CANNABIS: WHAT WE KNOW AND WHAT KEEPS US UP AT NIGHT

Secretaries' Innovation Group

July 20, 2017

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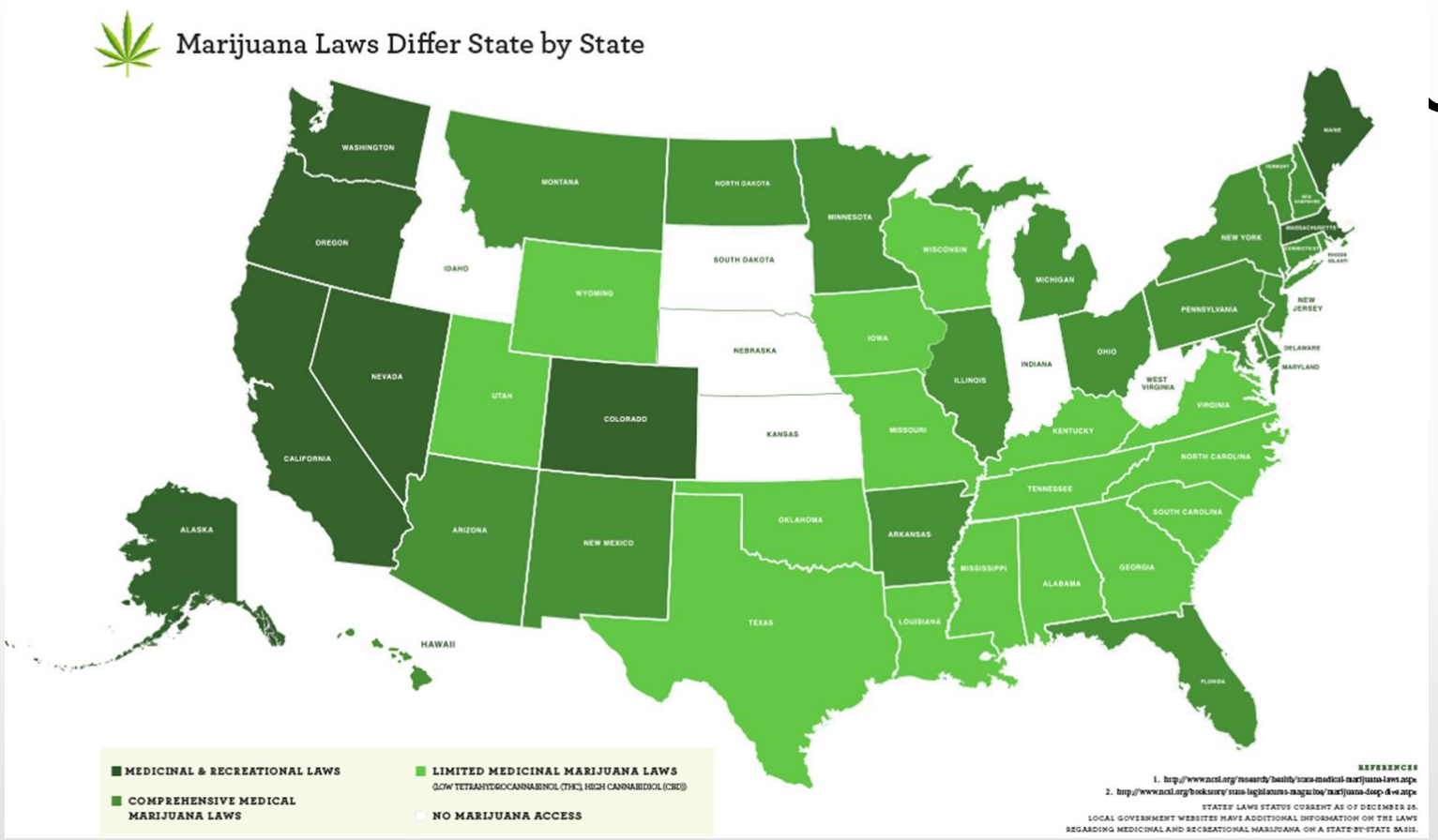
NIH
National Institute on Drug Abuse

DEPARTMENT OF HEALTH & HUMAN SERVICES • USA

CANNABIS LAWS IN THE U.S.



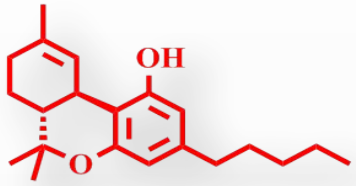
States with MML vary on:

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

States with Recreational Laws vary on:

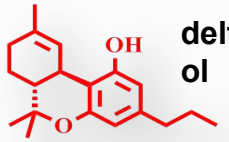
- Marketing, product labeling, distribution (home growth).
- Taxation.

CANNABIS CONTAINS ~100 CANNABINOIDS PLUS OTHER CHEMICALS IN VARYING CONCENTRATIONS



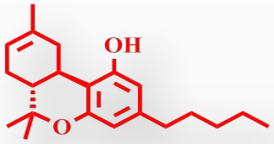
Δ^9-THC

delta-9-tetrahydrocannabinol



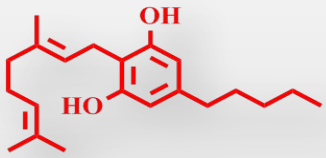
Δ^9-THCV

delta-9-tetrahydrocannabivarin



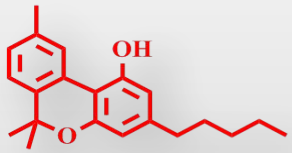
Δ^8-THC

delta-8-tetrahydrocannabinol



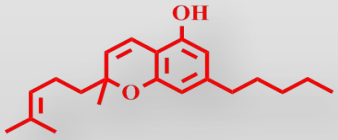
CBG

cannabigerol



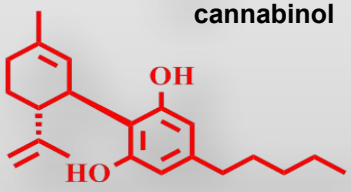
CBN

cannabinol



CBC

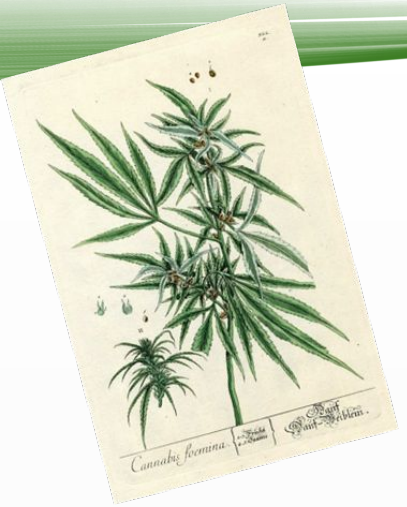
cannabichromene



CBD

cannabidiol

- Plant with long history of use worldwide
- Illegal under Federal law (Schedule I substance—not FDA approved)
- Legal for medical use in 29 States + D.C.
- High CBD variety (or extracts) legal in 16 states for medical use
- Versions of active ingredients approved *(or in clinical trials)* for medical indications in U.S. and other countries
  - Synthetic - Marinol, Syndros, Cesamet
  - Plant Derived- Sativex (THC/CBD)
  - *Plant Derived-Epidiolex (CBD: Phase III trials)*



CANNABIS RESEARCH BARRIERS

ADMINISTRATIVE

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

SCIENTIFIC

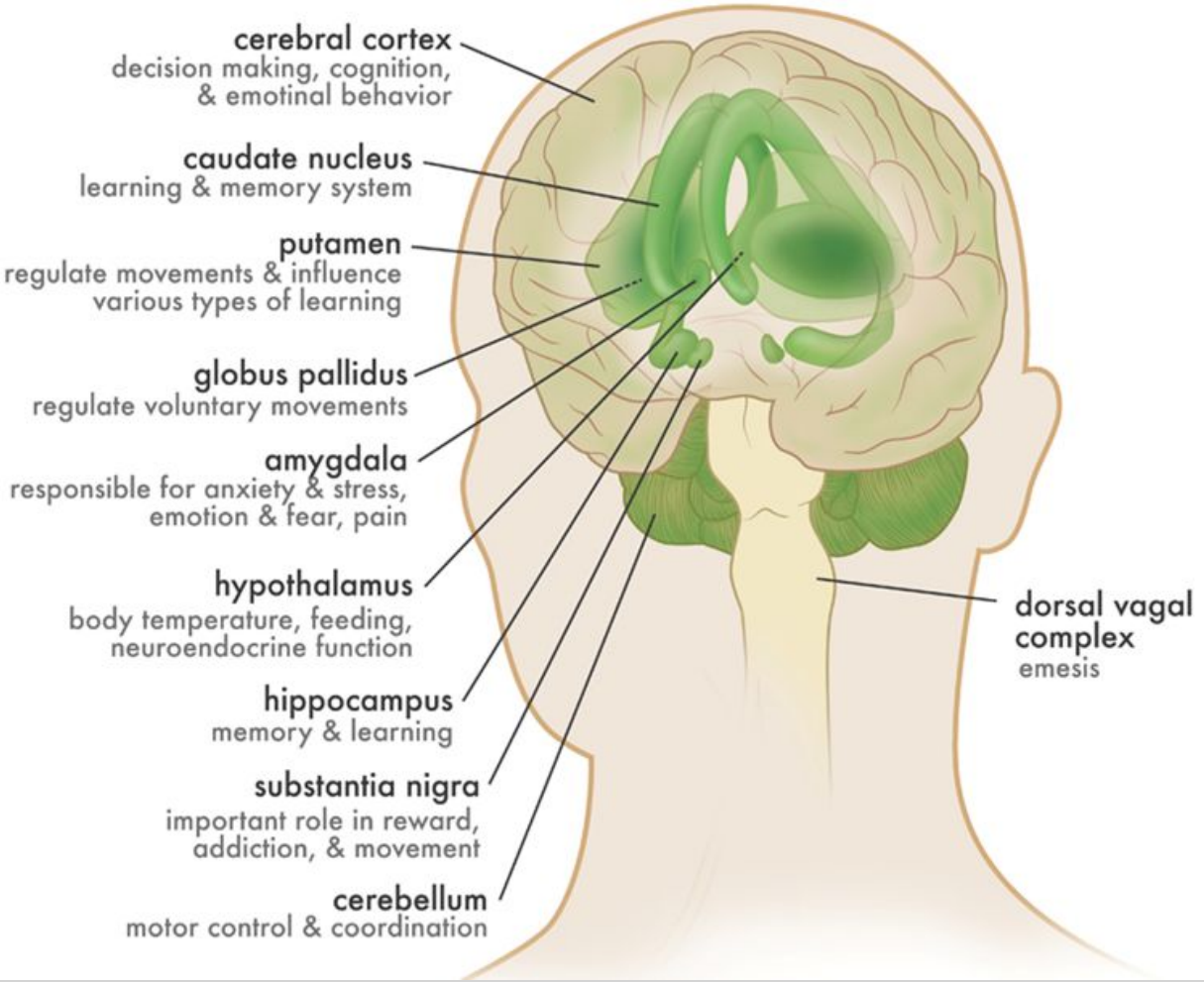
- Complexity of plant (100 cannabinoids + other components), entourage effect?
- Route of administration.
- Need proper controls, sufficient study duration (blinding, driving…)
- Should be taking advantage of what is already happening in the states (patient registries).

ADVERSE EFFECTS: WHAT DO WE KNOW?

CANNABINOID RECEPTORS ARE LOCATED THROUGHOUT THE BRAIN

Regulation of:

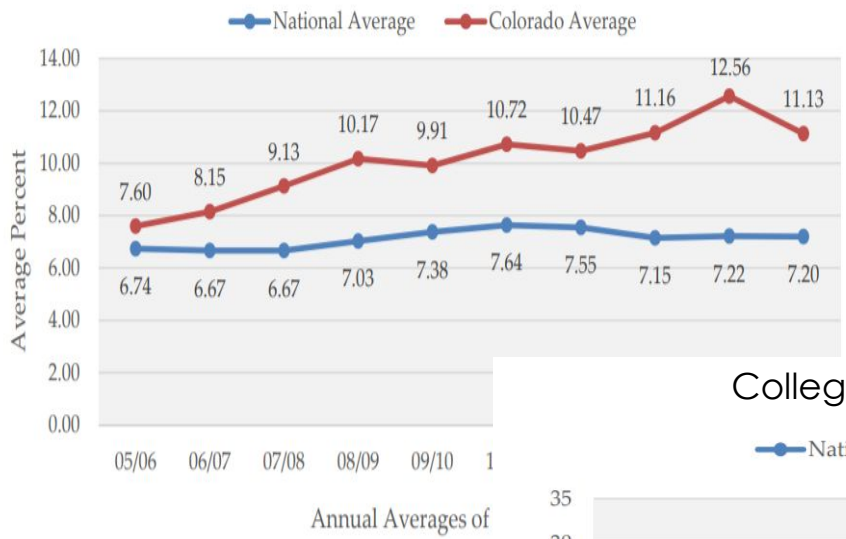
- Brain Development
- Memory and Cognition
- Movement Coordination
- Pain Regulation & Analgesia
- Immunological Function
- Appetite
- Motivational Systems & Reward



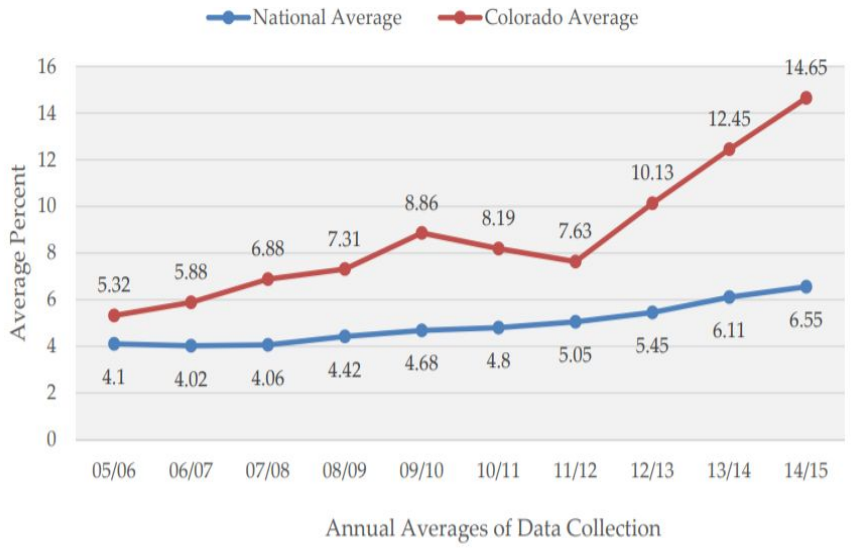
Source: Canadian Consortium for the Investigation of Cannabinoids, http://www.ccic.net/

PAST MONTH MARIJUANA USE

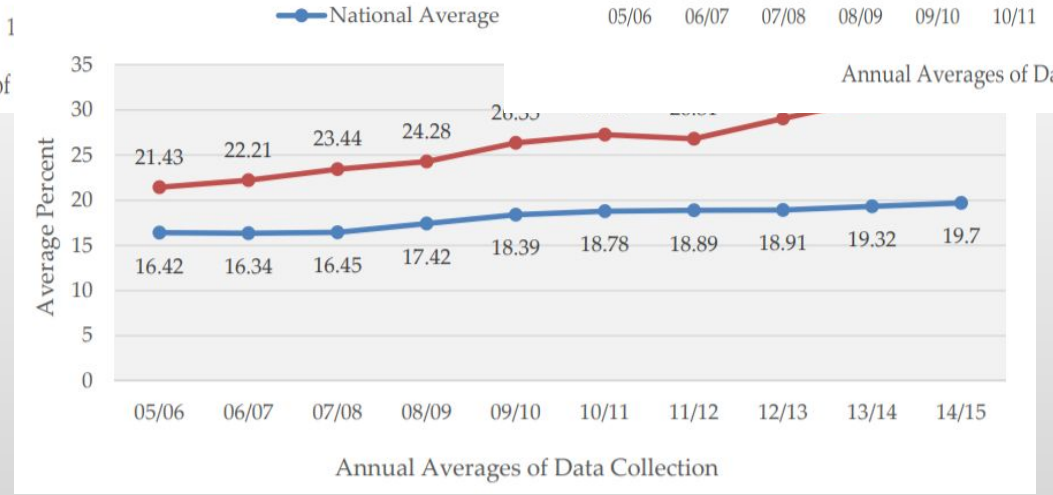
Youth Ages 12 to 17 Years Old



Adults Age ≥ 26 Years Old



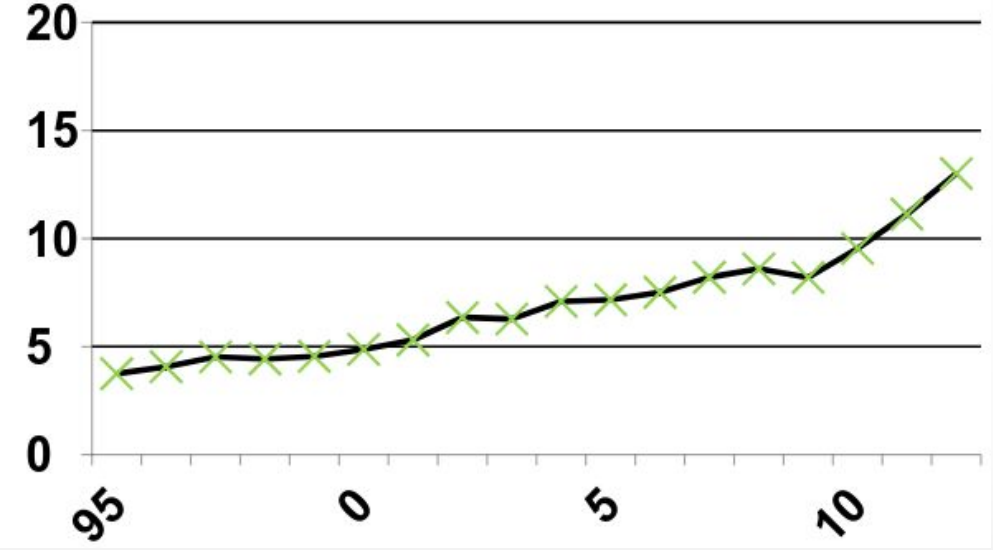
College Age 1



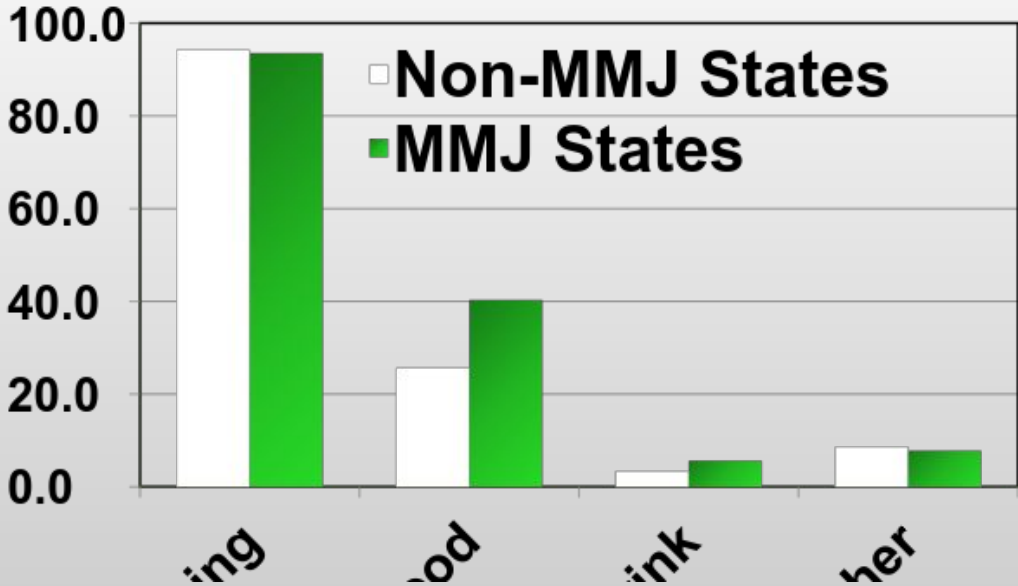
Rocky Mountain HIDTA Report www.rmhidta.org
Supplement: The Legalization of Marijuana in Colorado:
The Impact, Volume 4 (March 2017)

SOURCE: SAMHSA.gov, National Survey on Drug Use and Health 2014 and 2015

CHANGING LANDSCAPE: INCREASING POTENCY & NEW ROUTES OF ADMINISTRATION



12th grade Past Year Users



SOURCE: University of Mississippi; University of Michigan, 2014 Monitoring the Future Study

ENDOCANNABINOID SYSTEM INVOLVED IN BRAIN DEVELOPMENT: MOST VULNERABLE POPULATIONS?

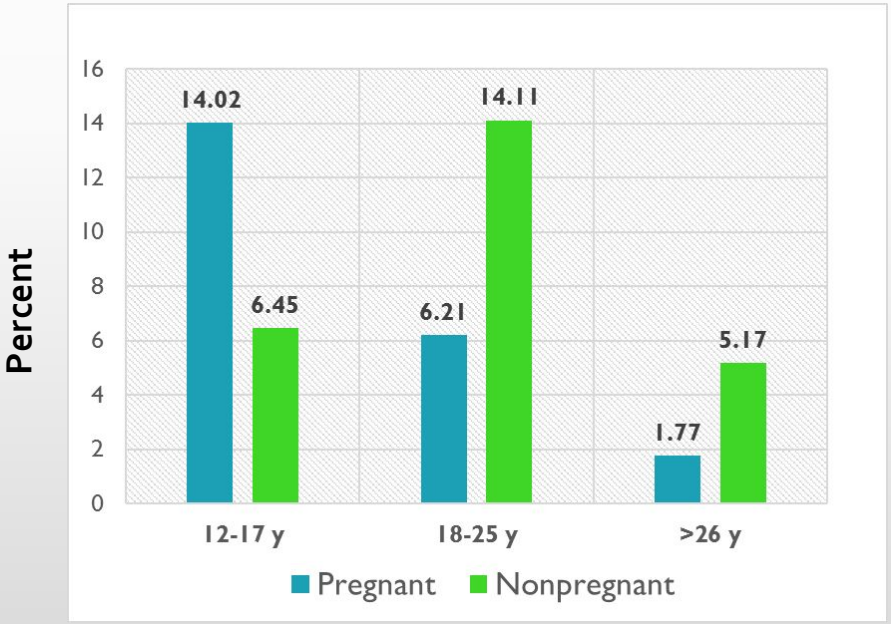
Prenatal

Adolescent

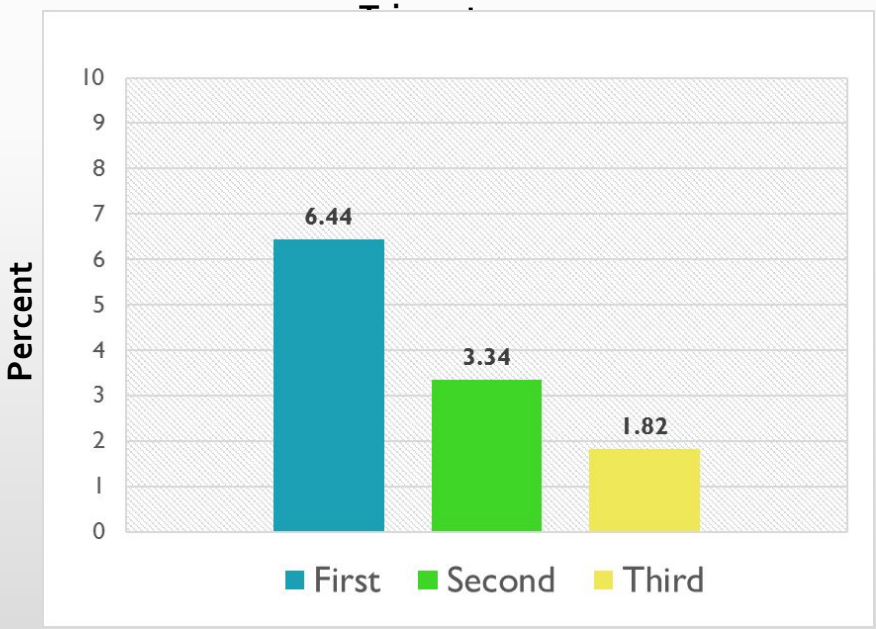
PREGNANT TEENS REPORT HIGH PAST MONTH USE OF MARIJUANA HIGHEST RATES OF USE IN FIRST TRIMESTER

2002 to 2015 National Survey on Drug Use and Health (NSDUH)

By Age



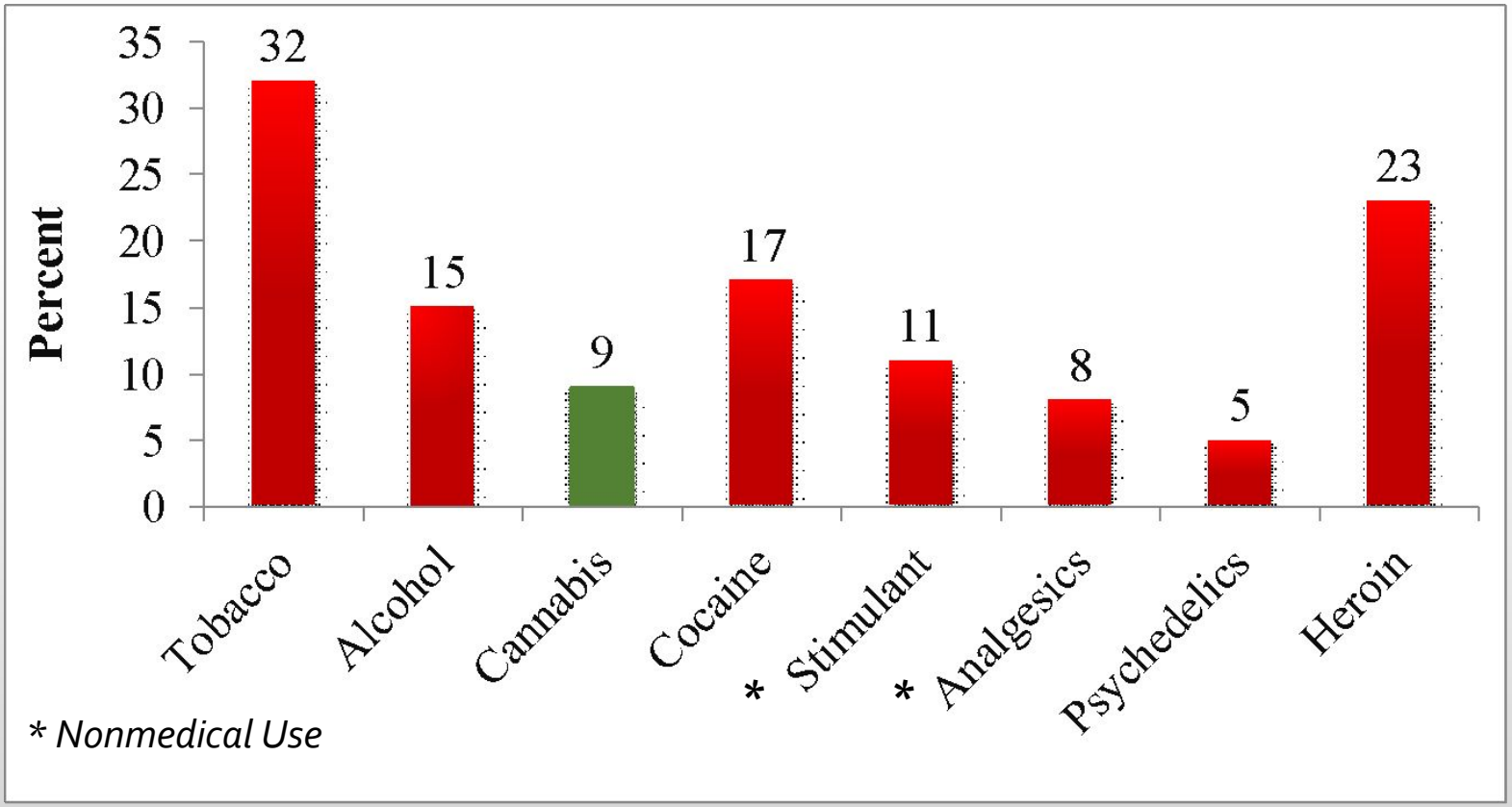
By



Volkow et al., Ann Intern Med. 2017; 166(10):763-764.

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

Estimated Prevalence of Dependence Among Users

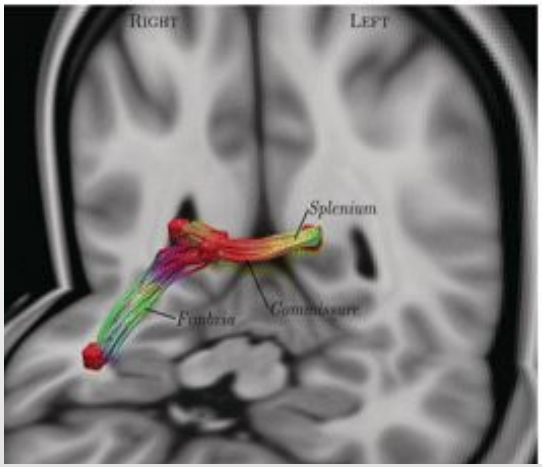


Source: Anthony JC et al., 1994

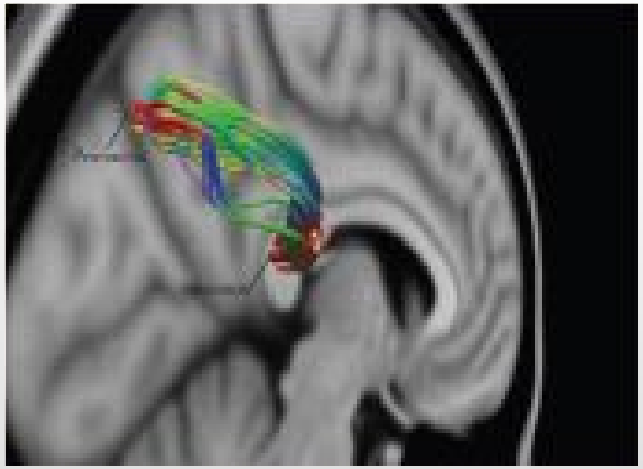
MULTIPLE STUDIES SHOW ALTERED BRAIN STRUCTURE AND FUNCTION IN YOUTH WHO REGULARLY USE CANNABIS

Early (<18y) Cannabis Use Decreases Axonal Fiber Connectivity

Precuneus to splenium



Fimbria of hippocampus, hippocampal Commissure, and splenium



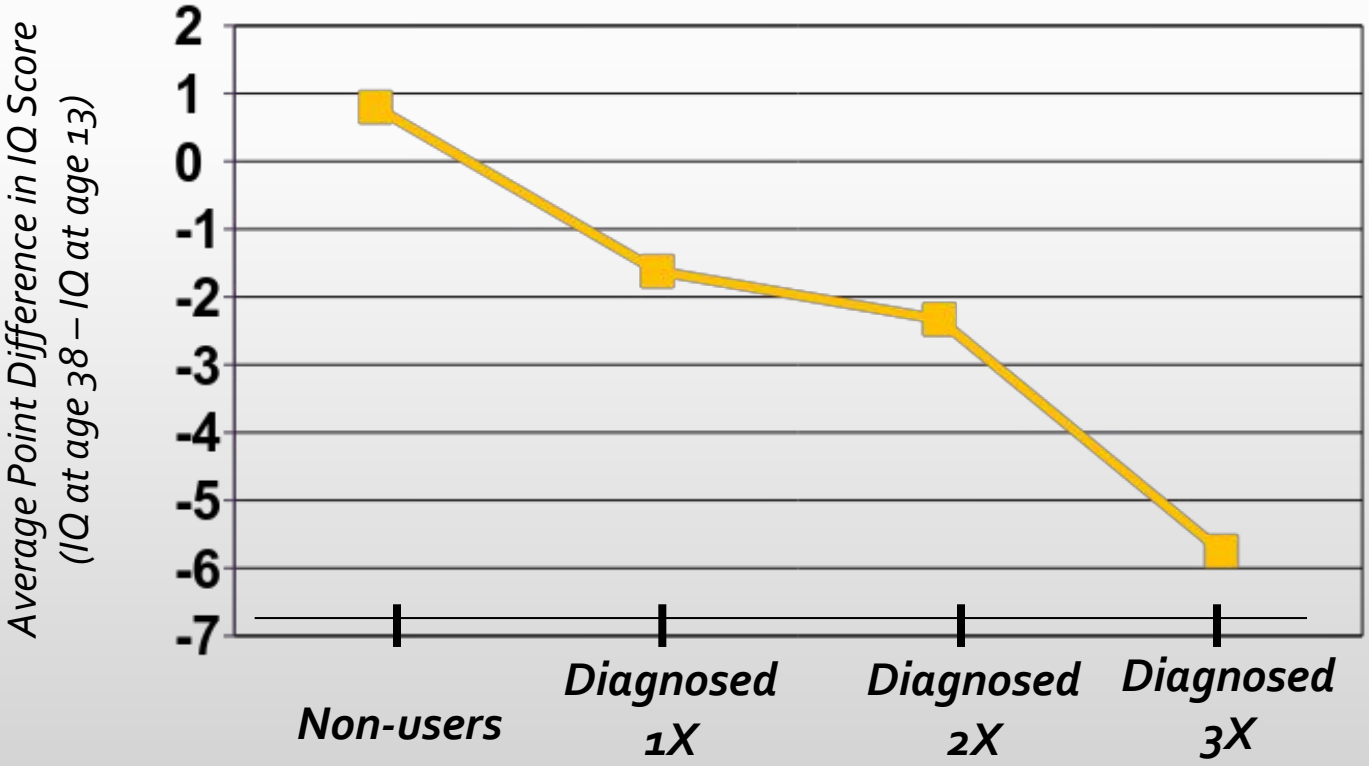
Axonal paths with reduced connectivity (measured with diffusion-weighted MRI) in cannabis users (n=59) than in controls (N=33).

Zalesky et al Brain 2012

COGNITION:

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

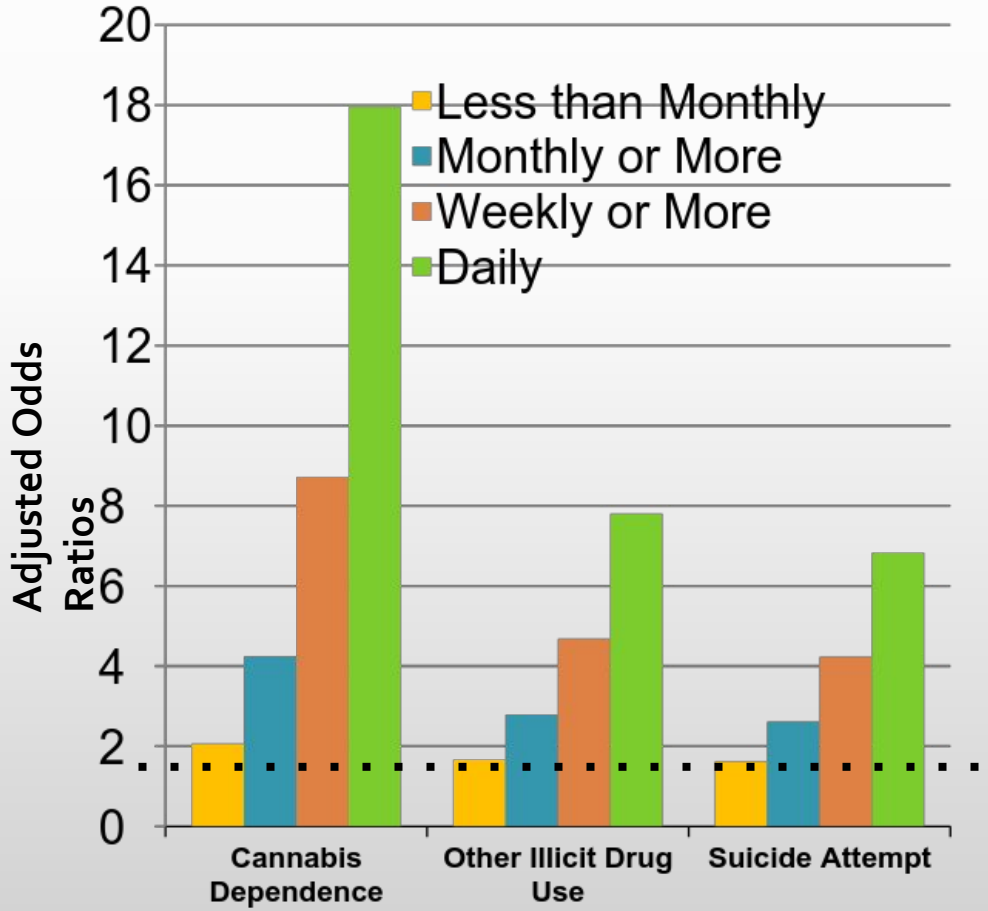
- Followed 1,037 individuals from birth to age 38.
- Tested marijuana use and disorders at 18, 21, 26, 32 and 38.
- Tested for IQ at ages 13 and 38

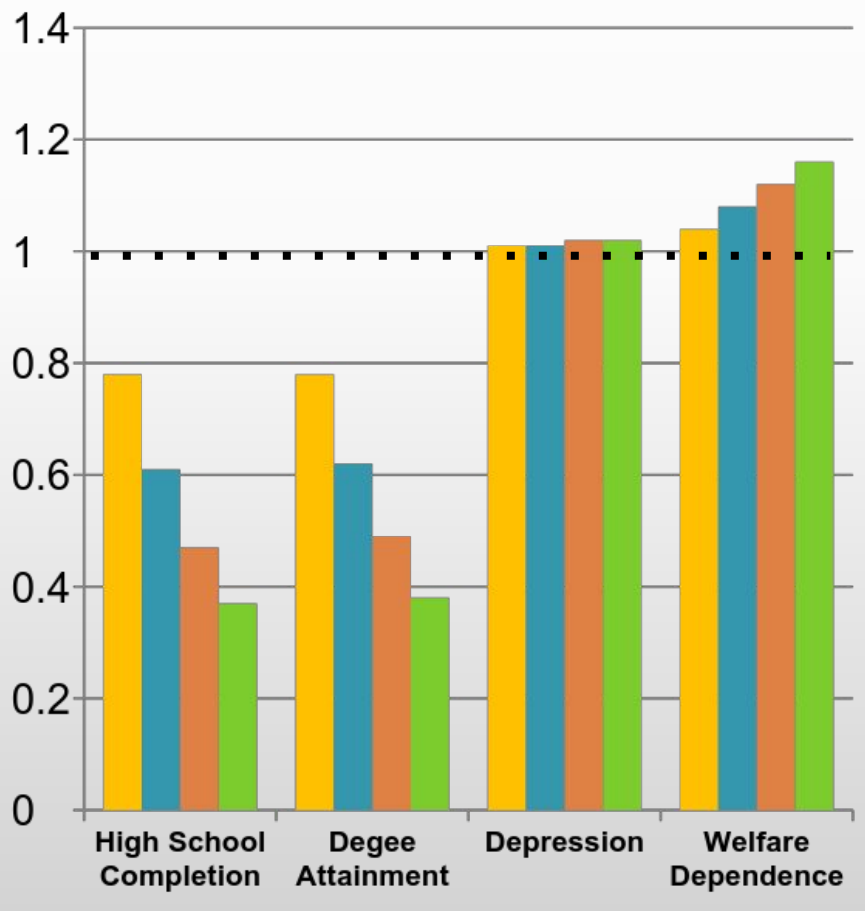


Source: Meier MH et al., PNAS Early Edition 2012

FREQUENCY OF CANNABIS USE BEFORE AGE 17 YEARS AND ADVERSE OUTCOMES (20 YEARS AGE) (N=2500-3700)

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





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

POLICY CHALLENGES:
HOW DO WE MINIMIZE HARM IN AN ENVIRONMENT WHERE POLICY DECISIONS ARE OUTPACING RESEARCH AND KNOWLEDGE?

- Identify what we know and what we don't
- Prioritize Research Needs
  - Health: brain, heart, lungs, reproductive system, medical use, others
  - Policy: different implementation models, regulations, taxation, marketing
- Communication: Develop credible, persuasive, simple messages for the public, the medical community, policymakers
- Consider the context: many uncertainties regarding State Legalization policies and Federal enforcement priorities

WHAT WE KNOW ABOUT ADOLESCENT CANNABIS EXPOSURE

- Adversely influences learning
- Effects on memory and attention outlast intoxication
- Appear worse with earlier age of onset, more chronic use
- Some neuroimaging data support these effects
- Increased risk of addiction (compared to adults)
- Worse educational outcomes, career achievement, life satisfaction
- Linked with suicidal ideation or behavior
- Earlier onset/worse course of psychotic illness *in vulnerable individuals*

WHAT WE NEED TO KNOW ABOUT CANNABIS AND NEURODEVELOPMENT

The precise nature of the association between cannabis use and neurodevelopment including who is at risk.

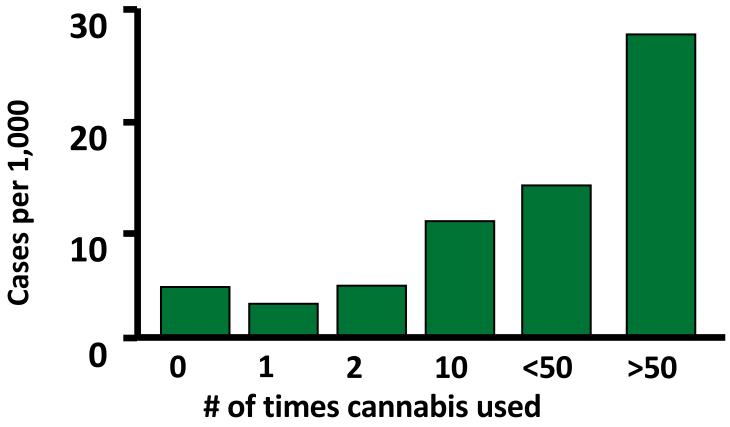
- What are the factors that moderate the impact of cannabis exposure?
- How should we quantify cannabis use: frequency, strain, potency, route of administration?
- Are there permanent effects; compensatory developmental responses; or reversible changes in structure/function?
- How much do other variables contribute to cannabis effects (alcohol, tobacco, prenatal care, BMI, physical activity…)?
- What are the effects of second- or third-hand smoke exposure from cannabis?

COMMUNICATION

- Learn from the past: don't want to re-create a "crack baby" scenario; or a reefer madness approach that will backfire.
- Recognize the complexities and nuances: effects may be modest, selective (individual differences), confounded with other drug use, or delayed in onset.
- Need concise, accurate health messages for diverse populations, especially teens and pregnant women (Warning labels).
- States with medical marijuana laws should recommend against cannabis for pregnant (or breastfeeding) women.
- Physicians who are recommending cannabis need better training on risks.

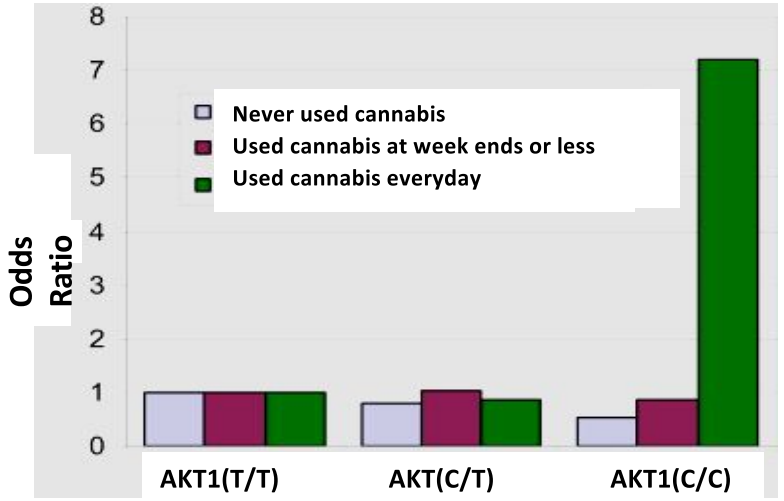
Cannabis-Associated Psychosis

Study of Swedish Conscripts (n=45570)



Andréasson et al Lancet, 1987.

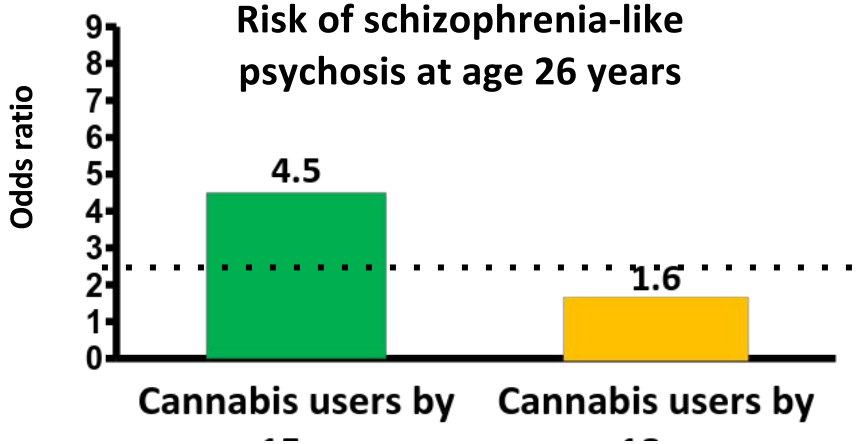
Regular Cannabis Use Increases Schizophrenia Risk in those with AKT1 rs2494732 genotype



GXE model: p*=0.014

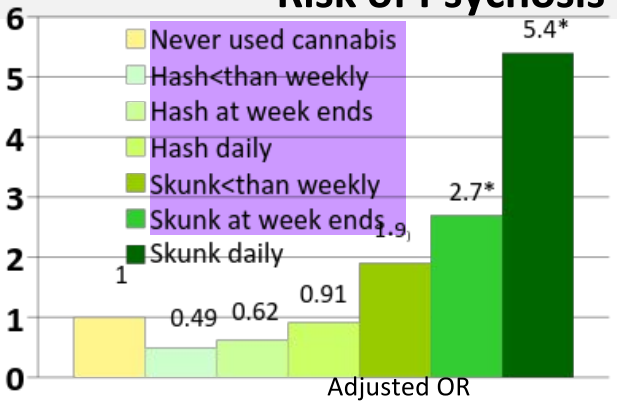
Di Forti et al., Biological Psychiatry, 2012.

Prospective Dunedin study (n=1037)



Arseneault et al BMJ 2002

Effect of High Potency Cannabis on Risk of Psychosis



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

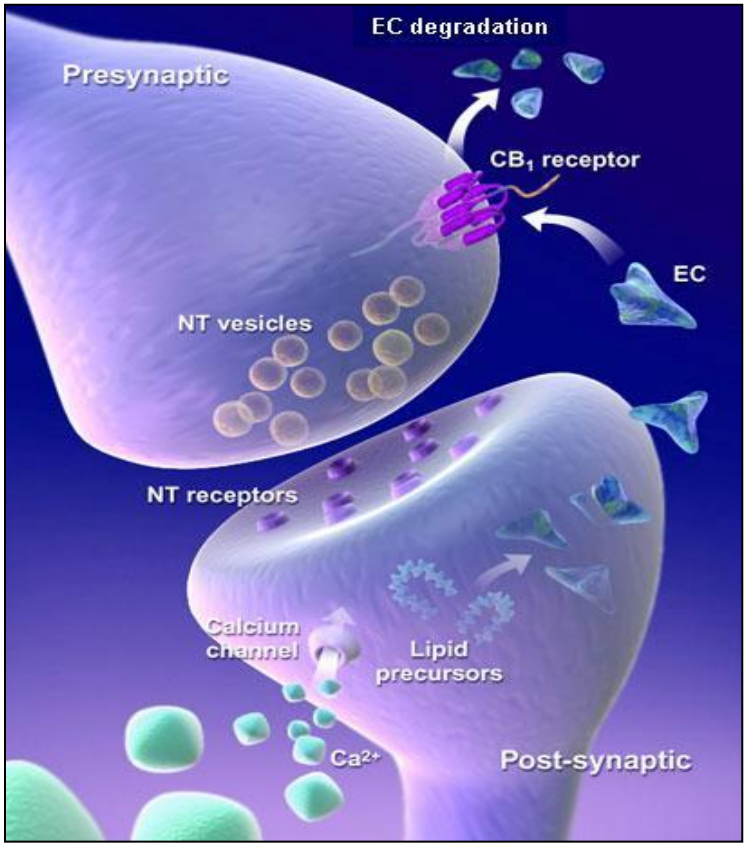
LEVEL OF CONFIDENCE IN THE EVIDENCE FOR *ADVERSE* EFFECTS OF CHRONIC MARIJUANA USE ON HEALTH AND WELL-BEING

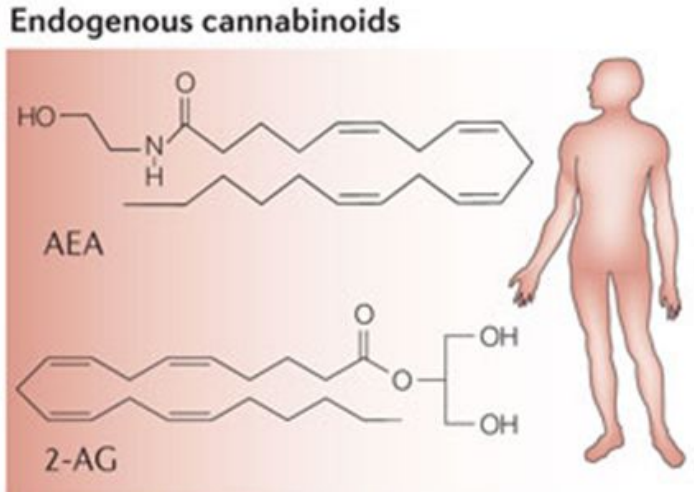
Effect	Overall Level of Confidence*
Addiction to marijuana and other substances	High
Abnormal brain development	Medium
Progression to use of other drugs	Medium
Schizophrenia	Medium
Depression or anxiety	Low
Diminished lifetime achievement	High
Motor vehicle accidents	High
Symptoms of chronic bronchitis	High
Lung cancer	Low

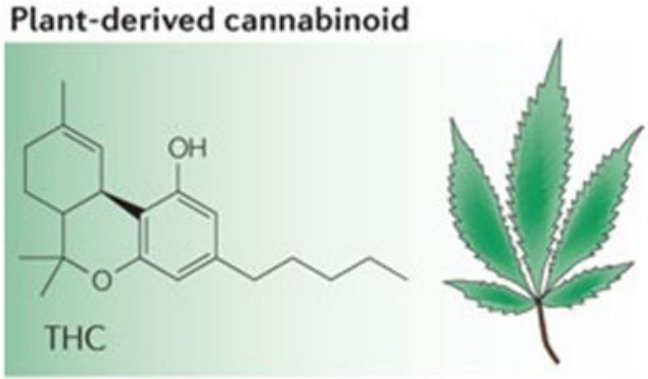
Source: Volkow ND et al. N Engl J Med 2014;370:2219-2227.

The NEW ENGLAND JOURNAL of MEDICINE

Mechanism of Action of Cannabinoids





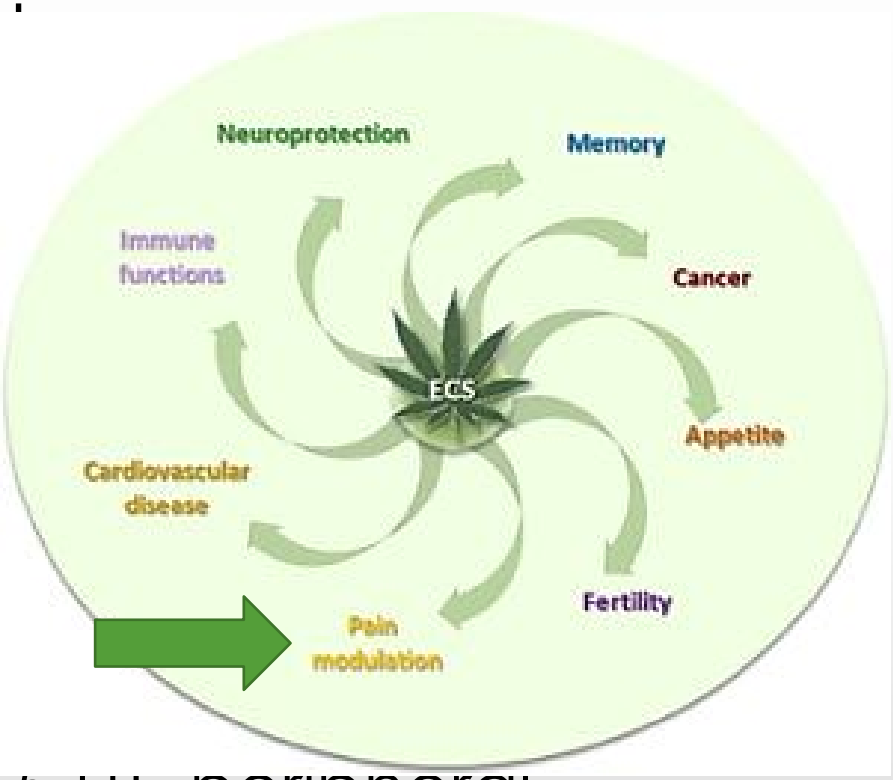


Endocannabinoids are produced *on demand*. They travel back to the transmitting neuron to dampen further activity.

Source: Mackie K. Ann Rev Pharmacol Toxicol., 2006

THE ENDOCANNABINOID SYSTEM: THERAPEUTIC POTENTIAL OF CANNABIS

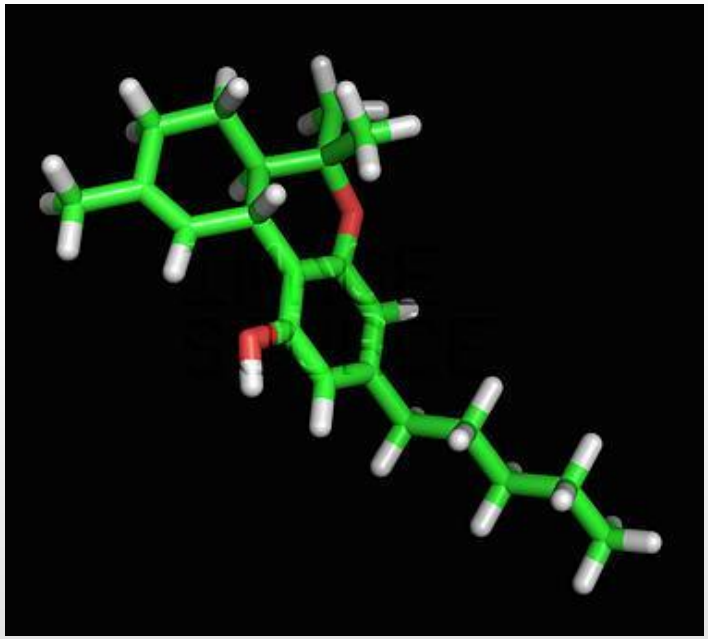
- Exogenous compound
  - Phytocannabinoids
    - THC, CBD, combinations
  - Synthetic cannabinoids
    - Dronabinol
- Endogenous manipulc
  - FAAH inhibitors
  - MAGL inhibitors
  - Allosteric modulators
- Receptor targets
  - CB1, CB2, TRPV1, PPAR, 5-H1, peripheral, others…



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

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

- Over 22 million Americans 12 and older were past month marijuana users.
- Approximately 4.0 million Americans met criteria for cannabis use disorders in 2015.
- An estimated 2.6 million Americans used it for the first time; 1.2 million were between the ages of 12 and 17.



Tetrahydrocannabinol (THC)
Psychoactive Ingredient in Marijuana

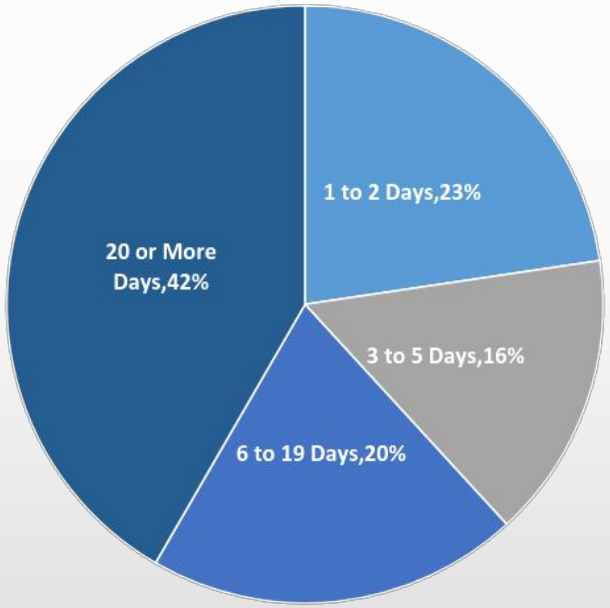
Source: 2016 National Survey on Drug Use and Health, SAMHSA

TRENDS AMONG CURRENT CANNABIS USERS: TWO IN FIVE ARE DAILY OR ALMOST DAILY USERS

Number of Days Used Cannabis in the Past Month

2002

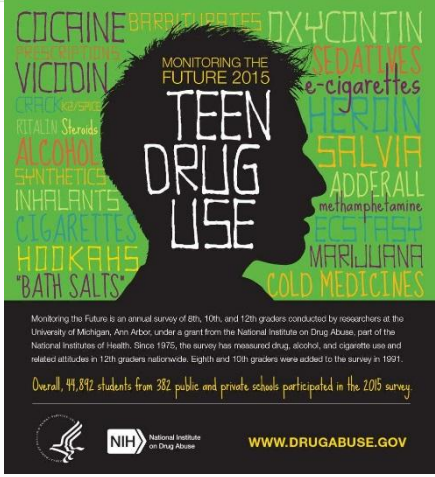
2014



22.2 Million Past Month Users of Cannabis in 2014
14.6 Million Past Month Users of Cannabis in 2002

Sources: SAMHSA, 2002 National Survey on Drug Use and Health (September 2003).
SAMHSA, 2014 National Survey on Drug Use and Health (September 2015).

PATTERNS AND TRENDS



What We Know:

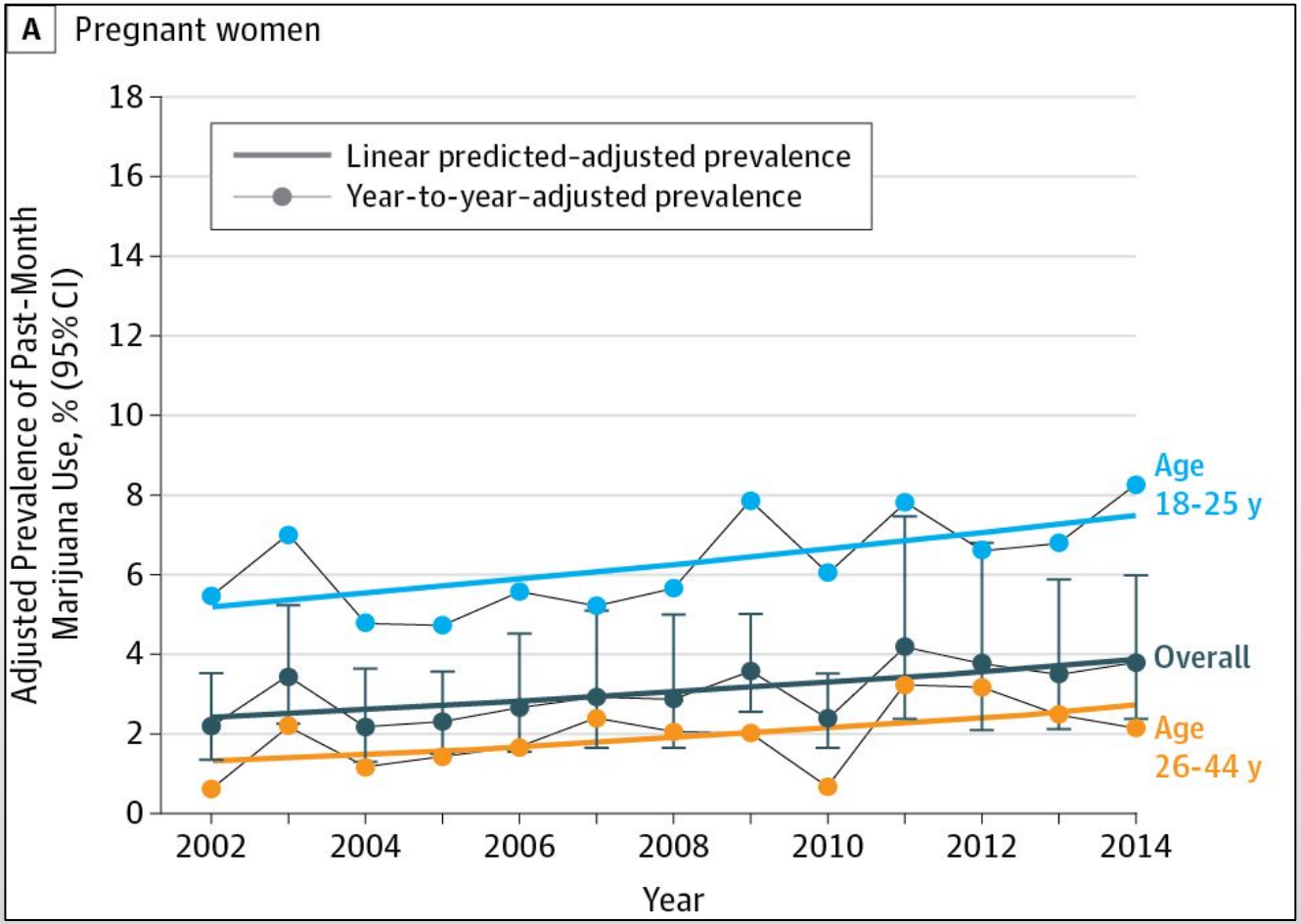
- Use among youth (12-17) has not increased in recent years despite decreased perception of risk
- Current users use more often (daily, nearly daily) than in 2002
- Potency is increasing; plant components are changing
- Cannabis is being administered through different routes

What We Need to Know:

- Need improved measures of frequency, dosage, patterns of use
- Persuasive Messaging (especially for youth) to counter the trend of decreasing harm perception
- Greater knowledge of the impact of changing potency (user titration?), constituents, and alternative routes of administration
- Regional differences based on changing laws, policies, and social norms
- Use of other substances: complementarity vs. substitution

CANNABIS USE DURING PREGNANCY IS INCREASING

Trends in Prevalence of Cannabis Use in Pregnant Women, 2002-2014-NSDUH



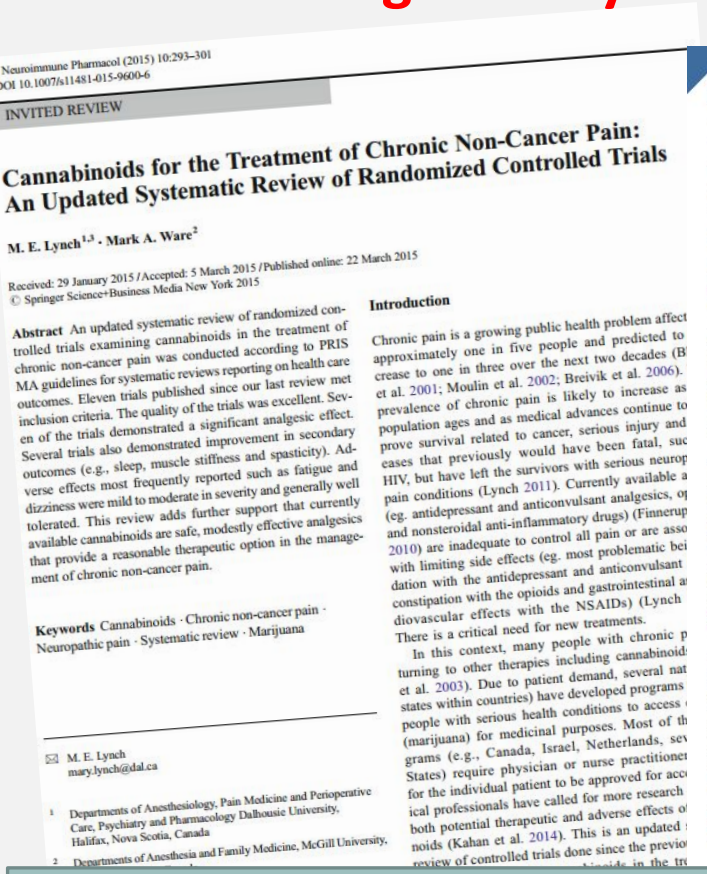
Source: Brown et al., 2017

Strength of the Evidence For Marijuana/Cannabinoid Medical Applications

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

Recent Meta-Analyses Support the use of Cannabinoids for Chronic Neuropathic Non Cancer Pain, but…..

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



Neuroimmune Pharmacol (2015) 10:293–301
DOI 10.1007/s11481-015-9600-6

INVITED REVIEW

Cannabinoids for the Treatment of Chronic Non-Cancer Pain: An Updated Systematic Review of Randomized Controlled Trials

M. E. Lynch[1,3] · Mark A. Ware[2]

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Abstract An updated systematic review of randomized controlled trials examining cannabinoids in the treatment of chronic non-cancer pain was conducted according to PRISMA guidelines for systematic reviews reporting on health care outcomes. Eleven trials published since our last review met inclusion criteria. The quality of the trials was excellent. Seven of the trials demonstrated a significant analgesic effect. Several trials also demonstrated improvement in secondary outcomes (e.g., sleep, muscle stiffness and spasticity). Adverse effects most frequently reported such as fatigue and dizziness were mild to moderate in severity and generally well tolerated. This review adds further support that currently available cannabinoids are safe, modestly effective analgesics that provide a reasonable therapeutic option in the management of chronic non-cancer pain.

Keywords Cannabinoids · Chronic non-cancer pain · Neuropathic pain · Systematic review · Marijuana

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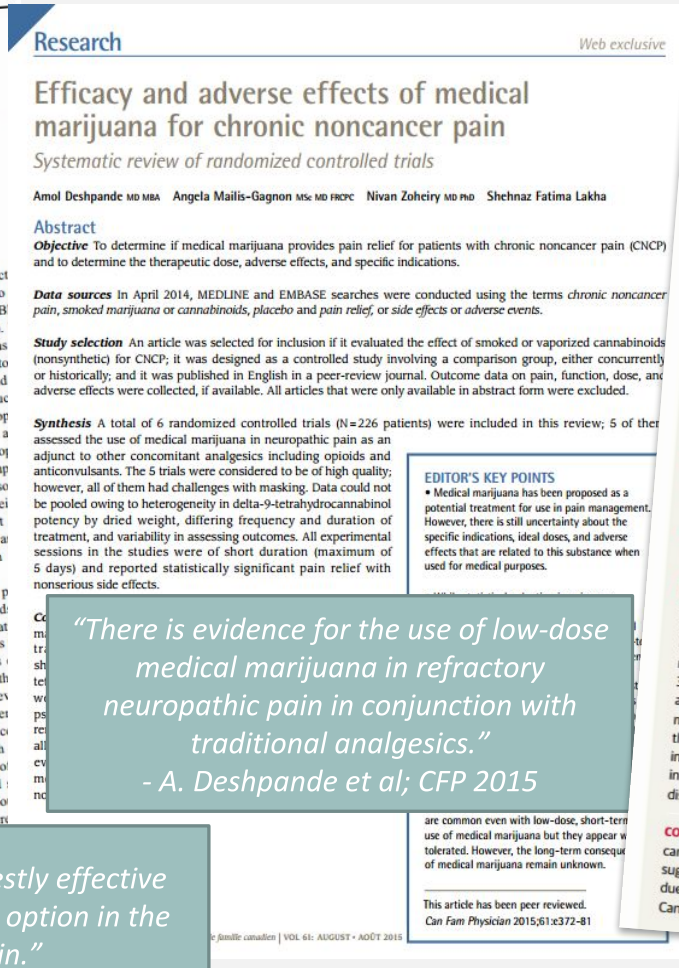
Introduction

Chronic pain is a growing public health problem affect approximately one in five people and predicted to crease to one in three over the next two decades (B et al. 2001; Moulin et al. 2002; Breivik et al. 2006). prevalence of chronic pain is likely to increase as population ages and as medical advances continue to prove survival related to cancer, serious injury and eases that previously would have been fatal, suc HIV, but have left the survivors with serious neurop pain conditions (Lynch 2011). Currently available a (eg. antidepressant and anticonvulsant analgesics, o and nonsteroidal anti-inflammatory drugs) (Finnerup 2010) are inadequate to control all pain or are asso with limiting side effects (eg. most problematic bei dation with the antidepressant and anticonvulsant constipation with the opioids and gastrointestinal a diovascular effects with the NSAIDs) (Lynch There is a critical need for new treatments.

In this context, many people with chronic p turning to other therapies including cannabinoid et al. 2003). Due to patient demand, several nat states within countries) have developed programs people with serious health conditions to access (marijuana) for medicinal purposes. Most of th grams (e.g., Canada, Israel, Netherlands, sev States) require physician or nurse practitioner for the individual patient to be approved for acc ical professionals have called for more research both potential therapeutic and adverse effects o noids (Kahan et al. 2014). This is an updated review of controlled trials done since the previo



Research — Web exclusive

Efficacy and adverse effects of medical marijuana for chronic noncancer pain

Systematic review of randomized controlled trials

Amol Deshpande MD MBA Angela Mailis-Gagnon MSc MD FRCPC Nivan Zoheiry MD PhD Shehnaz Fatima Lakha

Abstract

Objective To determine if medical marijuana provides pain relief for patients with chronic noncancer pain (CNCP) and to determine the therapeutic dose, adverse effects, and specific indications.

Data sources In April 2014, MEDLINE and EMBASE searches were conducted using the terms *chronic noncancer pain*, *smoked marijuana* or *cannabinoids*, *placebo* and *pain relief*, or *side effects* or *adverse events*.

Study selection An article was selected for inclusion if it evaluated the effect of smoked or vaporized cannabinoids (nonsynthetic) for CNCP; it was designed as a controlled study involving a comparison group, either concurrently or historically; and it was published in English in a peer-review journal. Outcome data on pain, function, dose, and adverse effects were collected, if available. All articles that were only available in abstract form were excluded.

Synthesis A total of 6 randomized controlled trials (N=226 patients) were included in this review; 5 of them assessed the use of medical marijuana in neuropathic pain as an adjunct to other concomitant analgesics including opioids and anticonvulsants. The 5 trials were considered to be of high quality; however, all of them had challenges with masking. Data could not be pooled owing to heterogeneity in delta-9-tetrahydrocannabinol potency by dried weight, differing frequency and duration of treatment, and variability in assessing outcomes. All experimental sessions in the studies were of short duration (maximum of 5 days) and reported statistically significant pain relief with nonserious side effects.

EDITOR'S KEY POINTS

- Medical marijuana has been proposed as a potential treatment for use in pain management. However, there is still uncertainty about the specific indications, ideal doses, and adverse effects that are related to this substance when used for medical purposes.

are common even with low-dose, short-term use of medical marijuana but they appear w tolerated. However, the long-term consequ of medical marijuana remain unknown.

This article has been peer reviewed.
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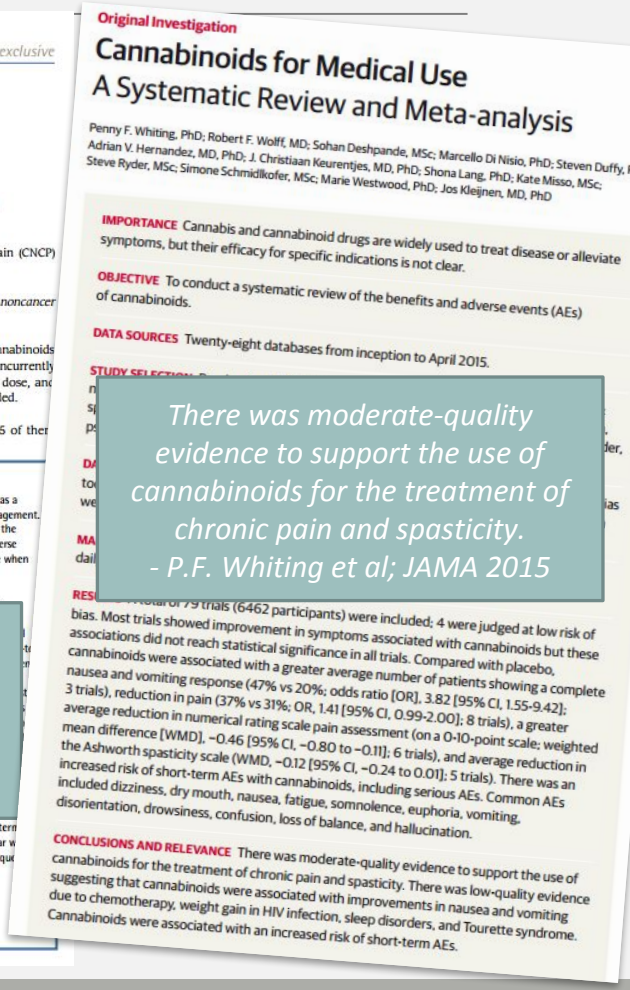

Original Investigation

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, 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

DA

MA

RES 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]; 3 trials), reduction in pain (37% vs 31%; OR, 1.41 [95% CI, 0.99-2.00]; 8 trials), a greater average reduction in numerical rating scale pain assessment (on a 0-10-point scale; weighted mean difference [WMD], −0.46 [95% CI, −0.80 to −0.11]; 6 trials), and average reduction in the Ashworth spasticity scale (WMD, −0.12 [95% CI, −0.24 to 0.01]; 5 trials). There was an increased risk of short-term AEs with cannabinoids, including serious AEs. Common AEs included dizziness, dry mouth, nausea, fatigue, somnolence, euphoria, vomiting, disorientation, drowsiness, confusion, loss of balance, and hallucination.

CONCLUSIONS AND RELEVANCE There was moderate-quality evidence to support the use of cannabinoids for the treatment of chronic pain and spasticity. There was low-quality evidence suggesting that cannabinoids were associated with improvements in nausea and vomiting due to chemotherapy, weight gain in HIV infection, sleep disorders, and Tourette syndrome. Cannabinoids were associated with an increased risk of short-term AEs.

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

"There is evidence for the use of low-dose medical marijuana in refractory neuropathic pain in conjunction with traditional analgesics."
- A. Deshpande et al; CFP 2015

"currently available cannabinoids are safe, modestly effective analgesics that provide a reasonable therapeutic option in the management of chronic non-cancer pain."
- M.E. Lynch & M.A. Ware; J Neuroimmune Pharmacology 2015