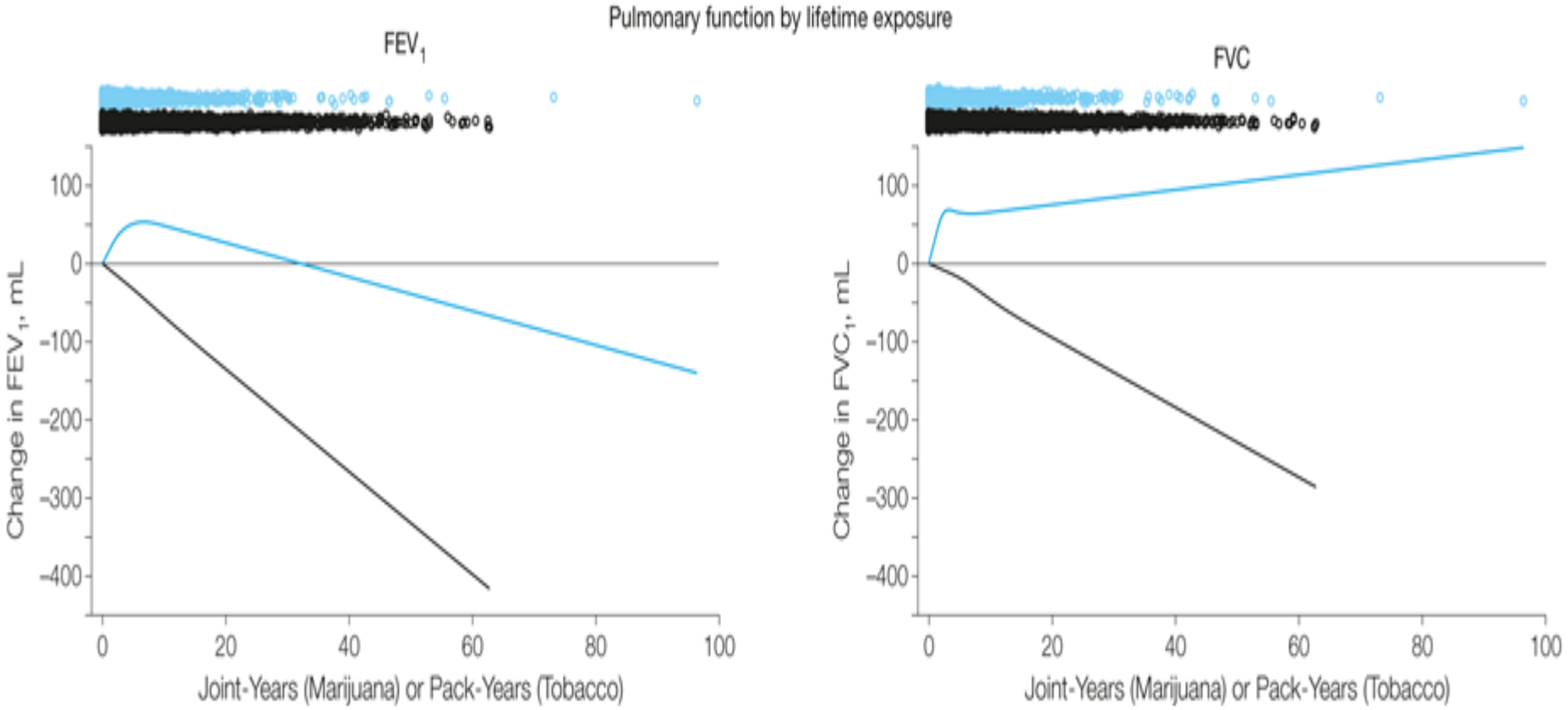
  - J. Of Clinical Pharm 42 (11s) 2002 p64

Association Between Marijuana Exposure and Pulmonary Function Over 20 Years FREE

Mark J. Pletcher, MD, MPH; Eric Vittinghoff, PhD; Ravi Kalhan, MD, MS; Joshua Richman, MD, PhD; Monika Safford, MD; Stephen Sidney, MD, MPH; Feng Lin, MS; Stefan Kertesz, MD

[+] Author Affiliations

JAMA. 2012;307(2):173-181. doi:10.1001/jama.2011.1961.



RESEARCH

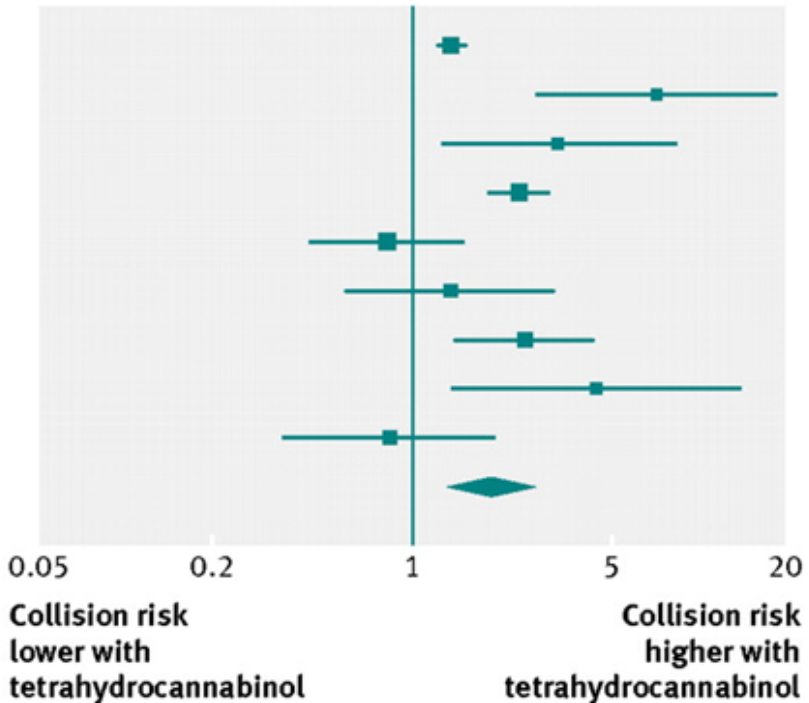
Acute cannabis consumption and motor vehicle collision risk: systematic review of observational studies and meta-analysis

BMJ 2012; 344 doi: http://dx.doi.org/10.1136/bmj.e536 (Published 9 February 2012)

Study	No of events/Total Case	Control	Weight (%)	Odds ratio (95% CI)
Bedard 2007	1106/19 511	541/13 032	18.0	1.39 (1.25 to 1.54)
Blows 2005	32/552	5/587	7.9	7.16 (2.77 to 18.52)
Drummer 2004	51/1214	5/376	8.1	3.25 (1.29 to 8.21)
Laumon 2005	322/3972	100/2793	17.0	2.38 (1.89 to 2.99)
Longo 2000	21/1038	23/937	12.0	0.82 (0.45 to 1.49)
Mathijssen 2005	6/108	148/3571	9.0	1.36 (0.59 to 3.15)
Mura 2003	49/321	21/310	12.8	2.48 (1.45 to 4.24)
Terhune 1982	13/129	4/161	6.2	4.40 (1.40 to 13.84)
Terhune 1992	16/541	9/258	9.1	0.84 (0.37 to 1.93)
Total (95% CI)	1616/27 286	856/22025	100.0	1.92 (1.35 to 2.73)

Test for heterogeneity: τ^2=0.18, χ^2=42.74, df=8, P<0.001, I^2=81%

Test for overall effect: z=3.63, P<0.001




The incompetence of NFL place-kickers costing teams games


Ballerinas from around the U.S. find perfect pointe shoes in Castle Rock


Denver lags recycling, c

DENVER AND THE WEST

More Colorado drivers in fatal crashes positive for pot, study says

By John Ingold
The Denver Post

POSTED: 05/15/2014 04:02:14 PM MDT | UPDATED: ABOUT A YEAR AGO 79 COMMENTS


A cannabis plant at a Denver grow house. (Seth McConnell, The Denver Post)

Two new University of Colorado studies paint an ominous picture of the direction of the state since marijuana commercialization, but neither provides conclusive evidence that legal pot is causing harm.

One study shows more drivers involved in fatal car accidents in Colorado are testing positive for marijuana — and that Colorado has a higher percentage of such drivers testing positive for pot than other states even when controlled for several variables. But the data the researchers use does not reveal whether those drivers were impaired at the time of the crash or whether they were at fault.

"The primary result of this study may simply reflect a general increase in marijuana use during this ... time period in Colorado," the study's authors write.

The other study shows that perceptions of marijuana's risk have decreased across all age groups with the boom in marijuana businesses in the state. The study also finds that near-daily marijuana use among adults increased significantly starting in 2009, relative to states without medical marijuana laws. But the study's authors acknowledge that they cannot show Colorado's marijuana laws are the reason for the shifts in attitudes and use.

Study: Fatal Car Crashes Involving Marijuana Have Tripled

February 4, 2014 9:14 PM

View Comments

(Photo by David McNew/Getty Images)

Related Tags: cannabis, drugged driving, drunk driving, fatalities, legal pot, MADD, Marijuana, pot

SEATTLE (CBS Seattle) – According to a recent study, fatal car crashes involving pot use have tripled in the U.S.

"Currently, one of nine drivers involved in fatal crashes would test positive for marijuana," Dr. Guohua Li, director of the Center for Injury Epidemiology and Prevention at Columbia, and co-author of the study told HealthDay News.

Researchers from Columbia University's Mailman School of Public Health gathered data from six states – California, Hawaii, Illinois, New Hampshire, Rhode Island, and West Virginia – that perform toxicology tests on drivers involved in fatal car accidents. This data included over 23,500 drivers that died within one hour of a crash between 1999 and 2010.

Work place accidents associated with cannabis use

- Macdonald S, Hall W, Roman P, Stockwell T, Coghlan M, Nesvaag S. Testing for cannabis in the work-place: a review of the evidence. *Addiction.* 2010;105:408-416.

Proceedings of the National Academy of Sciences of the United States of America

PNAS

Persistent cannabis users show neuropsychological decline from childhood to midlife

Abstract

Recent reports show that fewer adolescents believe that regular cannabis use is harmful to health. Concomitantly, adolescents are initiating cannabis use at younger ages, and more adolescents are using cannabis on a daily basis. The purpose of the present study was to test the association between persistent cannabis use and neuropsychological decline and determine whether decline is concentrated among adolescent-onset cannabis users. Participants were members of the Dunedin Study, a prospective study of a birth cohort of 1,037 individuals followed from birth (1972/1973) to age 38 y. Cannabis use was ascertained in interviews at ages 18, 21, 26, 32, and 38 y. Neuropsychological testing was conducted at age 13 y, before initiation of cannabis use, and again at age 38 y, after a pattern of persistent cannabis use had developed. Persistent cannabis use was associated with neuropsychological decline broadly across domains of functioning, even after controlling for years of education. Informants also reported noticing more cognitive problems for persistent cannabis users. Impairment was concentrated among adolescent-onset cannabis users, with more persistent use associated with greater decline. Further, cessation of cannabis use did not fully restore neuropsychological functioning among adolescent-onset cannabis users. Findings are suggestive of a neurotoxic effect of cannabis on the adolescent brain and highlight the importance of prevention and policy efforts targeting adolescents.

marijuana | longitudinal | cognition

New Zealand Dunedin Study

>1000 cohort studied over 38 years

- Updated summer 2012
- Neuropsychiatric declines across the board in MJ users
- **Age and dose dependent**
  - **Mental health**
  - **Verbal IQ**
  - **Academic achievement and job satisfaction**

- Adolescents who used marijuana regularly were significantly less likely than their non-using peers to **finish high school** or **obtain a degree**. They also had a much higher chance of later developing **dependence, using other drugs, and attempting suicide**

Marijuana use doubles in anxiety disorders and depression

- Adolescent marijuana use may cause anxiety disorders
  - Panic, depression, general anxiety

- Marijuana is also anxiety relieving
  - Social anxiety and PTSD

Buckner, Journal of Psyche Research, 2007

J. Of American Academy of Child and adol psych 46(3) 2007

Marijuana and Psychosis

- Worsening of preexisting schizophrenia
  - Increased psychiatric hospitalizations
- Acute reversible psychotic reaction
  - Increased likelihood of eventual schizophrenia
- Acute irreversible psychotic reaction
  - Psychotic break, Schizophrenia

Zammit brit journal of psyche nov 2008 193 (5) p357
D'souza, int. review of neurobiology 2007 (78) p289
Moore et al. LANCET July 28, 2007 P.319

Cannabis and psychosis

- 24% new psychosis cases linked to thc consumption

- BBC news 16, feb 2015

Cannabinoid Hyperemesis Syndrome: Cyclic Vomiting, Chronic Cannabis Use, and Compulsive Bathing

by Vikram Budhraja, Tarun Narang, Sulaiman Azeez

Marijauna is an illicit, but frequently used drug. Recently, a syndrome characterized by chronic marijuana use, cyclic vomiting, and compulsive bathing has been described in the literature. We report the third case of Cannabinoid Hyperemesis in the United States and its complete symptomatic resolution following abstinence from marijuana. This case represents the first reported case of Cannabinoid Hyperemesis in the Hispanic population. The case reported also demonstrates the earliest development of symptoms following habitual marijuana use and suggests a need to clearly define the characteristics of newly emerging diagnosis.

INTRODUCTION

Marijuana is one of the most frequently abused illicit substances in the United States (U.S.) (1). Cannabinoid Hyperemesis Syndrome was first reported recently in the literature with a series of patients exhibiting a triad of symptoms: cyclic vomiting, chronic marijuana use, and compulsive bathing

CASE REPORT

A 19-year-old Hispanic man presented to the emergency department with nausea and vomiting for three days, and daily marijuana use for the last 18 months. He was admitted for intractable nausea, non-bilious non-bloody vomiting 10–12 times per day, and epigastric pain. Nausea was relieved by hot showers, and he reported taking

Medical cannabis warnings

- Cannabis addiction and withdrawal is real!
- Cannabinoids are vasodilators
- Cannabinoids are associated with increased mental health symptoms, and mental health emergencies
- It is unsafe to drive on cannabinoids
- Heavy use in adolescence affect cognitive development
- Hyperemesis syndrome increasingly recognized

Medical Cannabis Topics

1. Minnesota Medical Cannabis: Law, enrollment, products, community practices, social effects

2. Cannabinoid physiology and pharmacology

3. Medicinal effects of medical cannabis

4. Adverse effects of and contraindications to medical cannabis

Thank you!
Questions?