Overview of Recreational & Medical Marijuana

Ethical, Scientific &Legal Issues Across the Lifespan

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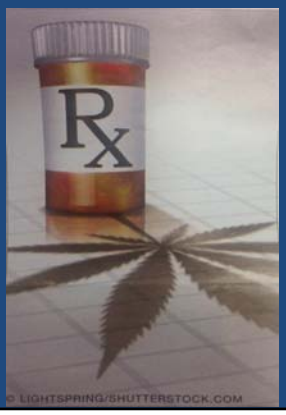
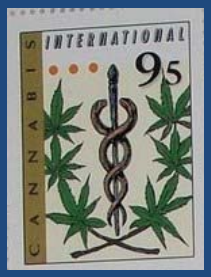
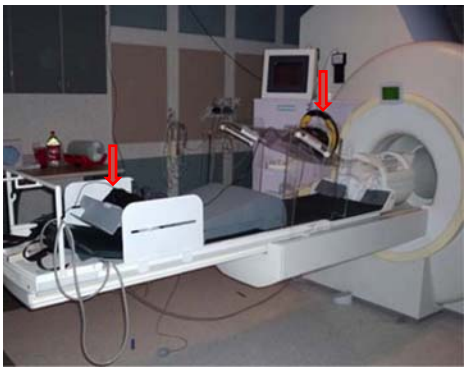




COI's

- NIDA- R01 Neuroscience of marijuana-intoxicated driving.



Outline of Today's Talk

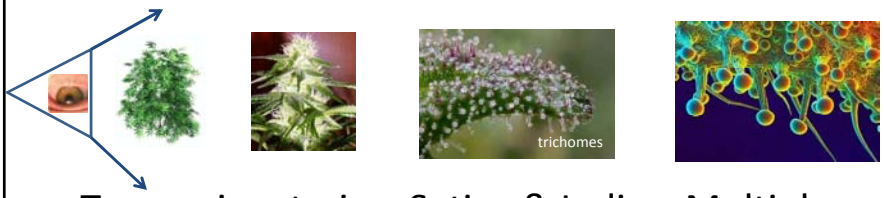
- Botany
- Sociology
- Pharmacology
- Drug administration
- Tissue levels/biomarkers
- Epidemiology
- Agriculture/agribusiness
- Economics
- Adverse effects
- Medical marijuana
- Marijuana legislation
- Summary, questions, dialogue

BOTANY

Phytocannabinoids vs Endocannabinoids

- 'Phytocannabinoids' refers to cannabinoids derived from the cannabis plant
- 'Endocannabinoids' are endogenous compounds that activate the human cannabinoid receptors

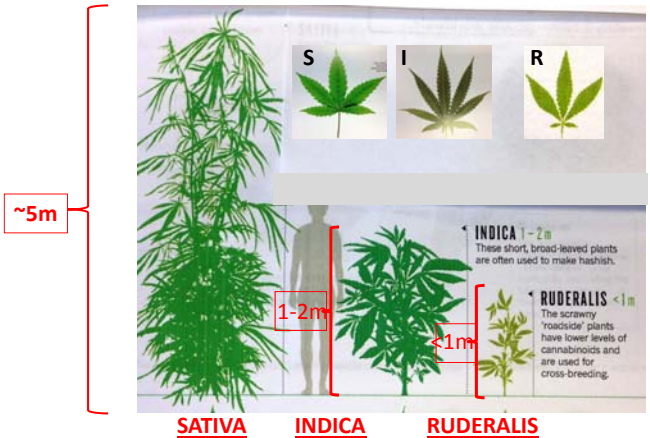
Basic Background



- Two major strains; Sativa & Indica. Multiple hybrids.
- Active chemicals mainly in resin, primarily produced by leaves & buds of female cannabis plant
- Plant Contains >500 other chemicals, including 70 to >100 THC relatives called 'cannabinoids'.

Various MJ Strains Exist

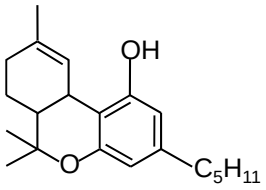
No consensus on taxonomy



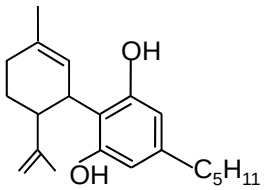
Tall, branched, ~5m
Common strain for all uses

Plant-Derived Cannabinoids (N=70) (Phytocannabinoids)

- **Δ^9-tetrahydrocannabinol-type (9)**
- D^8-tetrahydrocannabinol-type (2)
- **Cannabidiol-type (7)**
- Cannabigerol-type (7)
- Cannabichromene-type (5)
- Cannabicyclol-type (3)
- Cannabielsoin-type (5)
- Cannabitriol-type (9)
- Miscellaneous-type (14)
- Cannabinol-type (7)
- Cannabinodiol-type (2)

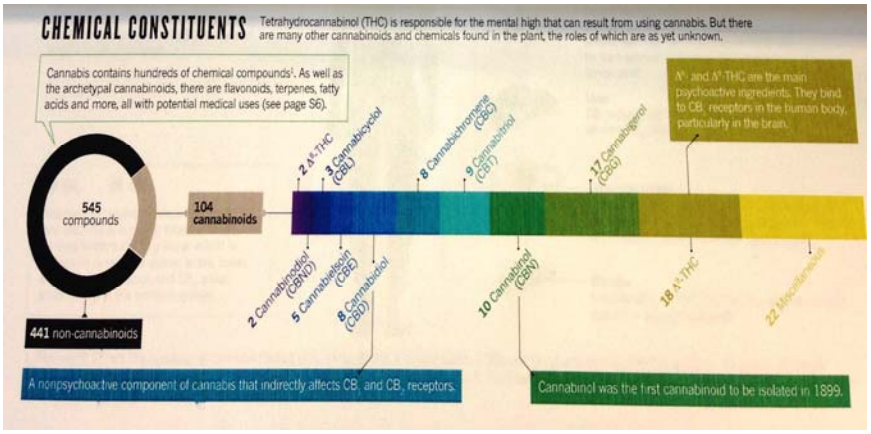


Δ^9-THC

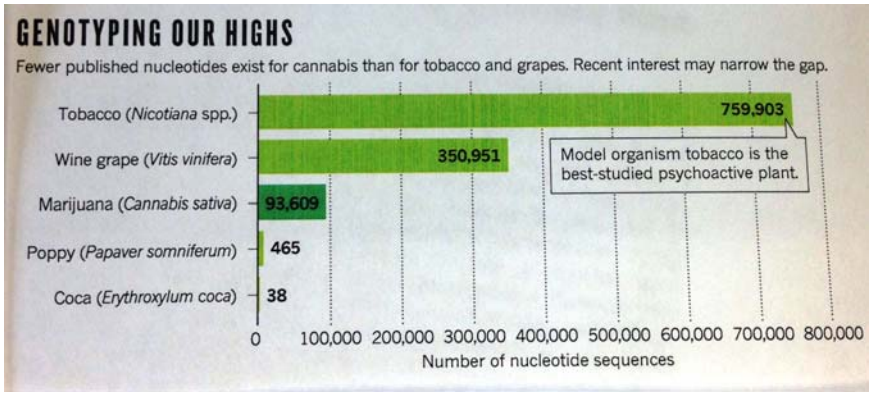


Cannabidiol

Chemical Constituents of MJ



Plant Genotypes

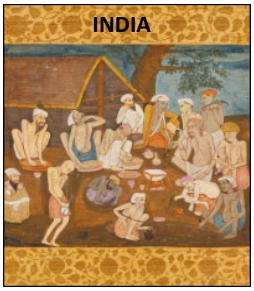


SOCIOLOGY

Cannabis

- First recorded use for medicinal purposes 2737 BC in China.
- 1851-US Pharmacopeia classified MJ as a legitimate medical compound.
- Effectively criminalized in the US in 1937, against the advice of the AMA; removed from USP in 1942.
- Social use- “Reefer Madness” 1910>.
- Currently classified as a schedule 1 substance by the FDA: very difficult to obtain permission to study (NIDA, DEA, FDA).
- Ronald Reagan’s “war on drugs”. Since 1990, primary focus has shifted to low-level MJ offenses, constituting 82% of the increase in drug arrests. Most dismissed or adjudicated misdemeanors, cost ~$4 billion per year.
- IOM study 1999 – recommends that cannabinoids may have a role in the treatment of pain, movement and memory disorders, but risks are associated with use. Major recommendations – evaluate physiologic and psychological effects, individual health risks and various delivery systems, as well as short-term (<6m) clinical trials to determine effectiveness for targeted medical conditions.
- 2015 Nora Volkow, NIDA Director, reported to Senate caucus on international narcotics control re: cannabidiol.

Culturally Normative Recreational Use



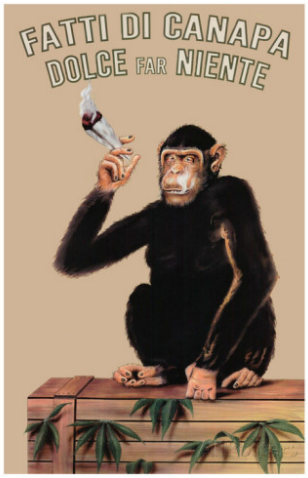
Culturally Normative Religious Use

Legal Status

Mexican Revolution 1910.

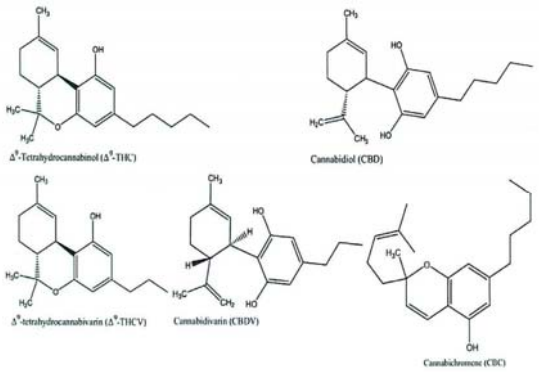
- Stream of refugees enter SW US.
- Introduce American public to recreational use of cannabis.
- Anti-immigrant sentiment links marijuana with crime.

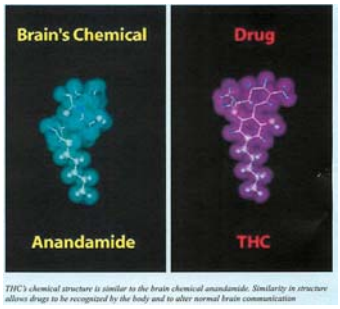
PHARMACOLOGY



Cannabinoid Molecular Structures

Endogenous cannabinoid system, with its own receptors and ligands



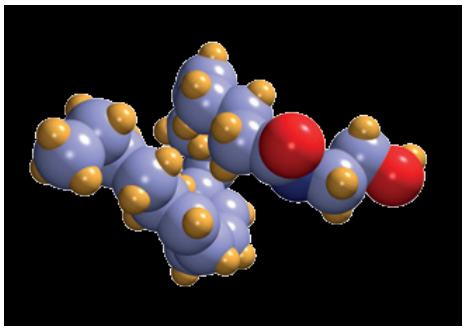


THC is a partial agonist, HU-210 (synthetic cannabinoid) is a full agonist,
Cannabidiol is an inverse agonist, rimonabant is a synthetic antagonist.
CBD has 100-fold less affinity than THC for CB1 receptors.
Activation of CB1 & CB2 acts indirectly on multiple other neurotransmitters, including ACh, DA and glutamate, while indirectly affecting NMDA, opioid and 5HT receptors.

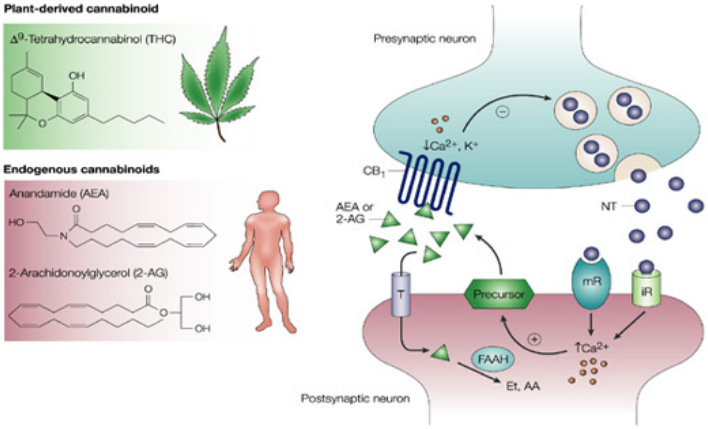
Endogenous Cannabinoid (Endocannabinoid) System

- CB1 versus CB2 receptors
- Anandamide etc. function as CNS neurotransmitters and influence synapse formation in early brain development & continues to evolve during adolescence.
- Includes axon elongation, neurogenesis, neural maturation, glial formation, neuronal migration and synaptic pruning.
- Neural communication networks using these neuro-transmitters (endocannabinoid system) critical in adult CNS normal functioning,
- Exposure to exo-cannabinoids e.g., THC activates the system in a prolonged non-physiological manner.
- Likely other multiple MJ effects outside of Endo-CB system, e.g. anti-inflammatory activity via prostaglandin synthesis inhibition, action on the vanilloid receptors

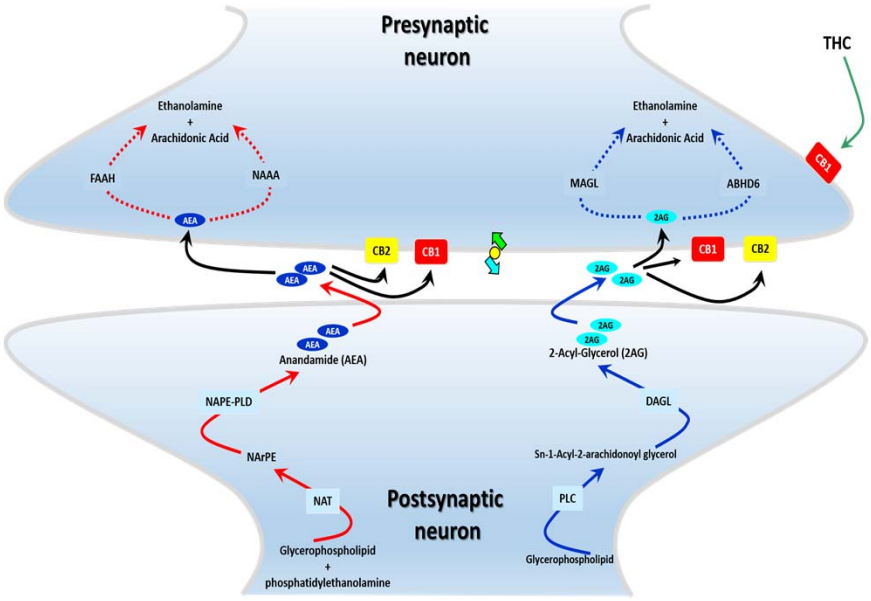
Raphael Mechoulam & Anandamide



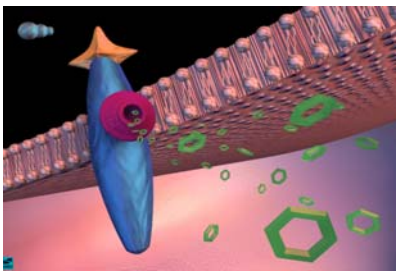
Cannabinoid System



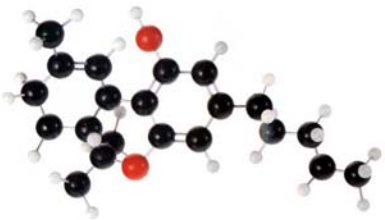
Cannabinoid system contributes to brain equilibrium (response to stress, inflammation)

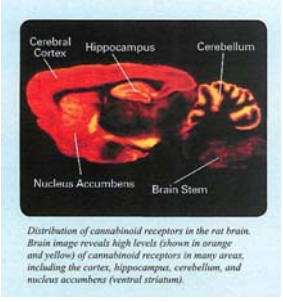


How Does MJ Produce its Effects?

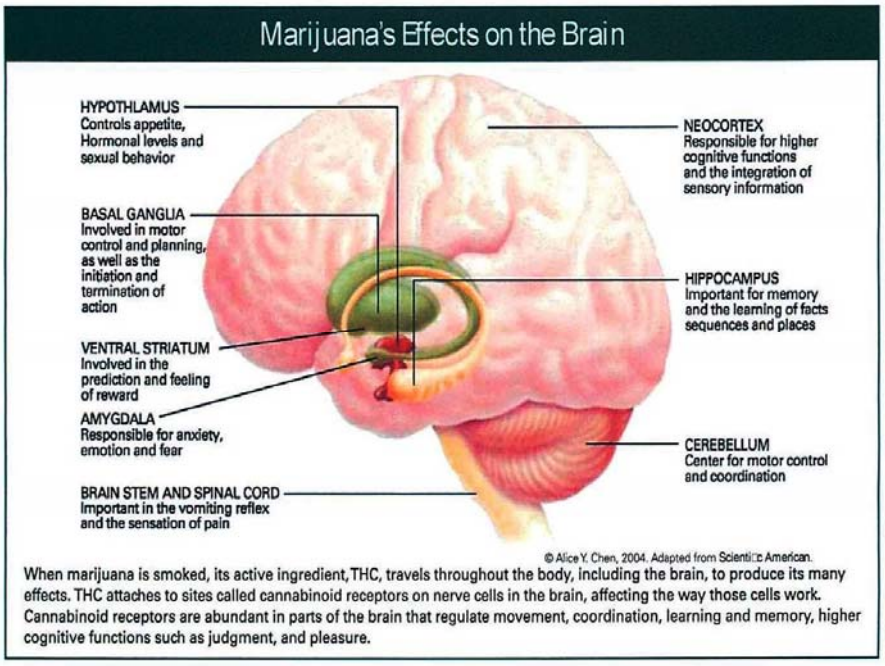


CB1 in PAG/dorsal horn- pain system. MJ acts on capsaicin responsive GCPRs.

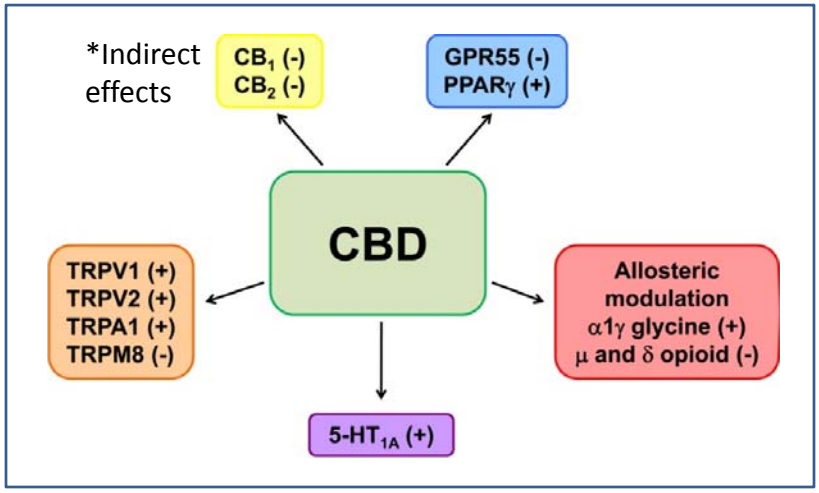




Distribution of cannabinoid receptors in the rat brain. Brain image reveals high levels (shown in orange and yellow) of cannabinoid receptors in many areas, including the cortex, hippocampus, cerebellum, and nucleus accumbens (ventral striatum).



Cannabidiol (CBD) additional pharmacologic activity



Campos et al, 2012; McPartland et al, 2015; Ibeas et al, 2015

Recreational Doses

- Typical joint = 0.5-1.0 gm; low THC dose 7mg, medium 7-18, high >18mg.
- THC is highly lipophilic. Half-life of distribution phase is 0.5 hrs; terminal phase variable with mean of 30 hrs for THC and 9 for CBD.

Typical Effects of Recreational MJ Use

Primarily THC-mediated

- Pleasant euphoria, sense of relaxation.
- Heightened sensory perception (e.g. brighter colors), synesthesia.
- Laughter, disinhibition.
- Altered time perception.
- Increased appetite.
- Tachycardia, postural hypotension, vasodilatation, red conjunctivae.
- Dose-dependent delirium, (esp. oral administration).
- Less often, anxiety, fear, distrust, panic attacks.
- No LD

DRUG ADMINISTRATION

Common Cannabis Preparations

Preparations	Description
Marijuana[a]	Dried plant product consisting of leaves, stems, and flowers; typically smoked or vaporized
Hashish	Concentrated resin cake that can be ingested or smoked
Tincture[a]	Cannabinoid liquid extracted from plant; consumed sublingually
Hashish oil	Oil obtained from cannabis plant by solvent extraction; usually smoked or inhaled; butane hash oil (sometimes referred to as "dabs"), for example
Infusion[a]	Plant material mixed with nonvolatile solvents such as butter or cooking oil and ingested

[a] These preparations are available from state-approved medical marijuana dispensaries.

Concentrates/“Dabbing”

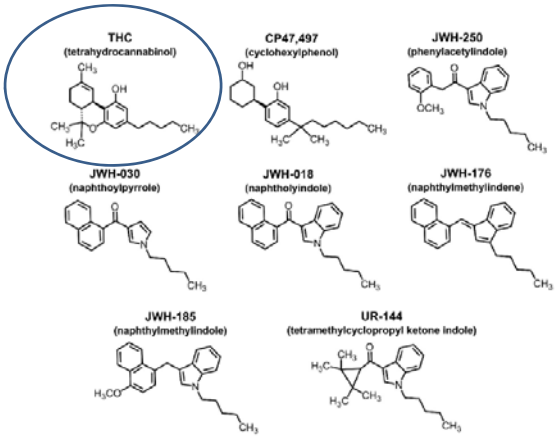
Synthetic Cannabinoids (Spice, K2)

- First synthesized in 1980s as laboratory tools– ligands for studying cannabinoid system
- First reported in US in November 2008
- Chemical structure frequently changing to avoid detection & identification as illegal substance

Synthetics

One step ahead of the law. Constantly changing
Consequence of legal status of MJ?
Often full CB1 agonists
Marked psychiatric morbidity
Cheap and readily available
ED visits, deaths

Chemical structures of synthetic cannabinoids



Baumann et al, J Neuroscience 2014

Why are synthetic cannabinoids toxic?

Compared to Cannabis & THC:

1. Higher affinity for CB1 receptors
2. Greater activity (full vs. partial agonist)
3. Longer duration (active metabolites)
4. Lack cannabidiol
5. Other, unidentified pharmacologic effects

Cannabinoid binding affinities for CB1 and CB2 activity

Compound	Ki CB_1 (nM)	Ki CB_2 (nM)	Ki CB_1/Ki CB_2	Properties
Endocannabinoids				
2-AG	472[b]	1400[c]	0.34	Mixed agonist
Anandamide	61[b]–543[b,c]	145[a]–1940[a,c]	1.17–11.5	Mixed agonist
Plant cannabinoids				
Cannabidiol	4350[a,b]–27.542[c]	2860[c]–10.000[c]	1.20–3.75	Mixed agonist
Δ^9-THC	5.05[b,c]–80.3[b]	3.13[b]–75.3[c]	0.71–9.05	Mixed agonist
Synthetic cannabinoids				
HU-210	0.06[b,c]–0.73[c]	0.17–0.52[c]	0.11–3.31	Mixed agonist
CP55940	0.5–5.0[b,c]	0.69–2.80[b,c]	0.18–2.78	Mixed agonist
WIN55,212-1	1.89[b,c]–123[c]	0.28[b,c]–16.2[b]	0.6–30	Mixed agonist
JWH-015	383[c]	13.8[c]	27.8	CB_2 agonist
JWH-133	677[b]	3.4[c]	199	CB_2 agonist
O-1966	5055 ± 984[d]	23 ± 2.1[d]	220	CB_2 agonist
HU-308	>10.000[b]	22.7[c]	441	CB_2 agonist
SR144528	50.3–10.000[b,c]	0.28–5.6[b,c]	728–1786	CB_2 antagonist
AM-630	5152[c]	31.2[c]	165	CB_2 inverse agonist
JTE 907	1,060+–90.0[a]	1.55+–0.09[a]	684	CB_2 inverse agonist
Methanandamide	17.9–20[b]	815–868[c]	0.021–0.025	CB_1 agonist
ACEA	1.4[b]	>2000[b]	<0.001	CB_1 agonist
Rimonabant/SR141716	1.98–12.3[b,c]	702–13.200[b,c]	0.001–0.017	CB_1 inverse agonist

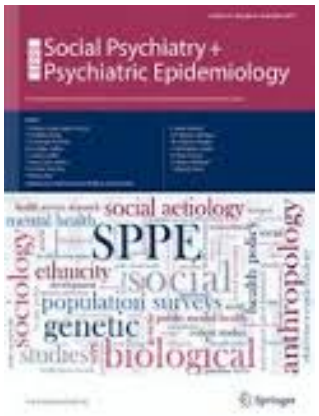
Vendel et al, Neuromol Med 2014

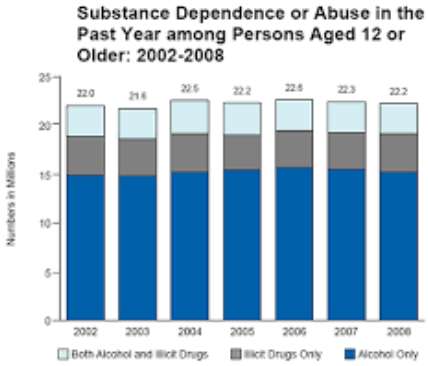
PHYSIOLOGIC LEVELS

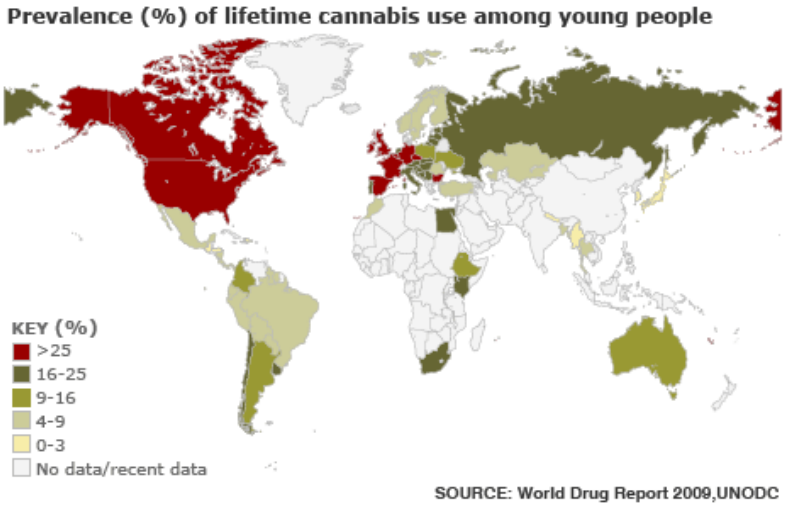
THC & Metabolites

- THC is lipophilic and levels rapidly diminish in blood.
- Can leach out of fat stores, and a positive test does not necessarily indicate recent use in chronic users.
- Carboxy-THC is 1/1000th of the concentration of THC in oral fluid .
- Presence of carboxy-THC indicates that subject has been actually smoking MJ, and this is not due to exposure to secondhand smoke.
- See high concentrations in regular smokers.
- No reliable measures of recent consumption that correlate with current intoxication reliably in both occasional and chronic users.

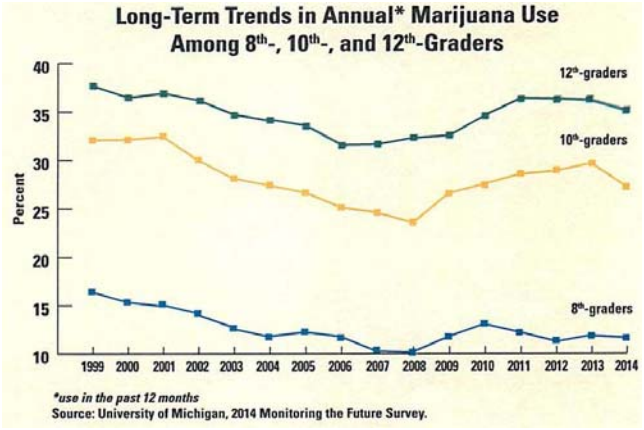
EPIDEMIOLOGY







High School Use



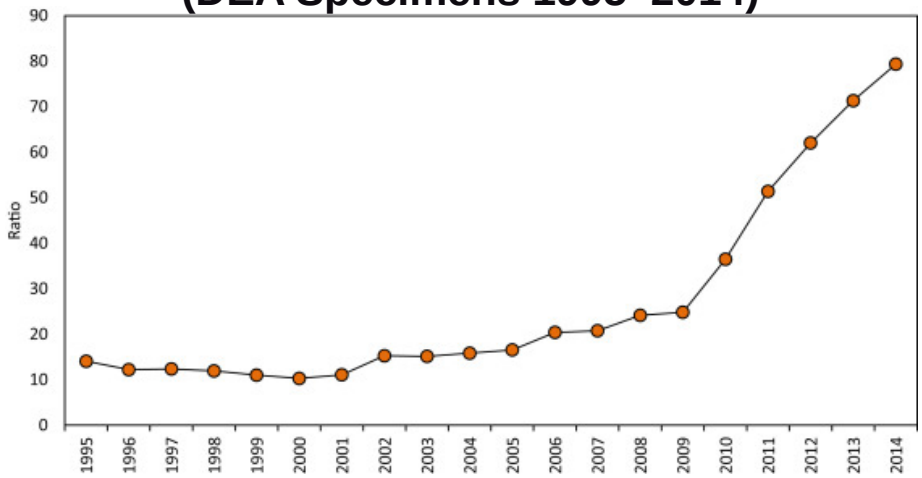
Use rates holding steady.
Teen perception of marijuana risk declined steadily over the past decade.
Among 12th-graders, 35% used in prior year, 21% current users, 6% used daily

AGRICULTURE/AGRIBUSINESS

Changes Since the 1960s

More varieties, much higher THC %, less CBD
A triumph of selective breeding

THC:CBD Ratio Continues to Change (DEA Specimens 1995–2014)



D. C. D'Souza

Mahmoud A. ElSohly, et al., 2016

Commercial Growing Operations

Both legal and illegal

Dispensaries

"BUDTENDERS"

Maybe a "catch-all" term to cover medical marijuana dispensary, plus a marijuana store for recreational use, as in Colorado, but not CT

ECONOMICS

"Cannabiz"

Cannabis Economics

- **$300 billion**. Estimated global value of cannabis crops by gross production value in 2014.
- **$35.8 billion**. Value of the US cannabis trade in 2006.
- **$6.5 million**. Monthly tax revenue collected by Colorado from legal cannabis sales. (Estimated $10 million/month in 2015)
- **$47.6 million**. Estimated value of cannabis per square kilometer.

Figures from Newsweek special edition, September 2015

Update on Colorado

Economics of cannabis

- Legal marijuana tax revenues are breaking records this summer, nearly doubling monthly numbers from 2014 and on pace to exceed projections of legal sales that bring revenue to the state.
- Through the first 7 months of 2015, Colorado has brought in nearly $73.5m, putting the state on pace to collect over $125m for the year.
- Sales totals fell short of projections in 2014, the first year of legalized recreational sales in the state (and the nation) But this year, tax revenue from marijuana sales exceeds initial projections of $70m.
- Many in the marijuana industry attribute the sales boom to a tipping point in social acceptance.
- "I attribute it to ... more and more people ... comfortable with the legalization of marijuana," said Tyler Henson, president of the Colorado Cannabis Chamber of Commerce. "They don't see it as something that's bad for them."
- Tim Cullen, CEO of Colorado Harvest Company, said: "People who would never have considered pot before are now popping their heads in." He noted that in his stores, where customers are primarily Colorado residents purchasing recreational marijuana, sales have been averaging 8% -12% growth month-over-month for much of this year.
- Support for marijuana legalization has grown in Colorado since voters approved Amendment 64 by a 10-point margin in November 2012. A poll from Quinnipiac University this February found that 58% of Coloradans support keeping cannabis legal, compared to just 38% who oppose the idea.

Commercial Distribution

Tobacco and other companies looking for potentially large new markets with legalization

ADVERSE EFFECTS

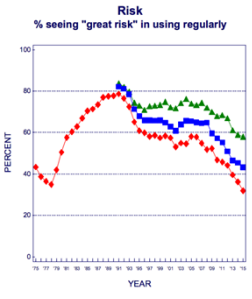
- Brain structure and function
- Medical adverse effects
- Psychological adverse effects, incl. dependence, psychosis
- Motor vehicle driving
- College and occupational performance

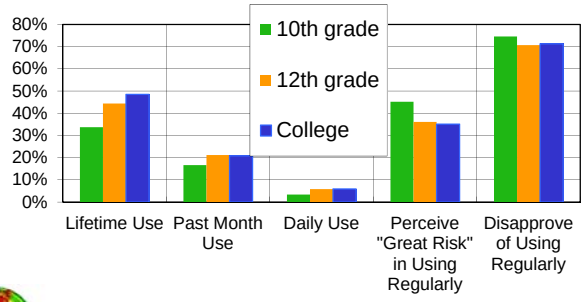
Potential Adverse Cannabis Effects

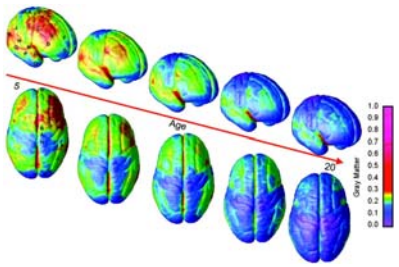
Potential adverse effects of marijuana[a]

Addiction (physiologic)
Withdrawal syndrome
Dependence (psychological) and with heavy use, tolerance
Variety of negative psychological reactions: anxiety, hallucinations, violent behavior, depression, fear
Overt precipitation of psychosis or depression
Insomnia (can be chronic and improved with trazodone)
Memory spans that are impaired
Blunted reflexes
Flu-like reaction (after stopping this drug after 24–60 h, lasting up to 2 weeks)
Confusion and cognition impairment
Alteration of time perception
Amotivational syndrome (lose interest in school or work success)
Physiologic responses can include cough, bronchospasm, bronchitis
Amenorrhea
Immunologic dysfunction

Adolescence



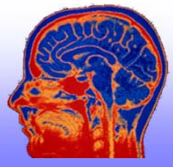




Disentangling cause from effect

IMAGEN: A longitudinal study of teenage drug use

Neuroimaging of cognitive control (STOP task), reward (Monetary Incentive Delay task), and social processing (angry faces) and brain structure in 14-year olds.



PI: Gunter Schumann
(Institute of Psychiatry, London)

Approx. 3,000 variables on drug use, personality, clinical symptoms, cognitive abilities …

Genetic data: SNPs; gene expression; methylation; CNVs.

Sample is >2,000 14-yr olds.

Age 16: Phone/Web assessments (drug use; mental health).
Age 18/19: Full imaging battery, genotyping and phenotyping.

Adolescent Brain Cognitive Development Study (ABCD)

- 10,000 kids aged 9-10.
- Followed for ten years.
- Extensive neuroimaging, genotyping and psychometrics.
- Data publicly available.

Cognition: Acute vs Chronic Effects

Executive Function Measured	Acute Effects	Residual Effects	Long-Term Effects
Attention/Concentration	Impaired (light users) Normal (heavy users)	Mixed findings	Largely normal
Decision Making & Risk Taking	Mixed findings	Impaired	Impaired
Inhibition/Impulsivity	Impaired	Mixed findings	Mixed findings
Working Memory	Impaired	Normal	Normal
Verbal Fluency	Normal	Mixed findings	Mixed findings

Acute Effects: 0–6 hours after last cannabis use;
Residual Effects: 7 hours to 20 days after last cannabis use;
Long-Term Effects: 3 weeks or longer after last cannabis use

Cannabis and Cognitive Decrements.

- Hotly debated topic.
- IQ drop seen most clearly in those who begin using marijuana < age 15 and continue through 20s and 30s.
- More profound effects on still-developing brain?
- NZ epi study found frequent/persistent MJ use starting in adolescence associated with loss of average eight IQ points measured in mid-adulthood (Caspi, 2012 PNAS).
- MJ smoking students have poorer educational outcomes than non-smoking peers.
- Forthcoming NIDA longitudinal ABCD study will separate predisposing causes from effects of substance abuse in childhood/adolescence

Pulmonary Effects

- From smoked marijuana, but dependent on <u>what</u> was smoked (e.g. MJ plant material <u>+</u> tobacco, cannabis resin),and <u>how</u> it was consumed, e.g. 'blunt' vs vaporizer.
- Chronic cannabis smoking associated with cell changes, cough, wheezing, bronchitis and phlegm production.
- Broncho-dilatation with acute use; long-term heavy smoking <u>may</u> lead to increased obstruction and/or decreased lung function.

Adverse Effects – Lung, G.I., Reproductive and Immune

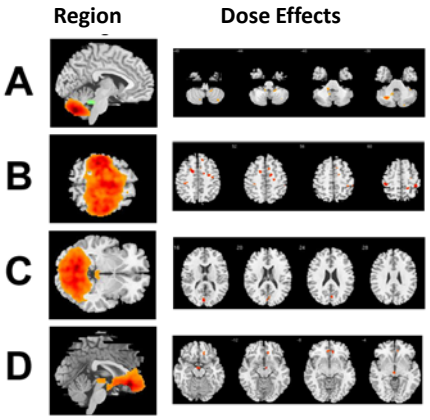
Table 3.—Adverse effects Reported With Use of Cannabis and Cannabinoids on Respiratory, Gastrointestinal, Reproductive, and Immune Systems

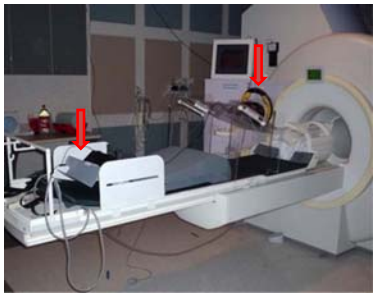
Respiratory System	Adverse Effects Reported
Carcinogenesis	Cannabis smoke contains many similar chemicals as tobacco smoke, and cannabis smoke condensates may be more cytotoxic and mutagenic then tobacco smoke condensates,[137,661,662] although evidence linking cancer and cannabis smoke are conflicting and inconclusive[137,663-666]
Inflammation	Chronic cannabis smoking associated with histopathologic changes, cough, wheezing, bronchitis, and phlegm production[137,667-671]
Bronchial tone	Acute use of smoked cannabis causes bronchodilatation,[667,672-674] but long term heavy smoking may lead to increased obstruction and decreased lung function[137,667,670,671,675,676]
Gastrointestinal System	**Adverse Effects Reported**
General	Decreased secretion, decreased motility and gastric/colonic emptying, anti-inflammatory[137,312-315,535]
Pancreas	Pancreatitis has been reported with heavy acute and chronic daily use[137,677-680]
Liver	Possible increased risk of hepatic fibrosis/steatosis, particularly in patients with hepatitis C[137,681-686]
Reproductive System	**Adverse Effects Reported**
Females	Inconclusive and unclear as most data are from animal studies; dose-dependent stimulatory or inhibitory effects on sexual behavior,[137,687] possible ovulation suppression and menstrual cycle changes[137,688-690]
Males	Inconclusive as most data are from animal studies with limited human studies. With chronic and daily use, possibly decreased sperm count, morphology, and motility, anti-androgenic,[137,490,689,691-693] possible inhibitory sexual effects[220,304]
Immune System	**Adverse Effects Reported**
General	Complex and unclear with both suppressive and stimulatory actions reported[137,574,694,695]

Does Marijuana Use Affect Driving?

- Risk of an MVA probably doubles after acute use
- Time course unknown – when are we safe following acute use?
- THC/metabolite levels in blood and saliva not yet helpful, due to rapid peaking and diminution.
- THC sequestered in fat tissue and slowly released – may be detectable for days to weeks after regular acute intoxication.
- Interaction effects of alcohol poorly studied – possibly interactive, but behavioral effects of intoxication vary between the two drugs.

Simulated Driving in the MRI





NHTSA Plans

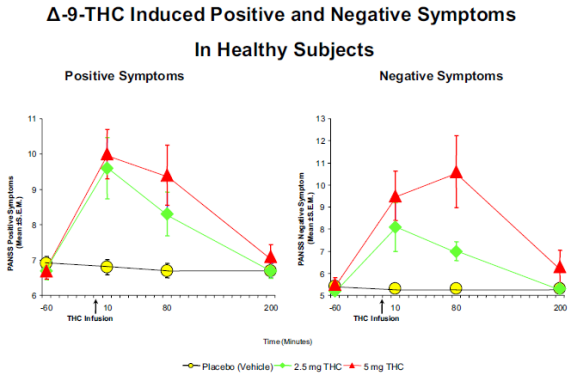
- Roadside sobriety testing.
- Alcohol/marijuana combinations.
- Relationship to blood and oral fluid THC and metabolite levels.
- Time courses.

Cannabis and Psychosis

Cannabis and Psychosis.

- Increasing prevalence? “Skunk” - cannabis strains bred for increased THC (and therefore lowered cannabidiol) content.
- THC % rises from ~3.7 to ~9.6. “Dabbing” of THC-rich products delivers very high levels to users.
- Changing ratio of THC to cannabidiol.
- Is cannabidiol an effective antipsychotic? (current clinical trials underway).
- Short-lived paranoia vs more chronic schizophrenia-like illnesses.
- Adolescence and young-adults seem at highest risk.
- Robin Murray’s studies in London, UK.
- Dunedin NZ study- increasing schizophrenia risk epidemiologically related to COMT genotype.
- Etiological mechanism unclear- possibly dopamine-related per studies of AKT1 and COMT.
- Less consistent associations with depression, anxiety, suicidal thoughts and amotivation

THC produces positive and negative symptoms in healthy subjects



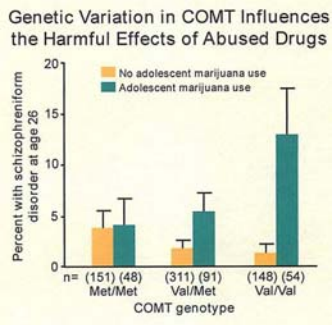
Radhakrishnan et al, Frontiers in Psychiatry 2014

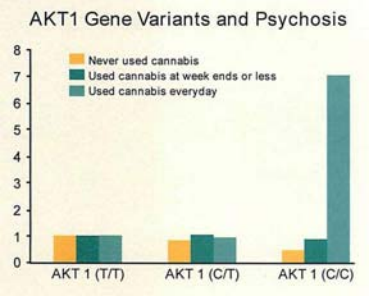
Cannabis Psychosis: Controversial Issues

Table 3 Facts, controversies, and myths relevant to the association between cannabis use and psychosis[a]

Statement	Consistency of evidence[b]	Evidence from multiple fields of investigation: epidemiology (E), neurobiology (NB), genetics (G)	Evidence grade[c]
The younger the age at onset of use, the higher the risk	+++	E, NB	A+
The balance between THC and CBD is a critical factor	++	E, NB	A
There is a synergistic interaction between early life stress and cannabis use to increase psychosis risk	+	E, NB	B
THC interferes with processes regulating synaptic plasticity	+++	NB	A
Cannabis affects cognitive ability in the short term	+++	E, NB	A+
Cannabis has enduring negative effects on cognition, even in the absence of current use	+/–	E, NB	C
Cannabis use is associated with generalized brain tissue loss	+/–	NB	C
Cannabis use is associated with brain tissue loss, especially in individuals at familial risk for psychosis	+/–	NB	C
Cannabis use is associated with specific brain tissue loss in hippocampus	+/–	NB	C
Cannabis use is associated with specific brain tissue loss in cerebellum	+/–	NB	C
Cannabis use induces striatal dopamine release	+/–	NB	C
Cannabis use induces striatal dopamine release in individuals at familial risk for psychosis	+/–	NB	C
Cannabis use impacts dopamine D2 receptor availability	–	NB	D
Cannabis use is associated with increased dopamine synthesis capacity	–	NB	D
Cannabis use is associated with increased striatal dopamine response to a challenge with amphetamine or stress	–	NB	D
Individuals at familial risk are more sensitive to the psychosis-inducing effects of cannabis	++	G, NB	A
COMT Val158Met is an important genetic risk factor for cannabis-induced psychosis	+/–	G, NB	C
AKT1 rs2494732 is an important genetic risk factor for cannabis-induced psychosis	+	G	B

Genetic Moderators ?

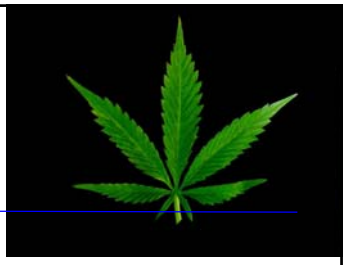




Cannabis & Schizophrenia

- Odds Ratio of schizophrenia:
  - Any use: 1.4
  - Heavy use: 2.1
- Associated with earlier Sz onset: mean of 2.7 years
- Cannabis produces positive & negative symptoms & worsens course of illness

Cannabis & Psychosis



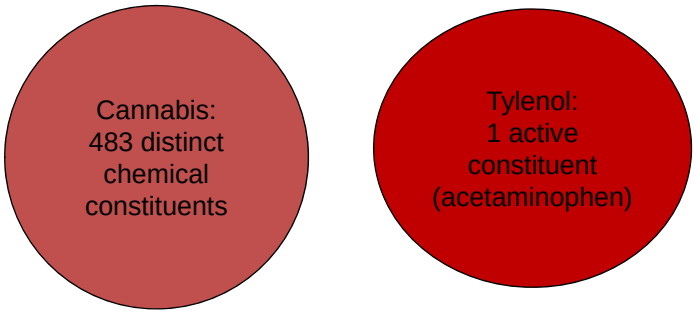
Overall message:

- Cannabis may precipitate/hasten psychosis in vulnerable individuals
- Though some risk factors (FHx, genetics, hx of abuse), unable to predict who is vulnerable *a priori*
- Cannabis exacerbates pre-existing psychotic disorders

MEDICAL MARIJUANA

Cannabis contains

- Cannabinoids
- Flavonoids
- Terpenoids



Whole plant vs. principal active constituent?

foxglove

digitalis

poppy

opioids

Variability of Product

- Content, e.g. THC, CBD
- Potency
- Inter- and intra-batch consistency

Who is responsible for monitoring the above?

Who compiles information on which strains are most effective for treating particular medical conditions?

Arguments for Use of Medical MJ.

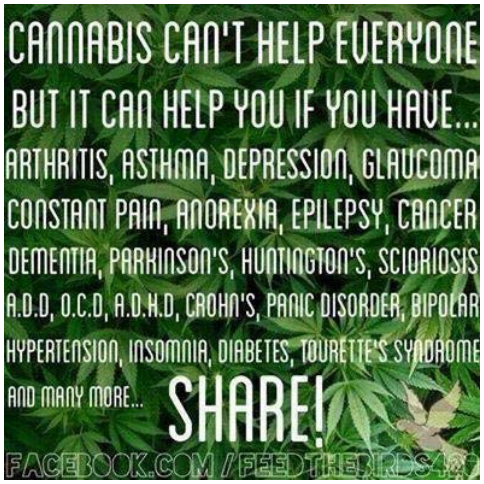
- Generally separate from arguments on decriminalization/legalization of recreational MJ.
- Relative safety, compared to opioids;-low morbidity, close to zero mortality.
- Suggestive evidence of utility in multiple medical conditions.

Reports of Medical MJ use by Condition

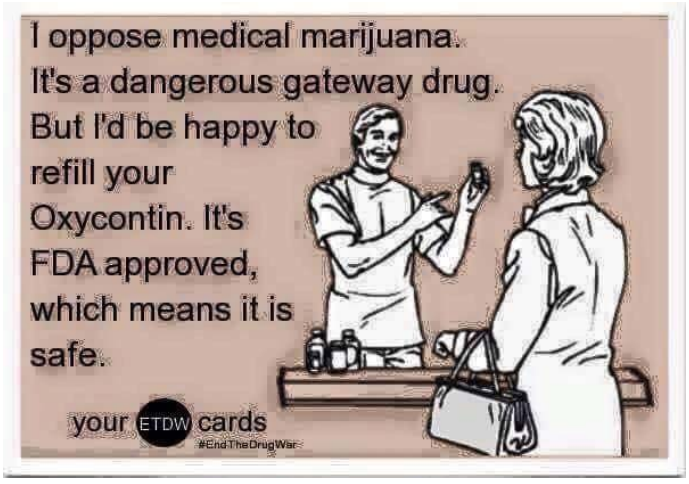
Table 1.—Medicinal Uses Reported With Cannabis and Cannabinoids

Central Nervous System (CNS)
Chronic non-cancer pain:[45,58,130,140,150,267-289] chronic neuropathic pain,[136,139,277,287-301] phantom limb pain,[302] fibromyalgia,[300,303-307] rheumatoid arthritis,[308-311] chronic abdominal pain from inflammatory bowel diseases,[312-318] cancer-related pain (especially with potent opiate failure)[150,244,268,319,320]
Headache and facial pain: chronic headaches,[146,196] migraine,[49,192-196,321] cluster headache,[217,221,222] pseudotumor cerebri,[198] multiple sclerosis-associated trigeminal neuralgia[226]
Epilepsy[80,104,105,322-339]
Spasticity and related central pain and bladder dysfunction in multiple sclerosis[53,121,140,226,250,328,340-376] and spinal cord injury[121,140,328,340,341,362,377-382]
Additional multiple sclerosis associated symptoms: tremor,[343] pendular nystagmus suppression,[383] dystonia[345]
Reduce muscle cramps and fasciculations in amyotrophic lateral sclerosis (ALS),[384] and delay disease progression (ALS and MS)[385-387]
Reduce intracranial pressure in traumatic brain injury, aid in cerebral ischemia and neuro/excitotoxicity,[199-203,388] and regulation of neuroinflammatory response[372,373,389-391]
Tourette's syndrome[392-403]
Dystonic movement disorders,[399,404-408] oral dyskinesia[409]
Parkinson's disease; reduction of levodopa-induced dyskinesia,[399,410] and disease progression[411-414]
Huntington's disease[415-417]
Meige's syndrome[418]
Intractable hiccups[419]
Depression, anxiety, and mood disorders[143,144,203,266,290,376,420-437]
Post-traumatic stress disorder (PTSD)[242,438-448]
Neuroprotective antioxidants[97,98,201,202,391]
Alzheimer's; behavioral/agitation,[449-451] disease progression and cognitive symptoms[452,453]
Insomnia (majority in setting of pain relief)[242,277,290,297,303,306-308,314,346,347,349,362,377-379,435-437,454,455]
Fulminant hepatic encephalopathy[456]
Autism and autistic spectrum disorders[457-461]
General Medical Systems
Nausea and vomiting from chemotherapy in adults[93,276,462-497] and children[497-500]
Appetite stimulation in healthy subjects as well as cancer and AIDS-associated anorexia/cachexia syndrome ± altered chemosensory perception[143,362,203,435-437,455,463,482,497,501-519] and associated nausea[519-521]
Reducing intraocular pressure in glaucoma[204-216]
Gastrointestinal disorders (irritable bowel syndrome, inflammatory bowel disease, pain)[312-318,522-536]
Anti-cancer/neoplastic including breast, brain (glioma), lung, colon, skin cancer (melanoma), leukemia[489,537-568]
Asthma (oral or aerosol rather than smoked)[569-571]
Regulation and decrease of inflammation associated with autoimmune diseases[572-574]

Hard to think of a mechanism that could underpin medical efficacy in so many diverse conditions



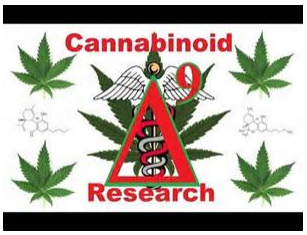
……But this is equally true



Putative Medical Benefits of Cannabis

Potential benefits of cannabis based on research studies

Remedy for inflammation
Remedy for pain (including chronic pain and neuropathic pain)
Remedy for diarrhea (as in Crohn's disease)
Treatment for dystonia
Treatment for multiple sclerosis
Treatment for rheumatoid arthritis
Treatment for glaucoma
Treatment for emesis due to chemotherapy
Treatment for epilepsy
Improvement of anorexia in AIDS patients
Treatment for Huntington's disease
Management of inflammatory bowel disease
Beneficial effect on atherosclerosis
Reduce brain infarct size
Block negative memories in posttraumatic stress disorder
Reduce cardiac reperfusion injury
Adjuvant treatment for prostate carcinoma
Others



Current THC-based Compounds

Medical Marijuana Laws by State

Currently 23 states and DC.
15 additional states enacted laws to allow access to CBD oil and/or high-CBD strains of MJ.

Table 1 States that have enacted medical marijuana laws

State	Year passed
Alaska	1998
Arizona	2010
California	1996
Colorado	1996
Connecticut	2012
Washington, DC	2010
Delaware	2011
Hawaii	2000
Illinois	2013
Maine	1999
Massachusetts	2012
Michigan	2008
Montana	2004
Nevada	2000
New Hampshire	2013
New Jersey	2010
New Mexico	2007
Oregon	1998
Rhode Island	2006
Vermont	2004
Washington	1998

Indications

Condition	States where approved as qualifying condition
Amyotropic Lateral Sclerosis	AZ, DE, IL, ME, MA, MI, MN, NJ, NJ, NM, NY
Cancer	AK, AZ, CA, CO, CT, DC, DE, HI, IL, ME, MA, MI, MN,MT, NV, NH, NJ, NM, NY, OR, RI, VT, WA
Glaucoma	AK, AZ, CA, CO, CT, DC, HI, IL, ME, MA, MI, MN, MT, NV, NH, NJ, NM, OR, RI, WA
HIV/AIDS	AK, AZ, CA, CO, CT, DC, DE, HI, IL, ME, MA, MI, MN, MT, NV, NH, NJ, NM, NY, OR, RI, VT, WA
Multiple Sclerosis and/or muscle spasticity	AK, AZ, CA, CO, CT, DC, DE, HI, IL, ME, MD, MA, MI, MN, MT, NV, NH, NJ, NM, NY, OR, RI, WA
Muscular dystrophy	IL, NH, NJ, NY
Nausea and/or vomiting	AK, AZ, CA, CO, DE, HI, ME, MD, MI, MN, MT, NV, NH, NJ, NM, OR, RI, VT, WA
Pain[a]	AK, AZ, CA, CO, DE, HI, IL, ME, MD, MI, MN, MT, NV, NH, NJ, NM, OR, RI, VT, WA
Parkinson's Disease	CT, IL, MA, NM, NY
Seizures/epilepsy	AK, AZ, CA, CO, CT, DE, HI, IL, ME, MD, MI, MN, MT, NV, NH, NJ, NM, NY, OR, RI, VT, WA
Traumatic Brain Injury	IL, NH
Posttraumatic Stress Disorder	AZ, CT, DE , ME, MI, NV, NM, NY, OR
Agitation in Alzheimer's disease	AZ, DE, IL, ME, MI, NH, NY, OR, RI
Tourette's Syndrome	IL, MN

[a]*Various states stipulate various subtypes of pain (i.e., chronic pain; chronic, severe pain; intractable pain)*

Inconsistency in Approval Process

As well as in patient registration

- Inconsistency within and across states
- e.g., Sickle cell disease – Tourette's syndrome: CT

CONDITION	STATES WHERE APPROVED AS A QUALIFYING CONDITION
Amyotropic Lateral Sclerosis	AZ, DE, IL, ME, MA, MI, MN, NJ, NM, NY
Cancer	AK, AZ, CA, CO, CT, DC, DE, HI, IL, ME, MA, MI, MN,MT, NV, NH, NJ, NM, NY, OR, RI, VT, WA
Glaucoma	AK, AZ, CA, CO, CT, DC, HI, IL, ME, MA, MI, MN, MT, NV, NH, NJ, NM, OR, RI, WA
HIV/AIDS	AK, AZ, CA, CO, CT, DC, DE, HI, IL, ME, MA, MI, MN, MT, NV, NH, NJ, NM, NY, OR, RI, VT, WA
Multiple Sclerosis and/or muscle spasticity	AK, AZ, CA, CO, CT, DC, DE, HI, IL, ME, MD, MA, MI, MN, MT, NV, NH, NJ, NM, NY, OR, RI, WA
Muscular dystrophy	IL, NH, NJ, NY
Nausea and/or vomiting	AK, AZ, CA, CO, DE, HI, ME, MD, MI, MN, MT, NV, NH, NJ, NM, OR, RI, VT, WA
Pain	AK, AZ, CA, CO, DE, HI, IL, ME, MD, MI, MN, MT, NV, NH, NJ, NM, OR, RI, VT, WA
Parkinson's Disease	CT, IL, MA, NM, NY
Seizures/epilepsy	AK, AZ, CA, CO, CT, DE, HI, IL, ME, MD, MI, MN, MT, NV, NH, NJ, NM, NY, OR, RI, VT, WA
Traumatic Brain Injury	IL, NH
Posttraumatic Stress Disorder	AZ, CT, DE , ME, MI, NV, NM, NY, OR
Agitation in Alzheimer's disease	AZ, DE, IL, ME, MI, NH, NY, OR, RI
Tourette's Syndrome	IL, MN

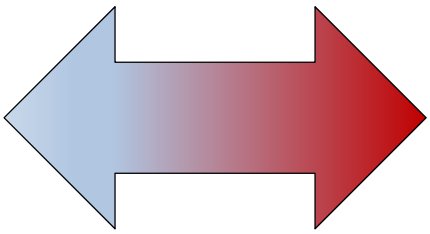
Inconsistencies in Supply Limit

Table 1. Medical Marijuana Laws by State[a]

State	Approved Conditions	Legal Limit
Alaska, 1998	Cachexia, cancer, chronic pain, epilepsy and other disorders characterized by seizures, glaucoma, HIV/AIDS, MS and other disorders characterized by muscle spasticity, and nausea; other conditions are subject to approval by the Alaska Department of Health and Social Services	1 oz usable; 6 plants (3 mature, 3 immature)
Arizona, 2010	Cancer, glaucoma, HIV/AIDS, hepatitis C, ALS, Crohn disease, Alzheimer disease, cachexia, severe and chronic pain, severe nausea, seizures (including epilepsy), severe or persistent muscle spasms	2.5 oz usable; 0-12 plants
California, 1996	AIDS, anorexia, arthritis, cachexia, cancer, chronic pain, glaucoma, migraine, persistent muscle spasms (including spasms associated with MS), seizures (including seizures associated with epilepsy), severe nausea, other chronic or persistent medical symptoms	8 oz usable; 6 mature or 12 immature plants
Colorado, 2000	Cancer, glaucoma, HIV/AIDS, cachexia, severe pain, severe nausea, seizures (including those characteristic of epilepsy), persistent muscle spasms (including those characteristic of MS); other conditions are subject to approval by the Colorado Board of Health	2 oz usable; 6 plants (3 mature, 3 immature)
Connecticut, 2012	Cancer, glaucoma, HIV/AIDS, Parkinson disease, MS, damage to the nervous tissue of the spinal cord with objective neurological indication of intractable spasticity, epilepsy, cachexia, Crohn disease, PTSD, or any medical condition, medical treatment, or disease approved by the Department of Consumer Protection	1-mo supply (exact amount to be determined)
Washington, DC, 2010	HIV/AIDS, cancer, glaucoma, conditions characterized by severe and persistent muscle spasms such as MS, patients undergoing chemotherapy or radiotherapy or using azidothymidine or protease inhibitors	2 oz dried; limits on other forms to be determined
Delaware, 2011	Cancer, HIV/AIDS, decompensated cirrhosis (hepatitis C), ALS, Alzheimer disease A chronic or debilitating disease or medical condition or its treatment that produces ≥1 of the following: cachexia; severe, debilitating pain that has not responded to previously prescribed medication or surgical measures for more than 3 mo or for which other treatment options produced serious adverse effects; intractable nausea; seizures; severe and persistent muscle spasms including but not limited to those characteristic of MS	6 oz usable
Hawaii, 2000	Cancer, glaucoma, HIV/AIDS, a chronic or debilitating disease or medical condition or its treatment that produces cachexia, severe pain, severe nausea, seizures including those characteristic of epilepsy, or severe and persistent muscle spasms including those characteristic of MS or Crohn disease; other conditions are subject to approval by the Hawaii Department of Health	3 oz usable; 7 plants (3 mature, 4 immature)
Illinois, 2013	Cancer, glaucoma, HIV/AIDS, hepatitis C, ALS, Crohn disease, agitation related to Alzheimer disease, cachexia/wasting syndrome, muscular dystrophy, severe fibromyalgia, spinal cord disease (including but not limited to arachnoiditis), Tarlov cysts, hydromyelia syringomyelia, rheumatoid arthritis, fibrous dysplasia, spinal cord injury, traumatic brain injury and postconcussion syndrome, MS, Arnold-Chiari malformation and syringomelia, spinocerebellar ataxia, Parkinson disease, Tourette syndrome, myoclonus, dystonia, reflex sympathetic dystrophy (complex regional pain syndromes type 1), causalgia, complex regional pain syndrome type 2, neurofibromatosis, chronic inflammatory demyelinating polyneuropathy, Sjogren syndrome, lupus, interstitial cystitis, myasthenia gravis, hydrocephalus, nail patella syndrome or residual limb pain, or treatment of these conditions	2.5 ounces usable cannabis during 14-d period
Maine, 1999	Epilepsy and other disorders characterized by seizures, glaucoma, MS and other disorders characterized by muscle spasticity, and nausea or vomiting as a result of AIDS or cancer chemotherapy	2.5 oz usable; 6 plants
Maryland, 2014	Cachexia, anorexia, or wasting syndrome, severe or chronic pain, severe nausea, seizures, severe or persistent muscle spasms, or other conditions approved by the commission	30-d supply, amount to be determined
Massachusetts, 2012	Cancer, glaucoma, HIV/AIDS, hepatitis C, ALS, Crohn disease, Parkinson disease, MS, and other conditions as determined in writing by a qualifying patient's physician	60-d supply (10 oz) for personal medical use
Michigan, 2008	Cancer, glaucoma, HIV/AIDS, hepatitis C, ALS, Crohn disease, agitation of Alzheimer disease, nail patella syndrome, cachexia or wasting syndrome, severe and chronic pain, severe nausea, seizures, epilepsy, muscle spasms, MS, PTSD	2.5 oz usable; 12 plants
Minnesota, 2014	Cancer (if the underlying condition or treatment produces severe or chronic pain, nausea, severe vomiting, or cachexia or severe wasting), glaucoma, HIV/AIDS, Tourette syndrome, ALS, seizures/epilepsy, severe and persistent muscle spasms/MS, Crohn disease, terminal illness with a life expectancy of <1 y	30-d supply of nonsmokable marijuana

What is the Evidence?

Anecdotal



RCT

- **Randomized**
- **Placebo-controlled**
- **Double-blind**

Issues Regarding Which Conditions to Include for Medical MJ Administration.

- What level and type of evidence to accept?
- Obvious dearth of double-blind, placebo-controlled trials in the US– need a balance between that and anecdotal evidence.
- Schedule 1 classification prevents adequate trials – great difficulty in conducting MJ research into benefits.
- For which specific illness symptoms is medical MJ being recommended (e.g. in MS, pain, spasticity, debilitation, etc.)?
- Should we deprive patients of a potentially helpful treatment avenue, even if adjunctive?

Qualifying Criteria for Adding a new Medical Condition in CT

- Multiple medical conditions already qualify as legitimate debilitating conditions including radiculopathies, PTSD, Crohn's disease, ulcerative colitis, cachexia + pain due to cancer, MS spasticity, complex regional pain syndromes, chemotherapy-induced nausea/vomiting, etc.
- Physicians don't 'prescribe MJ" but certify that a given patient has a condition for which medical MJ is legitimate. Provisions to prevent diversion and limit sharing
- **Criteria for Adding a new Medical Condition**
- 1. Is the condition treatment or disease disabling?
- 2. Is marijuana more likely than not to have the potential to be beneficial to treat or alleviate the debilitation associated with the medical condition, treatment or disease?
- 3. Other matters that seem relevant to the approval or denial of the petition (e.g. in multiple sclerosis medical marijuana may help with muscle spasms but worsen cognitive problems).
- Cyril D'Souza/GP is proposing more formal additional criteria including double-blind controlled trials of marijuana (rather than THC, Dronabinol etc), or in the absence of that convincing animal data, open label trials, or strong evidence linking the pathophysiology of the disorder to the endocannabinoid system.

Precautions in Prescribing Medical MJ

Table 4.—Suggested Contraindications and/or Precautions Requiring Evaluation of Risk/Benefit Ratio of Cannabis and Cannabinoids

Use with caution in patients with a history of substance abuse including alcohol, given abuse potential.
Use with caution in patients using sedative-hypnotics, alcohol, or other psychoactive drugs due to potential synergistic sedative effects.
Use with caution in severe renal or liver disease, including chronic hepatitis C (daily use not recommended due to potential for worsening steatosis severity).
Avoid use under the age of 18 due to potential for increased adverse effects on mental health during development and adolescence.
Avoid use while driving, operating heavy machinery, or performing other hazardous tasks or activities.
Avoid use with history of cannabinoid or smoke hypersensitivity.
Avoid use in patients with severe cardio-pulmonary disease due to risk for potential hypotension, hypertension, tachycardia, or syncope.
Avoid use of smoked cannabis in patients with pulmonary diseases including asthma and chronic obstructive pulmonary disease.
Avoid use in women who are pregnant or breastfeeding. Use with caution in women of childbearing age who are planning pregnancy or not using a reliable contraceptive.
Avoid use in patients with psychiatric disease, particularly schizophrenia, or a family history of schizophrenia.
Careful psychiatric monitoring is recommended for patients with mania or depression.

Arguments Against Use of Medical MJ.

- Diversion, especially to teenagers:-risk of psychiatric and cognitive morbidity.
- Lack of clear-cut data on medical benefits.
- Addiction potential – current estimates ~10%.
- Effects of repeated exposure need further study.
- Tolerance and dependence with accompanying down-regulation/desensitization of CB1 receptors with repeated exposure.
- More MJ-related DWIs.
- Cognitive problems – for example, in multiple sclerosis, relief of painful spasms vs worsened dementia
- Increased risk of chronic cough, bronchitis.
- Risk to fetuses during pregnancy?
- Represents a "veiled step towards allowing access to recreational marijuana"- (if so, decriminalize and leave medical community out of the process).

MJ and Epilepsy Treatment

Table 2. (A) Proposed molecular targets for plant cannabinoids investigated in animal models of seizure and (B) Cannabinoid efficacy in animal models of seizure and epilepsy

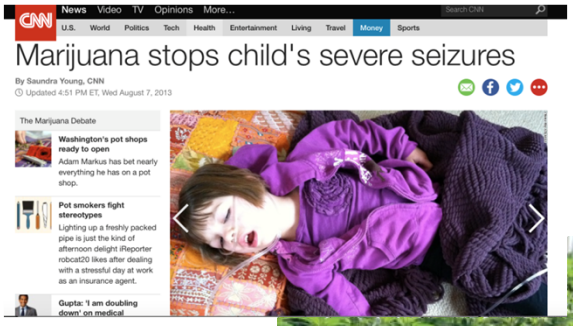
Cannabinoid	Molecular target(s)
(A)	
Δ^9-Tetrahydrocannabinol (Δ^9-THC)	CB1R, CB2R, TRPV1, TRPV2
Δ^9-Tetrahydrocannabivarin (Δ^9-THCV)	CB1, CB2, TRPV1, TRPV3, TRPV4
Cannabidiol (CBD)	ENT, GPR55, TRPV1, TRPV2, TRPV3, TRPA1, FAAH, TRPM8, adenosine, $5HT1_A$
Cannabidivarin (CBDV)	TRPV4, DAGLα
Cannabinol (CBN)	CB1R, TRPV4, TRPA1

Plant cannabinoid	Model	Efficacy
(B)		
Δ^9-Tetrahydrocannabinol (Δ^9-THC)	Generalized seizure (e.g., MES, PTZ, 6 Hz, 60 Hz, nicotine, and strychnine)	Y
	Temporal lobe epilepsy	Y
Synthetic CB1R agonists (e.g., WIN55-212)	Generalized seizure (MES, PTZ, amygdala kindling)	Y
	Partial seizure with secondary generalization (penicillin and maximal dentate gyrus activation)	Y
	Temporal lobe epilepsy	Y
	Absence epilepsy (WAG/Rij)	Mixed effect
Synthetic CB1R antagonists (e.g., SR141716A)	Generalized seizure (MES and PTZ)	N*
	Absence epilepsy (WAG/Rij)	N
	Partial seizures with secondary generalization (penicillin but not maximal dentate gyrus activation)	N*
	Epileptogenesis (juvenile head trauma but not kainic acid)	Y
Δ^9-Tetrahydrocannabivarin (Δ^9-THCV)	Generalized seizure	Y
Cannabidiol (CBD)	Generalized seizure (MES, PTZ, 6 Hz, 60 Hz, picrotoxin, isonicotinic acid, bicuculline, hydrazine, limbic kindling (electrical), and strychnine but not 3-mercaptopropionic acid)	Y
	Temporal lobe convulsions/status epilepticus	Y
	Partial seizures with secondary generalization (penicillin but not cobalt)	Y
Cannabidivarin (CBDV)	Generalized seizure (MES, PTZ, and audiogenic)	Y
	Temporal lobe convulsions/status epilepticus	Y
	Partial seizures with secondary generalization (penicillin only)	Y
Cannabinol (CBN)	Generalized seizure (MES only)	Y

*Indicates a proconvulsant effect.

Epilepsia, 55(6):791–802, 201

Charlotte's Web



A double-blind, randomized, placebo-controlled, parallel group trial of cannabidiol in schizophrenia

- 88 stable, symptomatic outpatients with schizophrenia
- CBD 500 mg or placebo add-on for 6 weeks
- Significant benefit for psychosis (p=.02) & global improvement (CGI-I) (p=.02)
- Side effect rate did not differ from placebo (34.9% vs 35.6%)

McGuire, Robson, Cubala, Vasile, Morrison, Wright: presented at SIRS 2016

Current Rx Cannabidiol Drugs

- THC/CBD mixtures, eg Sativex oral spray, in 15 countries for treatment of spasticity in MS
- Pure oral synthetic CBD (Epidiolex) has orphan drug status in USA for childhood epilepsy, completing second Phase III trial
- Pure CBD gel (Zynerba) in Phase I and II trials for several disorders
- FAAH inhibitors in early clinical trials

Purified Rx Chemicals Derived from or Based on Those in Cannabis Plants

- More promising therapeutically then use of whole MJ plant or crude extracts
- Two FDA-approved, THC-based medications currently
- **Dronabinol** (Marinol) – synthetic THC in an oily base – appetite stimulant in AIDS wasting syndrome and cancer
- **Nabilone** (Cesamet) – pill form for treatment of nausea in cancer chemotherapy patients.
- Also, **Nabiximols** (Sativex)-(THC plus CBD oral spray), currently available in UK, Canada and several European countries for treating spasticity and neuropathic pain that may accompany MS. Recent trials in US for schizophrenia.
- **Epidolex** currently tested in US for treatment of two forms of severe childhood epilepsy, (Dravet syndrome and Lennox-Gastault syndrome).

Neuropathic Pain

Reference	Design	Intervention	Sample Size	Duration	Outcome	Quality
Abrams et al 2007	RCT, parallel	Smoked cannabis (3.56% THC)	50 HIV patients	5 days	Reduction in pain rating v. placebo (34% v. 17%, p=0.03)	Very low quality
Ellis et al 2008	RCT, crossover	Smoked cannabis (1-8% THC)	28 HIV patients	5 days treatment, 2-wk washout	Reduction in pain rating v. placebo (p=0.016; effect size 0.60)	Very low quality
Ware et al 2010	RCT, crossover	Smoked cannabis (0, 2.5, 6, 9.4% THC)	23 post-surgical neuropathy patients	5 days treatment 9-day washout	Difference for highest dose v. placebo (p=0.023)	Low quality
Corey-Bloom et al 2012	RCT, crossover	Smoked cannabis	30 MS patients with neuropathic pain	3-day treatment 11-day washout	Greater reduction in pain v. placebo (p=0.008)	Very low quality
Selvarejah et al 2010	RCT, parallel	CBM oromucosal spray	30 diabetic patients	12 weeks	No difference: negative study	Very low quality
Zajicek et al 2012	RCT	CBM, oral	279 MS patients	12 weeks	Significant difference at 4, 8, and 12 weeks (p<0.025)	Low-moderate quality
Serpell et al 2014	RCT	CBM, oromucosal spray	240 peripheral neuropathy patients	15 weeks	-Response: 28% CBM v. 16% placebo (p=0.034) -No difference in objective measures	Moderate quality

RCT – randomized controlled trial; CBM – cannabis-based medicine

Neuropathic Pain

- Growing evidence for use in neuropathy
- Expectancy effects
- Blinding problems
- Objective measures of pain
  - Usually negative
- Reduces opiate burden?
  - Preclinical evidence in rodents
  - No human studies

Problems with Existing Studies

- FDA requires evidence from 2+ adequately-powered randomized clinical trials before approving a drug for any specific indication.
- Herbal MJ is a mixture of 70+ different cannabinoids- FDA trials examine single substances.
- Naturally-occurring compounds in cannabis occur in different proportions, and may have opposite effects-THC vs cannabidiol- increased vs lowered risk of psychosis; precise dosing is therefore difficult.
- Given variable composition, patients have to experiment with different strains & doses to achieve desired effects, without much physician oversight,
- Cannot extrapolate from studies on individual cannabinoids e.g., THC or CBD to herbal cannabis and vice versa
- Few double-blind, placebo-controlled trials, (in large part because of schedule 1 status and lack of NIH funding).
- Lack of active placebo designs.
- Variety of routes of administration: smoking, vaporizers, oral mucosal spray, 'vaping' and of formulations – e.g. smoked vs oral THC vs THC dronabinol, nabilone, herbal cannabis, waxes (waxy 'budder', hard 'shatter', hashish, hash oils, synthetics such as K2 and 'spice'
- Lack of long-term follow-up to assess both efficacy and development of problematic/adverse side effects.
- For pain studies, need adequate and comprehensive outcome measures, including reduction in opioid use.

Problems with Implementation of Medical Marijuana Regulations to Date

- Considerable state-to-state variability in allowable/qualifying conditions.
- Likely reflects absence of available scientific evidence and approval processes based on politics, not science.
- Also inconsistencies in how to evaluate and apply current evidence towards decision-making about qualifying indications
- Often not clear what standard for acceptance is – e.g. anecdotal reports, individual testimonials, legislative initiatives, public opinion.
- Is evidence for MJ trumped by that for other available effective and safe treatments?
- Is goal of medical MJ legislation a backdoor approach to attaining legalization of MJ?

Weighing the Evidence

In approving a new indication for medical MJ

- Are prior clinical trials randomized?
- Double-Blind?
- Placebo-Controlled?
- Active-Controlled?
- Sample Size >200?
- Full reporting of all outcomes?
- Effect size?
- Was the sample studied representative of the target population?
- Was the trial duration adequate?
- Were the outcome measures adequate to test the hypothesis?
- Were the primary outcomes met?
- Were the secondary outcomes met?
- Was whole plant marijuana tested, or a constituent? (e.g., THC, or CBG)
- Are there alternative existing treatments available that meet the standards mentioned above?

The GRADE working group (http://www.guidelinedevelopment.org/handbook/)
Him him him himBMJ Clinical Evidence (http://clinicalevidence.bmj.com/x/systematic-review/1108/grade-table.html)

Weighing the Evidence

Moderate Evidence

-Nausea/vomiting in chemotherapy (FDA approval for Marinol)

-HIV/AIDS cachexia (FDA approval for Marinol)

-Neuropathic pain

-MS Spasticity

Little Evidence

-Tourette's syndrome

-Crohn's disease

-Ulcerative Colitis

-Epilepsy

Very Little Evidence

-Parkinson's Disease

-PTSD

-Agitation in Alzheimer's disease

-Schizophrenia

Medical MJ -Conclusions

- MS spasticity, neuropathic pain, chemotherapy nausea and vomiting
- Poor quality evidence for most indications
- Tolerance?
- Acute and persistent side- effects
- **Need more Federal/State funded research $**

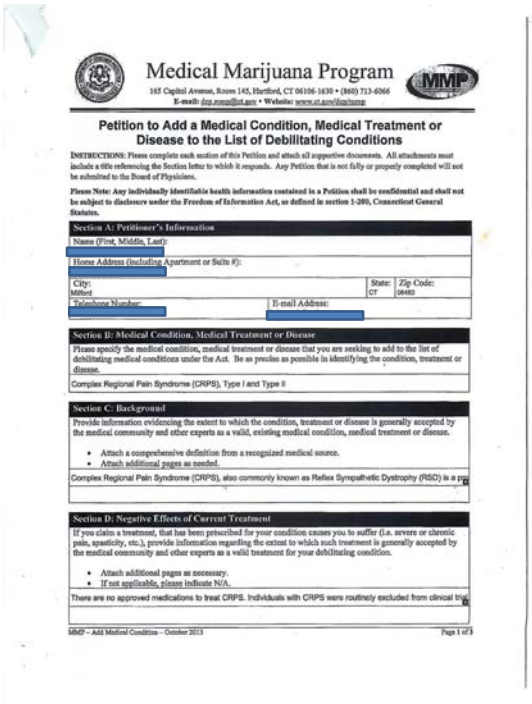
MARIJUANA LEGISLATION

Medical Marijuana in Connecticut

- CT Legislation- decriminalization of small amounts of recreational MJ with separate use of medical MJ for approved conditions
- **Jonathan Harris** new commissioner, Connecticut Department of Consumer Protection since retirement of William M Rubenstein in November 2014.
- ~4900 registered patients, ~250 participating M.D.'s, 4 growers, 4 dispensaries. Need additional dispensary facilities New Haven and Fairfield County. Project ~6000 patients by 12-2015.
- Contrast with Denver, CO – 117 licensed pharmacies vs 198 medical MJ dispensaries (both Rx and recreational).
- Multiple forms of medical marijuana allowed, including herbal material, tinctures, forms for oral administration.

CT Board of Physicians Medical MJ Program

- Members = All MD's- Vincent Carlesi, Jonathan Kost, Cyril D'Souza, Godfrey Pearlson, Mitchell Prywes.
- Hearings are regular & public and anyone can petition for a new debilitating condition to be added to the approved list
- **DCP staff:** Michelle Seagull deputy commissioner, Elisa Nahas director legal division, Claudette Carveth director communication office, Xaviel Soto health program supervisor, Marguerite Poisson license and applications analyst



Medical Marijuana Program

165 Capitol Avenue, Room 145, Hartford, CT 06106-1630 • (860) 713-6066
E-mail: dcp.mmp@ct.gov • Website: www.ct.gov/dcp/mmp

Petition to Add a Medical Condition, Medical Treatment or Disease to the List of Debilitating Conditions

INSTRUCTIONS: Please complete each section of this Petition and attach all supportive documents. All attachments must include a title referencing the Section letter to which it responds. Any Petition that is not fully or properly completed will not be submitted to the Board of Physicians.

Please Note: Any individually identifiable health information contained in a Petition shall be confidential and shall not be subject to disclosure under the Freedom of Information Act, as defined in section 1-200, Connecticut General Statutes.

Section A: Petitioner's Information

Name (First, Middle, Last):

Home Address (including Apartment or Suite #):

City: Milford | State: CT | Zip Code: 06460

Telephone Number: | E-mail Address:

Section B: Medical Condition, Medical Treatment or Disease

Please specify the medical condition, medical treatment or disease that you are seeking to add to the list of debilitating medical conditions under the Act. Be as precise as possible in identifying the condition, treatment or disease.

Complex Regional Pain Syndrome (CRPS), Type I and Type II

Section C: Background

Provide information evidencing the extent to which the condition, treatment or disease is generally accepted by the medical community and other experts as a valid, existing medical condition, medical treatment or disease.

- Attach a comprehensive definition from a recognized medical source.
- Attach additional pages as needed.

Complex Regional Pain Syndrome (CRPS), also commonly known as Reflex Sympathetic Dystrophy (RSD) is a pa

Section D: Negative Effects of Current Treatment

If you claim a treatment, that has been prescribed for your condition causes you to suffer (i.e. severe or chronic pain, spasticity, etc.), provide information regarding the extent to which such treatment is generally accepted by the medical community and other experts as a valid treatment for your debilitating condition.

- Attach additional pages as necessary.
- If not applicable, please indicate N/A.

There are no approved medications to treat CRPS. Individuals with CRPS were routinely excluded from clinical tri

MMP – Add Medical Condition – October 2013 Page 1 of 3

Legislation Pending in Connecticut.

- Labs to test medical marijuana constituents, proposals to license employees at hospices, allow medical research, legal immunity for dispensing nurses, licensed dispensaries to transport medical marijuana to labs and hospices.
- As yet, no mandatory labeling for concentration, or purity.

US Senate Legislation

- Pending -Kirsten Gillebrand, Rand Paul- reclassification of medical marijuana from schedule 1 to schedule 2 (potential for abuse but recognized medical utility e.g. certain opioids, amphetamines).

Presidential Approval??

SUMMARY AND CONCLUSIONS

Summary

- Rapidly-expanding field of study……so stay tuned.
- Medical MJ is used to treat "a host of indications, a few of which have evidence to support treatment with MJ and many that do not" (Hill, JAMA 2015).
- Use of cannabis is now common in clinical practice, nationwide.
- Important to understand risk: benefit ratio – medical care professionals have a responsibility to provide evidence-based guidance on these issues.
- No insurance companies cover medical MJ. The synthetic cannabinoids dronabinol and nabilone are expensive medications, that are covered by some insurance companies for their FDA indications, usually on a case-by-case basis.
- Different strains of herbal cannabis may have different effects, in part because of their variable THC and cannabidiol contents and ratios.
- Significant benefits: Apart from nausea and appetite stimulation (2 FDA-approved synthetics) high-quality evidence exists for chronic and neuropathic pain, MS spasticity.
- Significant potential health risks, e.g., addiction and worsening of psychiatric illnesses, including, anxiety, mood and psychotic disorders.

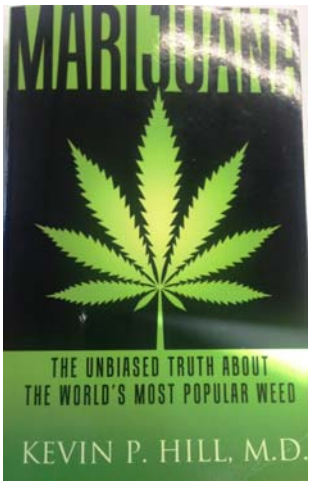
Recommendations 1

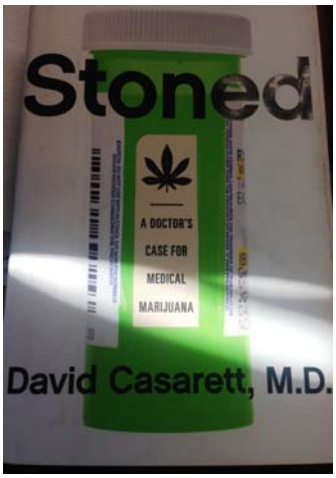
- Federal and state governments need to support and encourage research using FDA standards.
- Stop classifying all cannabinoids as if they were THC, in terms of regulation.
- Need to understand mechanisms underlying potential beneficial effects of MJ and its constituents- other specific pathways or mechanisms versus nonspecific subjective relief e.g., similar to BZ's.
- Need, high-quality evidence to guide decisions about medical MJ use for conditions for which existing evidence is insufficient, or of poor quality.
- This will involve adequately powered, double-blind, randomized, placebo/active controlled clinical trials to test short and long-term efficacy and safety.
- Need explicit exclusions/contraindications e.g. schizophrenia, bipolar disorder or substance dependence.

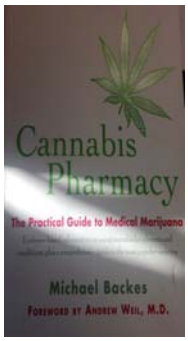
Recommendations 2

- Need to establish clinical follow-up programs to monitor long-term outcomes prospectively.
- Need to study interactions of MJ with concurrently prescribed drugs e.g. cross-tolerance with opioid analgesics, differential risk/benefit profiles.
- Include medical MJ in monitoring databases as done for opiates and BZ's?
- QC and standardization of medical MJ through regulation and licensure of producers.
- Need new synthetic compounds to target the endocannabinoid system by molecules other than those found in cannabis.
- Need better drug delivery systems other than through the lungs or gut-e.g., oral, sublingual.

Further Reading







+ Cyril D'Souza/ Mohini Ranganathan JAMA editorial 2015