An old crop with a new lease of life

NIH RESEARCH ON CANNABIS AND ITS CONSTITUENTS

Steven Gust, Ph.D.

Office of the Director

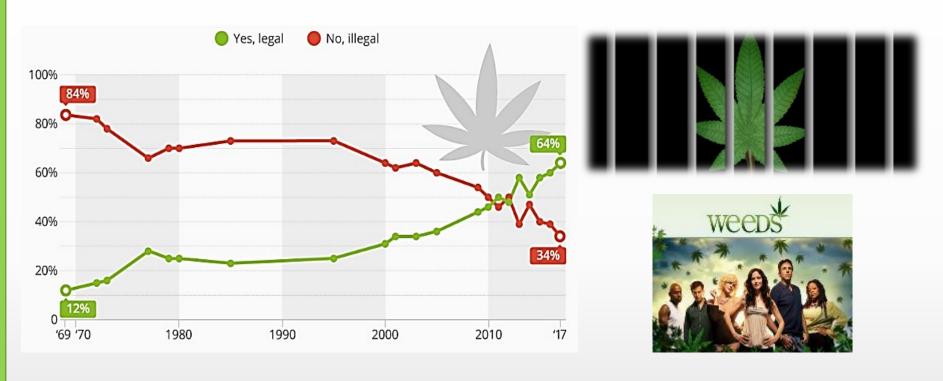
National Institute on Drug Abuse







PUBLIC OPINION ON CANNABIS IS CHANGING



- Public Opinion
- > Economic Considerations
- ➤ Interest Groups:
 - Pro and Con Legalization

- Lobbying and Other Political Activity
- > Media
- Federal Agencies
- > Science (we hope)

STATE CANNABIS LAWS



States with MML vary on:

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

States with Adult Use Laws vary on:

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

FEDERAL POLICY

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





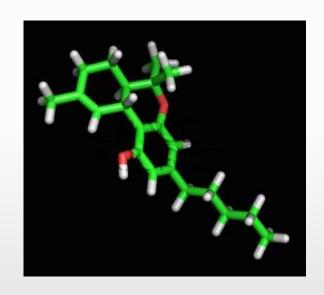
CONSEQUENCES OF CONFLICTING FEDERAL AND STATE POLICIES

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





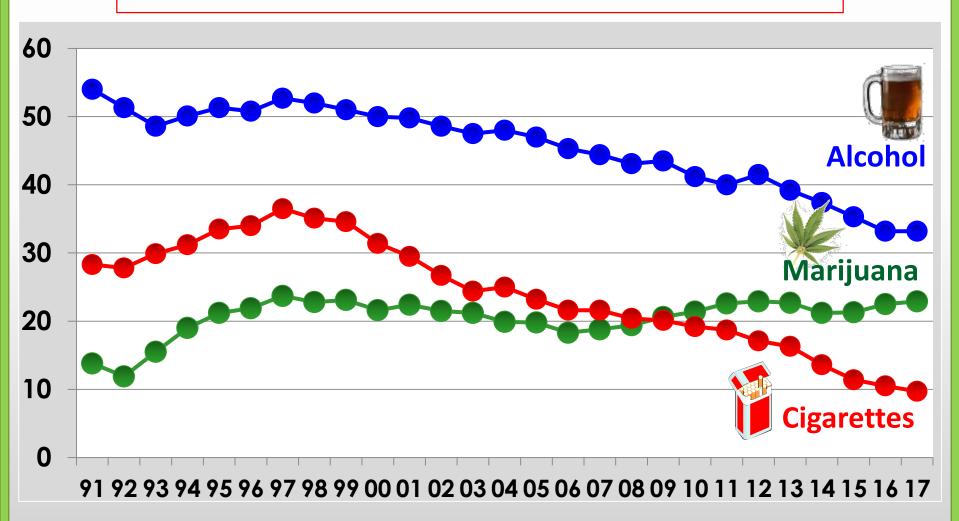
- Over 26 million Americans 12 and older report past month cannabis use.
- Approximately 4.0 million
 Americans met criteria for cannabis use disorders in 2017.
- An estimated 3.0 million
 Americans used cannabis for the first time; 1.2 million were between the ages of 12 and 17.



Tetrahydrocannabinol (THC)
Psychoactive Ingredient in Marijuana

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

nearly 6% report daily use of marijuana



Source: University of Michigan, 2017 Monitoring the Future Study

CANNABIS' EFFECTS

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

CANNABIS' ACUTE EFFECTS



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

CHANGING LANDSCAPE:

INCREASING POTENCY & NEW ROUTES OF ADMINISTRATION

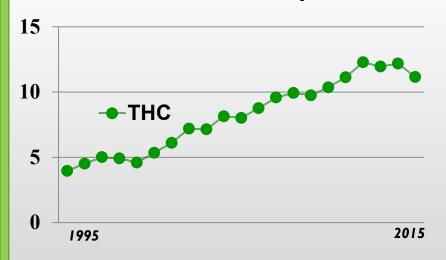




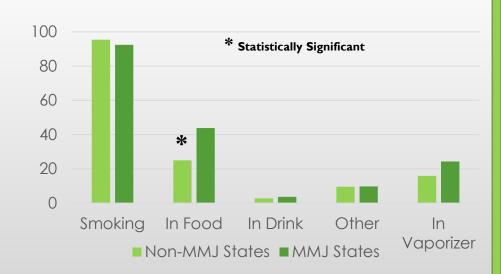




THC Potency

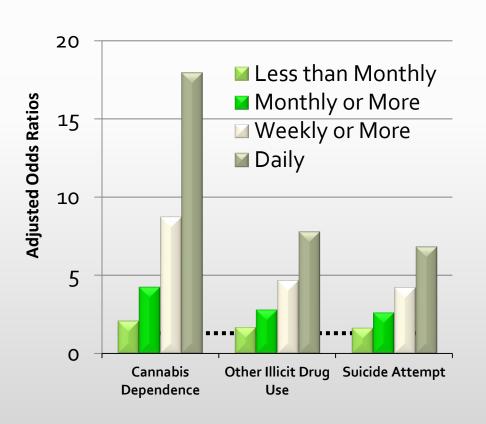


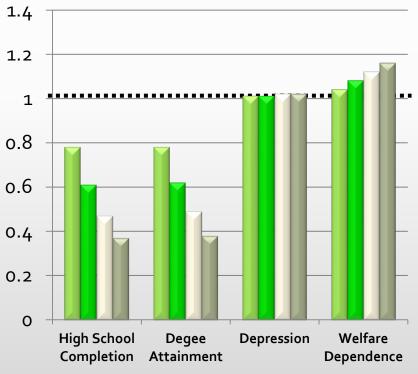
12th Grade Past Year Users



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

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

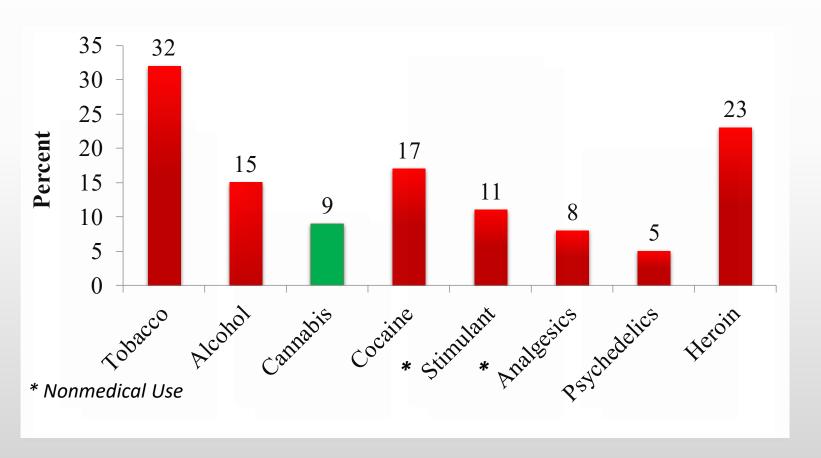




Source: Silins E et al., The Lancet, 2014

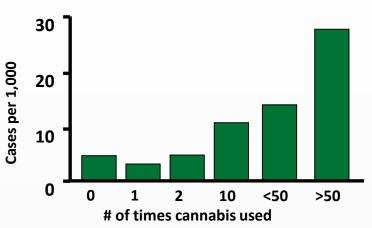
ADDICTION: ABOUT 9% OF USERS BECOME DEPENDENT, 1 IN 6 WHO START USE IN ADOLESCENCE, 25-50% OF DAILY USERS

Estimated Prevalence of Dependence Among Users



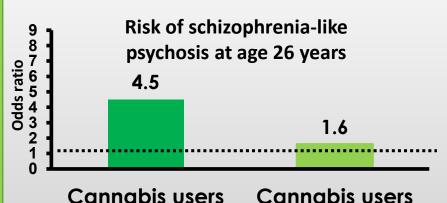
Cannabis-Associated Psychosis

Study of Swedish Conscripts (n=45570)



Source: Andréasson et al Lancet, 1987

Prospective Dunedin study (n=1037)

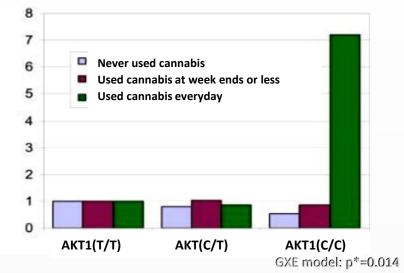


by age 15 years

Source: Arseneault et al BMJ 2002

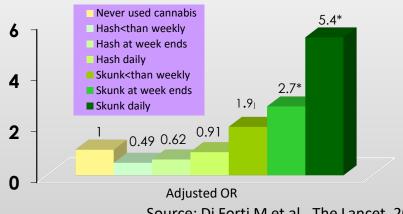
by age 18 years

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



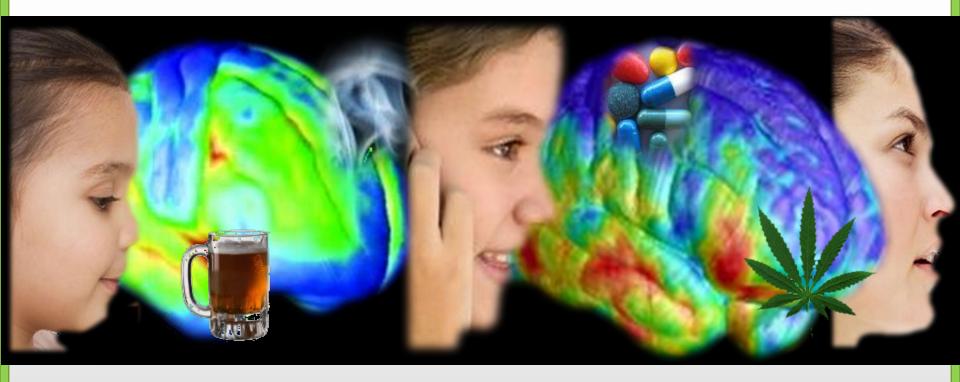
Source: Di Forti et al., Biological Psychiatry, 2012

Effect of High Potency Cannabis on Risk of Psychosis



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

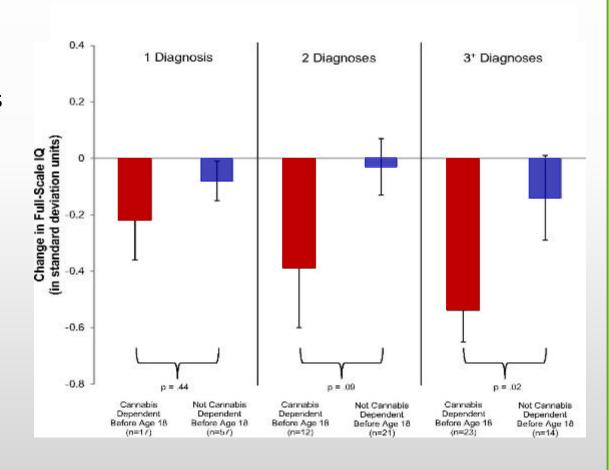
THE BRAIN CONTINUES TO MATURE INTO EARLY ADULTHOOD



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

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

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





CANNABIS USE AND DEVELOPMENT: PROBABLE FACTS

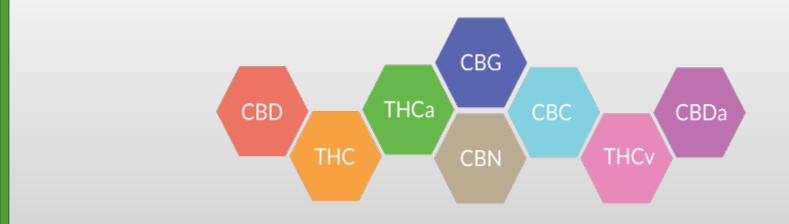


- > Some populations more vulnerable to adverse consequences than others: those exposed pre- or postnatally, adolescents, older adults (?), individuals with mental disorders
- Several cohort studies have documented modest neurodevelopmental deficits in children, adolescents, and young adults who were prenatally exposed to cannabis (multiple caveats)
- ➤In adolescents: effects on learning, IQ, motivation, long term academic and career outcomes.
 - But....heavy using adolescents often use multiple substances
 - And....we don't know whether effects persist if cannabis use is stopped

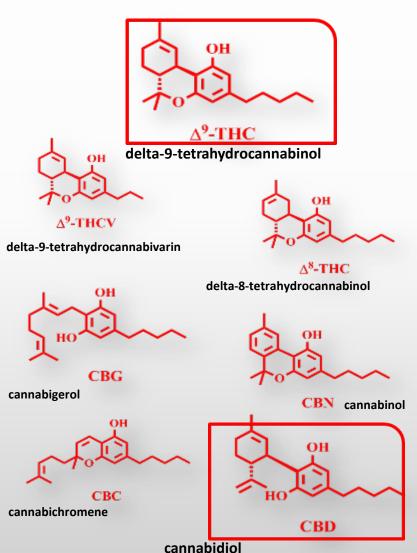
Biological plausibility:

- Cannabinoids are lipid soluble, cross the placenta and accumulate in fetal tissues, especially brain
- Also found in breast milk
- Endocannabinoid system (ECS) is important for neural development, glial differentiation, axonal migration, myelination, etc.
- Preclinical studies of prenatal or adolescent exposure show lasting effects of THC exposure on adult drug seeking behavior, stress responses, brain reward systems, which may involve epigenetic mechanisms

THERAPEUTICS: PROMISE OF CANNABIS AND THE ENDOCANNABINOID SYSTEM



CANNABIS CONTAINS ~100 CANNABINOIDS PLUS OTHER CHEMICALS IN VARYING CONCENTRATIONS



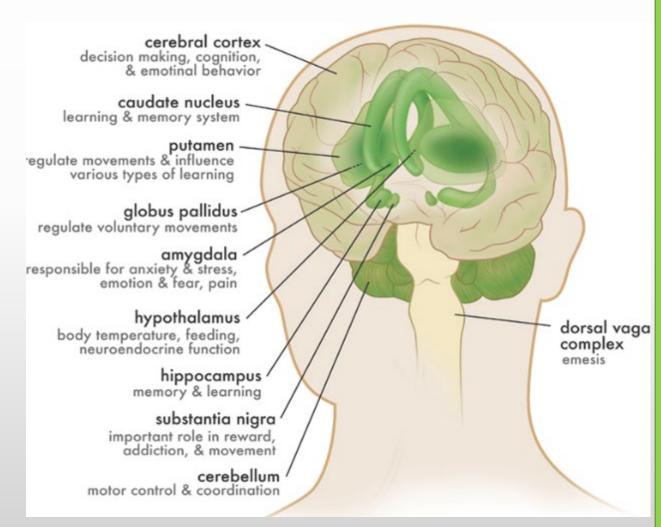
- Plant with long history of use worldwide
- Illegal under Federal law (Schedule I substance—not FDA approved)
- Legal for medical use in 31 States + D.C.
- High CBD variety (or extracts) legal in 17 states for medical use
- Versions of active ingredients approved (or in clinical trials) for medical indications in U.S.
 and other countries
 - Synthetic Marinol, Syndros, Cesamet
 - Plant Derived- Sativex (THC/CBD)
 - Plant Derived-Epidiolex (CBD: FDA-approved, waiting for Scheduling decision)



CANNABINOID RECEPTORS ARE LOCATED THROUGHOUT THE BRAIN

Regulation of:

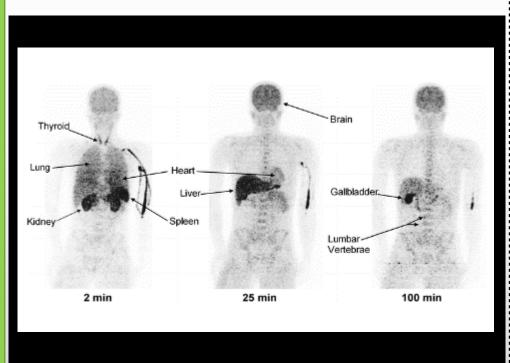
- Brain Development
- Memory and Cognition
- Movement Coordination
- Pain Regulation& Analgesia
- Immunological Function
- Appetite
- Motivational Systems& Reward



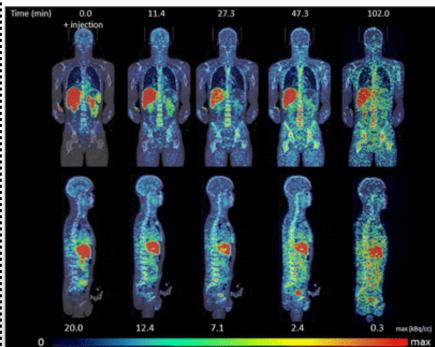
Source: Canadian Consortium for the Investigation of Cannabinoids, http://www.ccic.net/

CANNABINOID RECEPTORS ARE ALSO LOCATED THROUGHOUT THE BODY

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



Distribution of CB2 Receptors [11C]-NE40

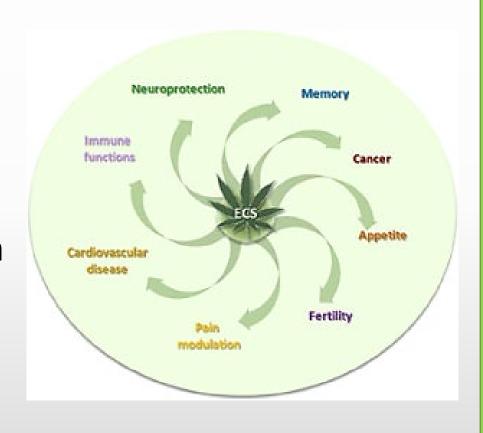


Source: Terry et al., Eur J Nucl Med Mol Imaging. 2010

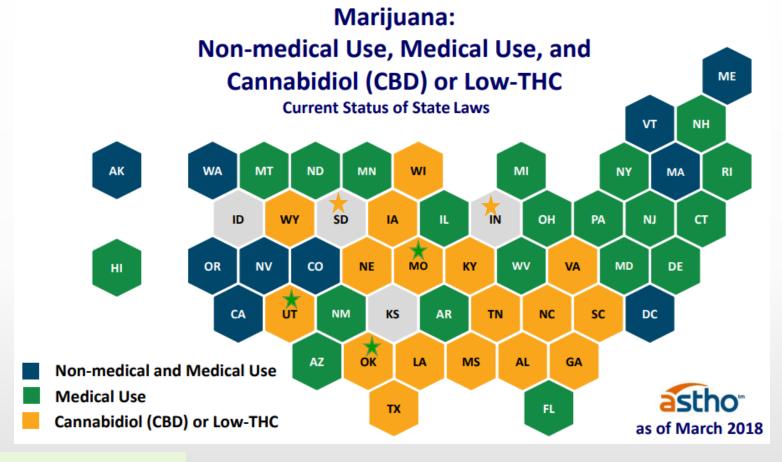
Source: Ahmad et al., Mol Imaging Biol. 2013 A

EXPLOITING THE CANNABINOID SYSTEM FOR THERAPEUTIC PURPOSES

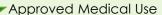
- Exogenous compounds
 - Phytocannabinoids
 - •THC, CBD, combinations
 - Synthetic cannabinoids
 - Dronabinol, Nabilone
- Endogenous manipulation
 - FAAH inhibitors
 - MAGL inhibitors
 - Allosteric modulators
- Receptor targets
 - •CB1, CB2, TRPV1, PPAR, 5-HT, peripheral, others...



CANNABIS LAWS IN THE US



Changes in 2018



- Missouri
- Oklahoma
- Utah



Approved CBD or Low-THC Use

- Indiana
- South Dakota

States with MML vary on:

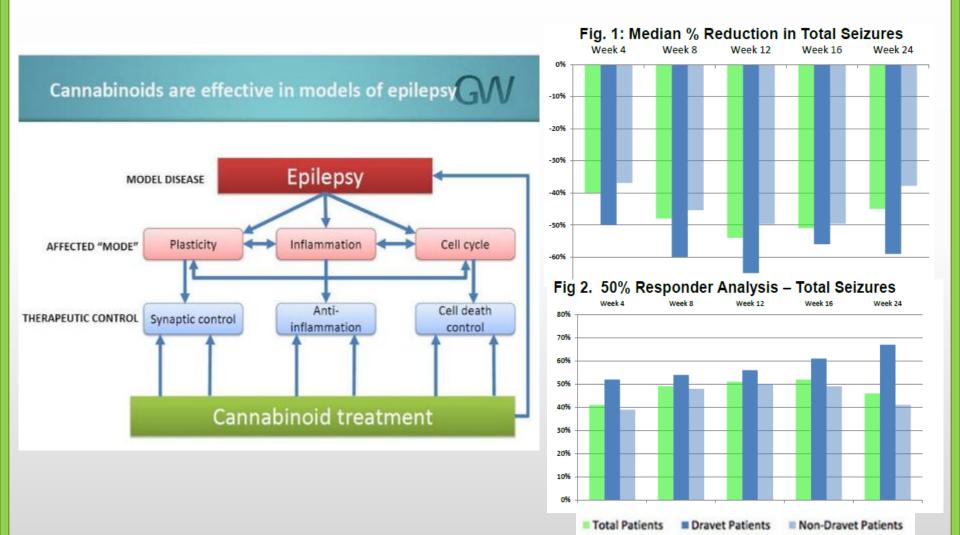
- CBD only vs. broad medical use
- Allowable conditions and routes of administration
- Dispensaries/home growth and registries
- Testing, regulatory requirements

What is Cannabidiol (CBD)?



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

Epidiolex (Cannabidiol) in Tx Resistant Epilepsy



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

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

- Acne
- ADD and ADHD
- Addiction
- AIDS
- ALS
- Alzheimer's
- Anorexia
- Antibiotic Resistance
- Anxiety
- Atherosclerosis
- Arthritis
- Asthma
- Autism
- Bipolar
- Cancer
- Multiple Sclerosis (MS) Migraine

- Digestive Issues
- Depression
- Diabetes
- Endocrine Disorders
- Epilepsy and Seizures
- Fibromyalgia
- Glaucoma
- Heart Disease
- Huntington's Disease
- Inflammation
- Irritable Bowel Syndrome
- Kidney Disease
- Liver Disease
- Metabolic Syndrome

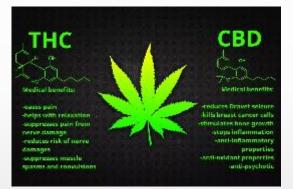
- Mood Disorders
- Neurodegeneration
- Motion Sickness
- Nausea
- Chronic Pain
- Obesity
- OCD
- Osteoporosis/Bone Health
- Parkinson's Disease
- Prion/Mad Cow disease
- PTSD
- Rheumatism
- Schizophrenia
- Sickle Cell Anemia

- Skin Conditions
- Sleep Disorders
- Spinal Cord Injury
- Stress
- Stroke and TBI



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

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



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

Strength of the Evidence For Marijuana/Cannabinoid Medical Applications

Some human Evidence

Preclinical Evidence

Weakest Evidence

- Nausea (Cancer chemotherapy)
- Spasticity and Pain (MS)
- Appetite Stimulant (AIDS-associated wasting)
- Pain esp. neuropathic
- Anticonvulsant (CBD)
- Glaucoma
 (decreases intraocular pressure; no evidence it slows disease progression; and short acting)

- Anti-inflammatory (CBD)
- Antitumor (THC/CBD)

 (animal models/cell cultures: glioblastoma; breast cancer cells; others (mechanisms: apoptosis; inhibition of tumor angiogenesis)
- PTSD
- ADHD
- Alzheimer's
- Depression



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

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

0 10.1007/s11481-015-9600-6

NVITED REVIEW

Cannabinoids for the Treatment of Chr An Updated Systematic Review of Rand

Received: 29 January 2015 / Accepted: 5 March 2015 / Published ordine: 22 March 2015

Abstract An updated systematic review of randomized controlled trials examining cannobinoids in the treatment of chronic non-career pain was conducted according to PRIS MA 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 significent analysise 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 careabinoids are safe, modestly effective analysiscs 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

- M. H. Lynch mary.lynchistdal.ca
- Departments of Anaschesiology, Pain Medicine and Penoperative Care, Psychiatry and Pharmacology Dulhousic University. Halifax, Nova Scotia, Carada
- Departments of Anesthesia and Family Medicine, McGill University

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Objective To determine if medical marij and to determine the therapeutic dose, as

Data sources in April 2014, MEDLINE pain, smoked marijuana or cannabinoids,

Study selection An article was selected (nonsynthetic) for CNCP; it was design or historically; and it was published in adverse effects were collected, if availa

Synthesis A total of 6 randomized assessed the use of medical marijuan adjunct to other concomitant analog anticonvulsants. The 5 trials were con however, all of them had challenges be pooled owing to heterogeneity in potency by dried weight, differing treatment, and variability in assessin sessions in the studies were of s

> "There is evide medical n neuropathic

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dical marijuana for patie

"There is substantial evidence that cannabis is an effective treatment for chronic pain in adults."

- Conclusion 4-1; National Academies of Sciences, Engineering, and Medicine. 2017.

c Pain and a Cannabinoids for Medical Use The National Academies of SCIENCES ENGINEERING MEDICINE The Health Effects of Cannabis and Cannabinoids CURRENT STATE OF EVIDENCE AND RECOMMENDATIONS FOR RESEARCH

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

IMPORTANCE Cannabis and cannabinoid drugs are widely used to treat disease of symptoms, but their efficacy for specific indications is not clear. CRIECTIVE TO conduct a systematic review of the benefits and adverse events (As not refle cability to DATA SOURCES Tweenty-eight databases from inception to April 2015. se cernel RELECTION Randomized clinical trials of cannabinoids for the following indicate and veen age due to chemotherapy, appetite stimulation in HIVAIDS, chronic due to multiple scienosis or paraplegia, depression, anxiety disorder, sleep de exists ACTION AND SYNTHESIS Study quality was assessed using the Cochrane risk of low stages were conducted independently by 2 reviewers. Where possible, da les AND MEASURES Patient-relevant/kisease-specific outcomes, activities of any 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 bass. Most trace shower improvement in symptoms associated with compared with placebo. associators did not reach statistical algorithms in an ariast. Compared with praceto, Canabinoids were associated with a greater were ge number of patients showing a complete. Consideration were assistance with a greater average manner or parameter streaming account national and vernifing response (47% vs 20%; odds ratio [08], 3.82 [95% CL 155-942]; and the constant average manner of the co Autoes and vorming response (4/7% vs. 2076; 0005 (800 1004), 3.82 (9276-11.120-944).

3 trais), reduction in pain (37% vs. 31%; 0R, 1.41 [95% CI, 0.99-2.00]; 8 trais), a greater 3 trans, resuction in pain (3/70 vs 3/76; On, 14/1/3/70 Lt, U/3/7/LVU); a trans, a granter average reduction in numerical rating scale pain assessment (on a 0-80-point scale; were considered to the constant of the constant mean difference (WMD), -0.46 [95% Ct. -0.80 to -0.0]; 6 trials), and a

A Systematic Review and Meta-analys

Perny F, Whiting, PhD; Robert F, Wolff, MD; Sohan Deshponde, MSC; Marcelo DI/Neile PhD; Automorate Agn, Blanc, J Production for Committee SAN, Oct., Champion of Champions of

Penny F. Whiting, PriD; Robert F. Wolt, Mily Sorial Destruction Mich. Marcell Uniforce, PriD; Addish V. Hernandez, MD, PhD; J. Christiani Restrotties, MD, PhD; Shono Lang, PhD; Kate M. Gaussiani, Gallery, MC, Canada, C. Landelle, MC, Marcell Montaness (1991), No. District. MC, PhD; Shono Lang, PhD; Kate M. Gallery, MC, PhD; Marcelle, MC, PhD; Mc, PhD

Adrian V. Hernandez, MD, PhD: J. Christiaan Neurontjes, MD, PhD; Shona Larg, PhD; Rate M Saeve Ryder, MSc; Simone Schmid Boder, MSc; Marie Westwood, PhD; Jos Kleijner, MD, PhD

There was moderate-quality cannabinoids for the treatment of - P.F. Whiting et al; JAMA 2015

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





States with MML/ Dispensaries report:

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

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

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



AMA Evidence Missing for Cannabis as Medication

Cannabis research is low quality

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

Cannabis for pain

- Low-strength evidence that cannabis alleviates neuropathic pain
- Insufficient evidence that cannabis alleviates other types of pain

Cannabis to treat opioid addiction

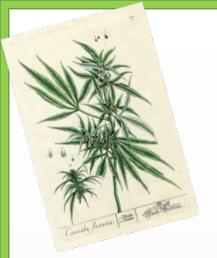
- No prospective evidence to demonstrate any benefit
- Substituting cannabis for methadone or buprenorphine may increase risks
- **31%** of people reporting any past-year cannabis use meet criteria for cannabis use disorder





MEDICAL CANNABIS USE: WHAT DO WE NEED TO KNOW?

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



CANNABIS RESEARCH BARRIERS

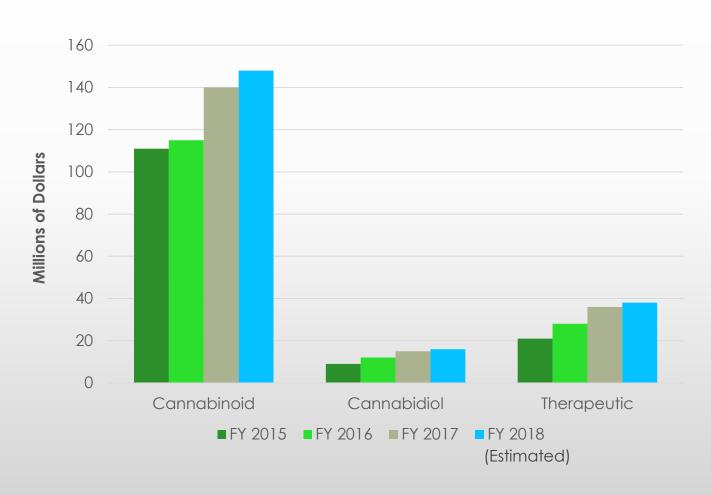
ADMINISTRATIVE

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

SCIENTIFIC

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

NIH Spending on Cannabis Research



- NIH tracks research area expenditures year-by-year
- > 285 categories reported online
 - https://report.nih.gov/categorical_spending.aspx
 - Standardized categories defined by NIH experts
 - Individual projects may be included in multiple research categories

> Primary categories related to cannabis

- Cannabinoid Research
 - Therapeutic Cannabinoid Research
 - Cannabidiol Research
 - Endocannabinoid Research



Research, Condition, and Disease Categorization

Cannabinoid Research – FY17 \$140M

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



Research, Condition, and Disease Categorization

Research Therapeutic Cannabinoid

Therapeutic Cannabinoid Research - FY17 \$36M



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

Cannabidiol (CBD) – FY17 \$15M

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

Endocannabinoid System – FY17 \$63 M

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

FY 2017 NIH Grants on Cannabis Research

