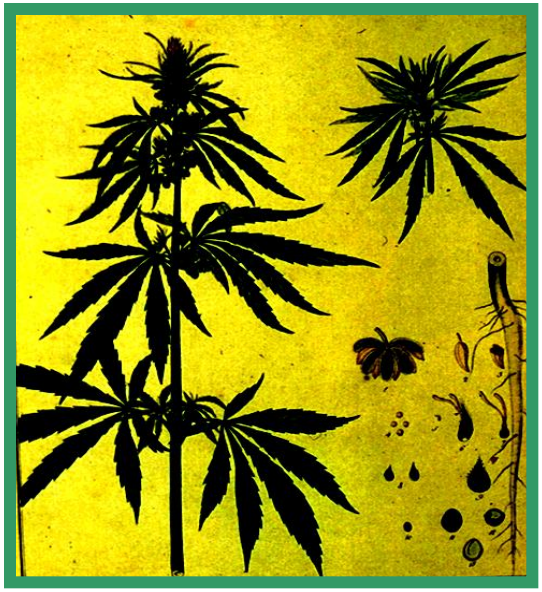
Marijuana as Medicine?



Bertha K. Madras, PhD (Hon.)
Professor of Psychobiology
Department of Psychiatry
Harvard Medical School

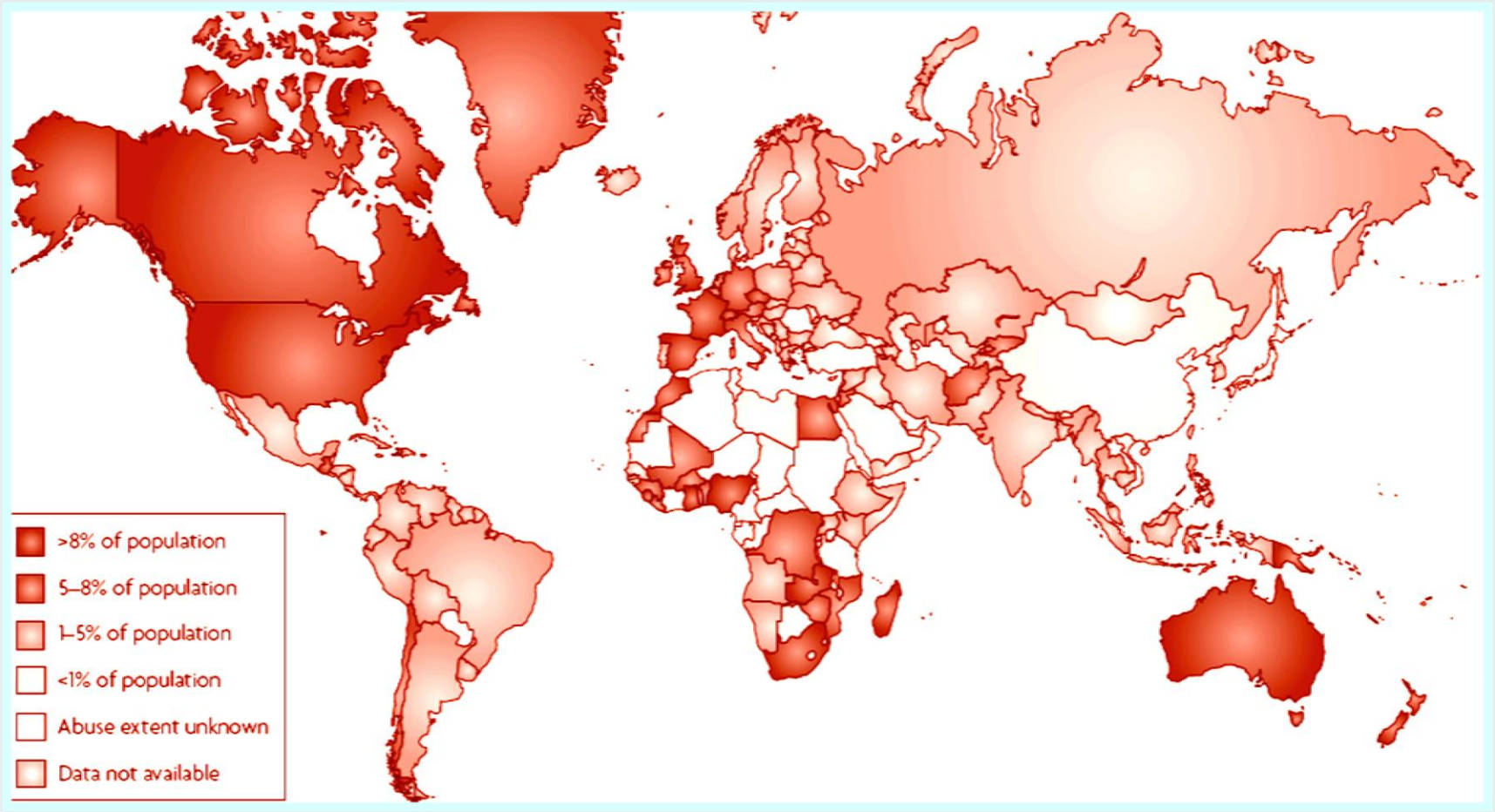
Former Deputy Director for Demand Reduction
White House Office of national Drug Control Policy

Pharmakon

Poison

Medicine

World Use of Marijuana



Adapted from Murray et al., Nat Rev Neurosci. 2007 Nov;8(11):885-95.

1938

Professor Walton of Medical College of South Carolina stated:

"The therapeutic application of cannabis is more history than present day practice. Synthetic analgesics and hypnotics have almost entirely displaced these preparations from their original field of application. The newer synthetics are more effective and reliable… the drug has certain remarkable properties and if its chemical structure were determined and synthetic variations developed, some of these night be particularly valuable as therapeutic agents and as experimental tools."

WHAT HAPPENED?????

Introduction

- History of plant products as medicines 
- Marijuana history and mechanisms 
- Food and Drug Administration, FDA approval process
- FDA ruling on marijuana as medicine 

- Ballot initiatives referenda, state legislation 
- **Why is marijuana a medical disaster?** 
- Future of cannabinoids 

History of Plant Products as Medicines

Composition unknown, unregulated

Treatment of symptoms, not illnesses

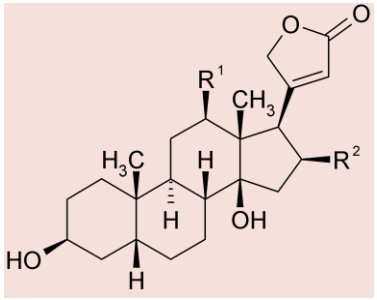
Poor understanding of pathology

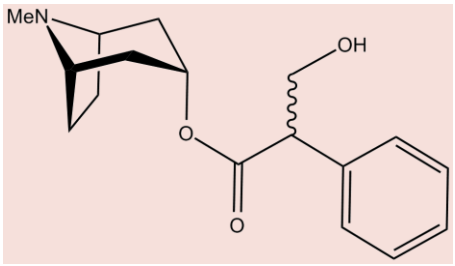
Poor understanding of mechanisms

Quantities inconsistent, unregulated

Modern Medications

Active chemical isolated from plants



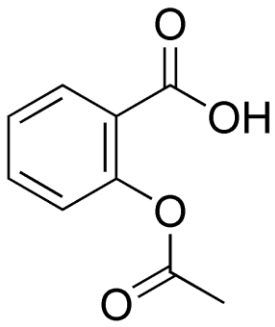


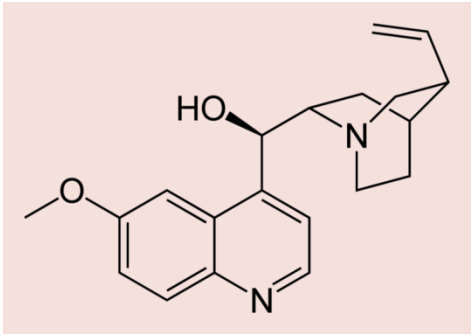
Highly purified and defined

Treat specific illness

Mechanism of action known

Administered in controlled, consistent doses





Marijuana History and Mechanisms

2727 BC

China

Pen-ts'ao Ching

Pharmacopeia

Medicinal properties of marijuana

Psychiatric side-effects

1200 BC

1894 AD

India

Indus valley

Marijuana is 1/5 sacred plants

British Report of Indian Hemp Drugs Commission

400 AD

Israel

Negev desert

Ashes of marijuana metabolite found near skeleton of pregnant women

1928 -1942

United Kingdom

United States

Recreational use of marijuana banned

Marijuana tax essentially prohibits marijuana use

Marijuana removed US Pharmacopeia

1961

60 Nations

Sign Uniform Drug Convention, which pledges to end marijuana use within 25 years

1976

Netherlands

Opium Act separates marijuana from "hard drugs".

Sale of marijuana is tolerated

1980

United States

Marinol (THC) approved for nausea in cancer patients

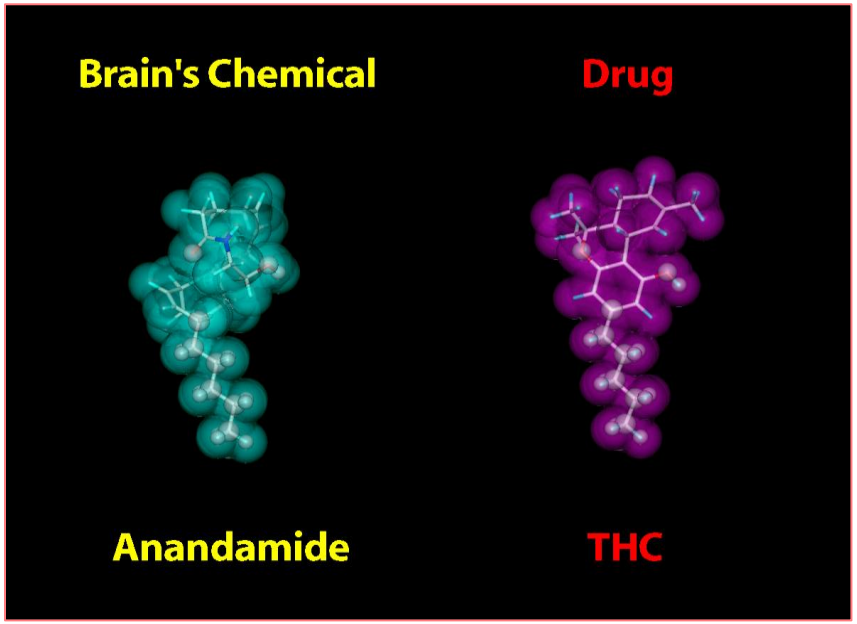
1992

Marinol approved for treatment anorexia/AIDS

Adapted from Murray et al., Nat Rev Neurosci. 2007 Nov;8(11):885-95; additions by BK Madras

Similar to other Specific Plants, Marijuana Has a Long History of Medical Use

- Marijuana resembles endogenous cannabinoids
- Cannabinoids are produced by the body.
- The cannabinoid signaling systems in brain and body have multiple functions: learning, memory, inflammation, pregnancy



Two Different Signaling Systems for Endocannabinoids in Brain, Body

CB1 system

marijuana response

- Appetite, pain, coordination, hormones
- L earning and memory, cognition
- Marijuana and opioid addiction
- Placenta, uterus: regulates early pregnancy, fertility, implantation, maintenance of pregnancy
- Skeletal nerve terminals

CB2 system

no marijuana response

- Neurogenesis
- Immune system
- Inflammatory response, pain
- Gastrointestinal tract
- Liver
- Cardiovascular system
- Lung airways

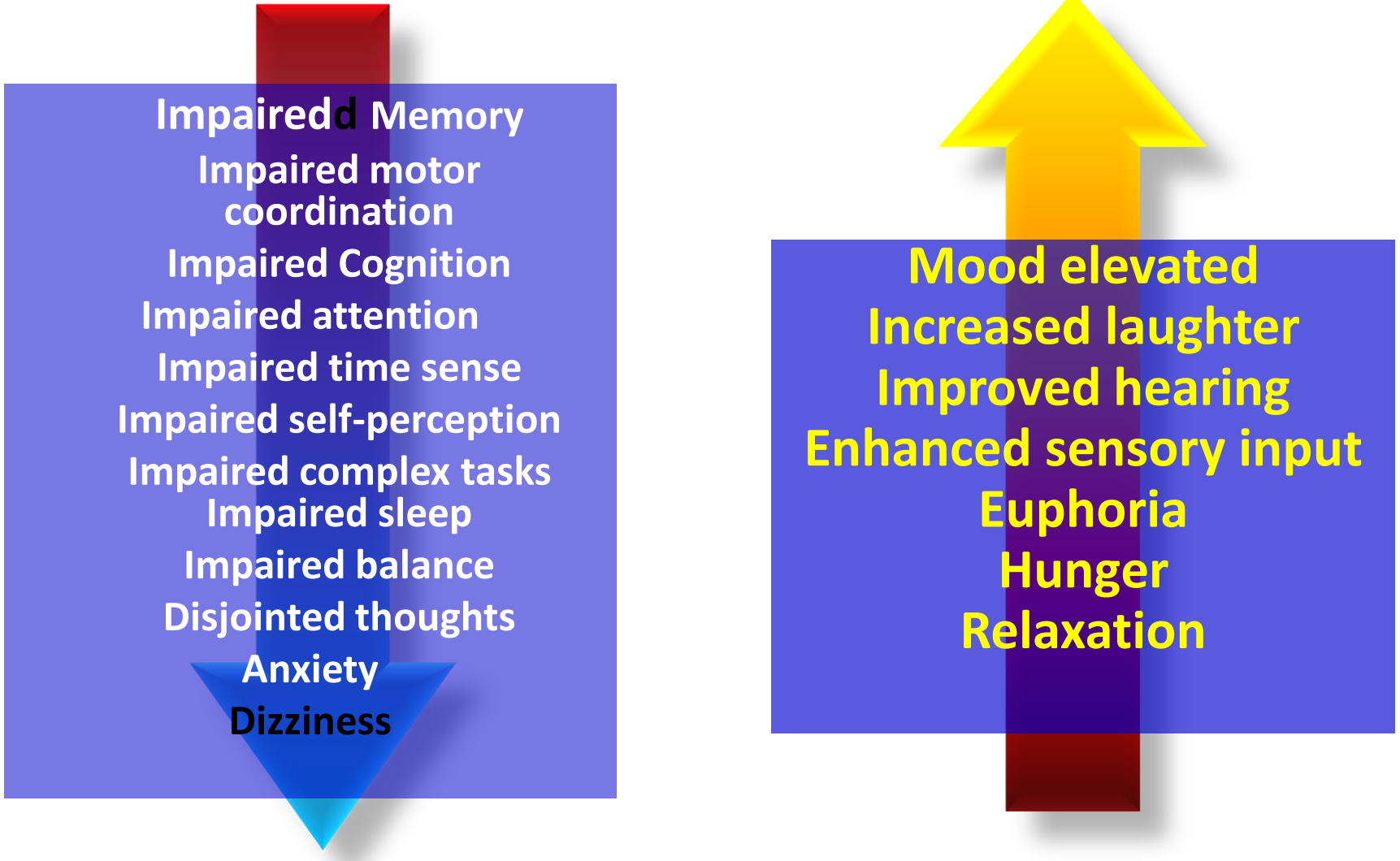
Cannabinoids' Effects in Preclinical studies

- Mediate rewarding effects of drugs/alcohol
- Modulate brain cell (neuron) connections
- Reduce/increase pain in brain, body
- Reduce anxiety
- Increase appetite
- Suppress motor activity
- Reduce nausea

- Produce hypotension, bradycardia +/-
- Increase fat synthesis liver, adipose tissue +/-
- Reduce energy expenditure +/-
- Promote liver fibrogenesis +/-
- Reduce oviductal transport, embryo implantation, pregnancy duration -
- Anti-inflammatory +/-
- Reduce GI motility +/-
- Reduce intraocular pressure +/-
- Neuroprotection +/-
- Suppress seizures: +/-

Why Is Marijuana a Concern?

Acute Effects of Marijuana are significant



Why is Marijuana a Concern?
Other Acute Effects of Marijuana

High Doses

Hallucinations

Delusions

Paranoia

Confusion

Anxiety

Cardiovascular Effects

<u>Increased</u>

- heart rate
- blood pressure lying down

<u>Decreased</u> blood pressure standing

Why is Marijuana a Concern?
Long-term Marijuana Use

Brain health and function

- Abuse, addiction: addiction potential is ~9-10%; rising
- Associated with increased risk of psychosis, schizophrenia
- Associated with increased risk of depression
- Early onset associated with cognitive impairment

Other Concerns

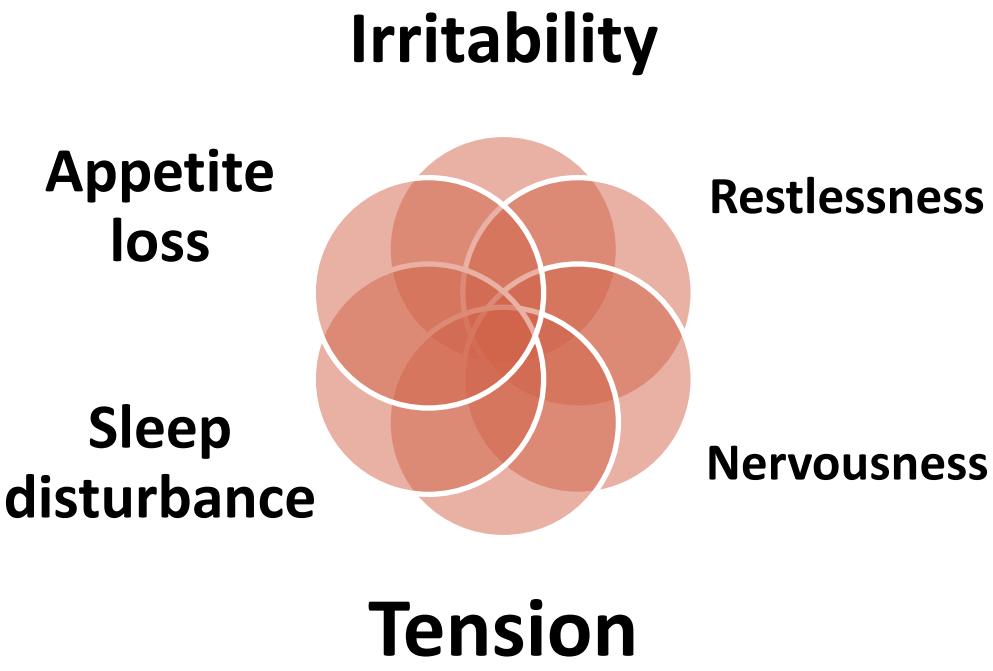
- Bronchitis, compromised pulmonary function
- Lung changes
- Cardiovascular effects
- Pregnancy
- Teratogenic effects
- Hormonal effects

Why is Marijuana a concern?

Addiction

- Progression to chronic use as rapid as nicotine
- More rapid than alcohol
- Tolerance and withdrawal may reflect more severe addiction

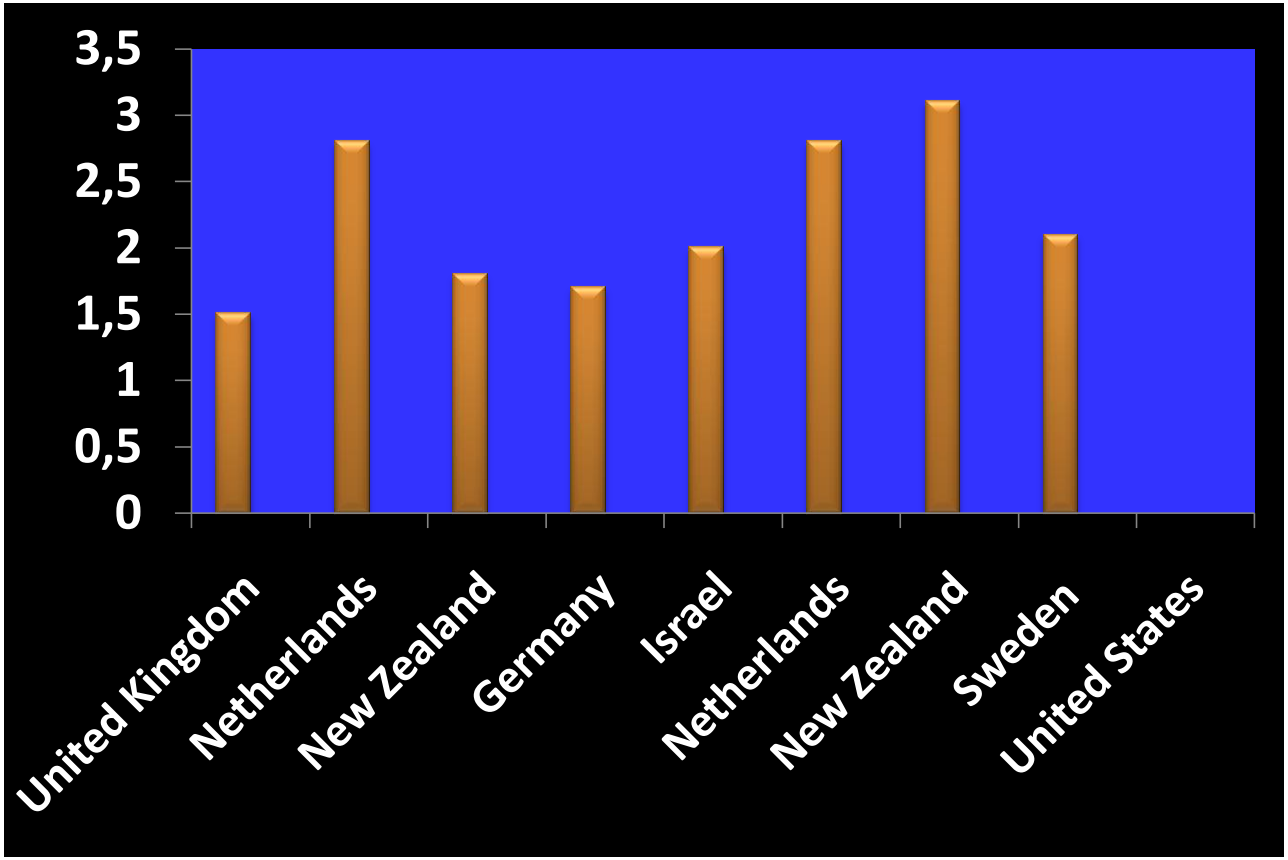
Withdrawal



Why is Marijuana a Concern?

Marijuana and psychosis

Odds ratio



Adapted from Nat Rev Neurosci. 2007 Nov;8(11):885-95. Cannabis, the mind and society: the hash realities. Murray RM, Morrison PD, Henquet C, Di Forti M.

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The future: policies and cannabinoids

How do drugs get approved in the United States? Food and Drug Administration

FDA is the *sole* Federal agency that approves drugs as safe and effective for intended indications.

The Federal Food, Drug, and Cosmetic (FD&C) Act requires: new drugs be shown *safe and effective for their intended use* before US marketing.

FDA approval process requires: controlled research, clinical trials to base approval on safety, efficacy and labeling decisions.

To bypass the FDA drug approval process might expose patients to unsafe and ineffective drug products.

LAETRILE

Food and Drug Administration:
Drug Development Process

Test Tube to New Drug Application Review: ~12 years; ~$350 Million

3.5 years:

laboratory testing; application to FDA for human testing ; 1/1000 compounds go to human testing

1 year: PHASE I:

0-80 healthy volunteers to establish safety and profile

2 Years PHASE II:

100-300 patient volunteers to assess the drug's effectiveness

3 years: PHASE III:

1000-3000 patients in clinics and hospitals to determine effectiveness and adverse reactions

2.5 years:

Application for approval

100,000 pages!!!!!

Ongoing:

If approved, requirement to report cases of adverse reactions, other clinical data to the FDA.

FDA Criteria

- Pure compound
- Chemistry, manufacturing , and controls of composition of matter
- Production methods are validated
- Non-clinical pharmacology and toxicology
- Human pharmacokinetics and bioavailability
- Clinical microbiology
- Clinical data: dose response, efficacy, safety
- Side effect profile
- Case reports, safety updates

Marijuana: Pure Compound? Reproducible Production?

	extreme	
	TOBACCO	**MARIJUANA**
tar (mg/cig)	80.3	103
pH	5.47	7.73
NO (µg/cig)	151	685
NOx (µg/cig)	158	693
CO (mg/cig)	41.5	35.3
nicotine (mg/cig)	5.2	0.002–0.007*
ammonia (µg/cig)	67	1315
HCN (µg/cig)	320	1668
NNN	160	<1.49*
NAT	125	<1.87*
NAB	8.26	0.063–2.00*
NNK	158 ± 15	<3.72*
mercury	5.35	3.51
cadmium	284	14.6
lead	43.8	7.7–25.7*
chromium	11.9–39.6	11.9–39.6
nickel	12.9–43.1	<12.9
arsenic	12.7	2.25–7.49*
selenium	4.42–14.7	4.42–14.7

Ma… …pure produc…

Mari… in to… …marijuana smoke …

Hydr… mari… …d some aromatic a… …ions 3–5 times tho…

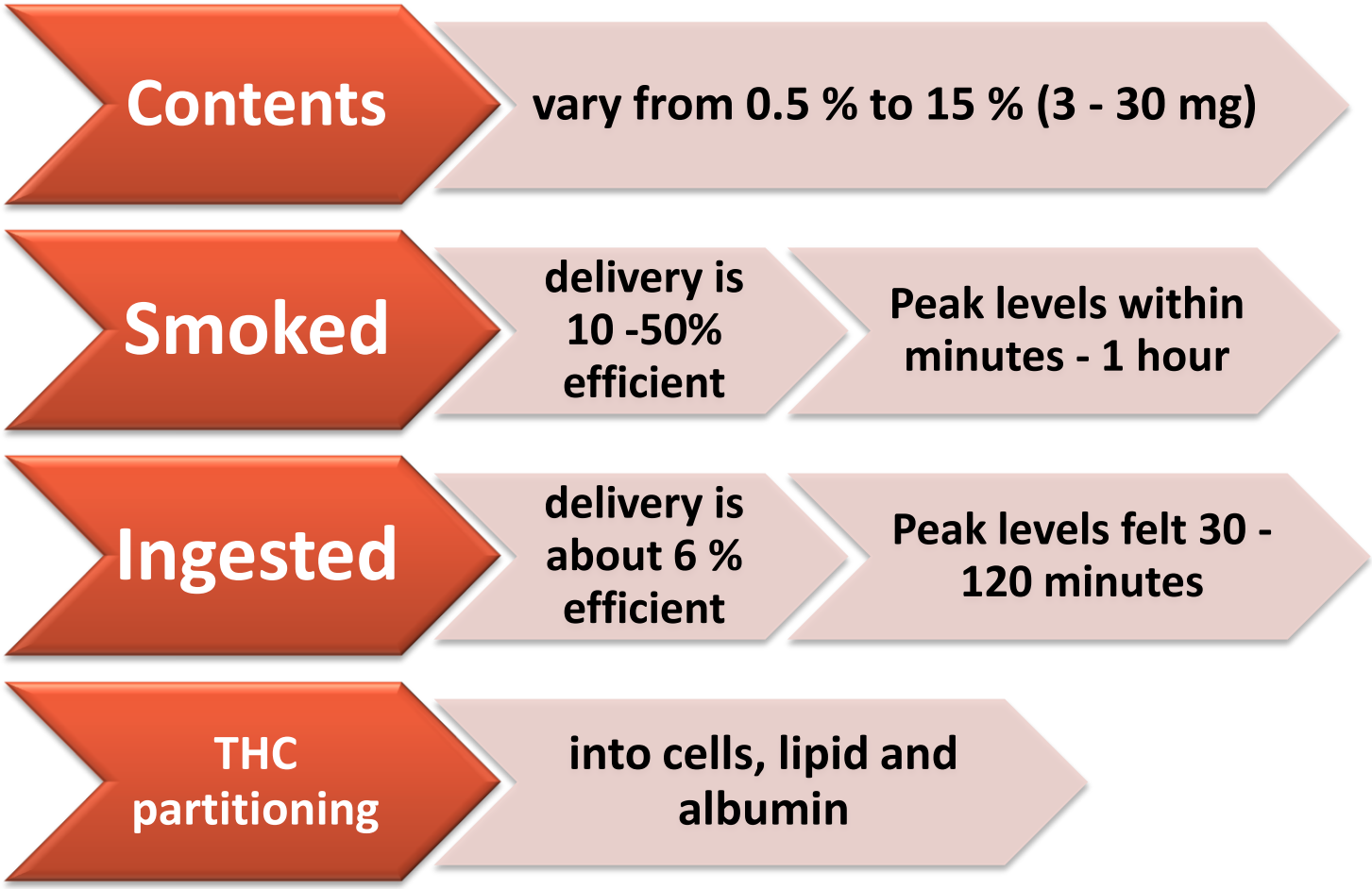
Mari… chem… …tained known carc… …tory diseases.

	TOBACCO	**MARIJUANA**
naphthalene	4908	4459
1-methylnaphthalene	4888	4409
2-methylnaphthalene	3666	2917*
acenaphthylene	711	459*
acenaphthene	309	213*
fluorene	1369	659*
phenanthrene	515	476
anthracene	162	136*
fluoranthene	171	117*
pyrene	154	82.3*
benzo(a)anthracene	52	43.1*
chrysene	61.7	56.3
benzo(b)fluoranthene	21.9	16.2*
benzo(k)fluoranthene	7.45	4.54*
benzo(e)pyrene	19.2	12.6*
benzo(a)pyrene	25.1	15.5*
perylene	10.8	6.10*
indeno(1,2,3,-cd)pyrene	10.1	8.65
dibenz(a,h)anthracene	4.84	2.83*
benzo(g,h,i)perylene	7.17	6.03
5-methylchrysene	<0.071	<0.071
benzo(b)fluoranthene	19.1	17.6
benzo(j)fluoranthene	13.3	12.2
dibenz(a,h)acridine	<0.628	<0.628
dibenz(a,j)acridine	<0.519	<0.519
7H-dibenzo(c,g)carbazole	<0.278	<0.278
dibenz(a,l)pyrene	<0.634	<0.634
dibenz(a,e)pyrene	<0.313	<0.313
dibenz(a,i)pyrene	2.55	<0.329*
dibenz(a,h)pyrene	<0.354	<0.354

Moir et al, A Comparison of Mainstream and Sidestream Marijuana and Tobacco Cigarett… Conditions. *Chem. Res. Toxicol.*, **2008**, *21* (2), pp 494–502

Standard conditions employed a puff volume of 35 ml, a puff duration of 2 s, and a puff interval of 60 s. These conditions are termed “ISO” throughout. Conditions more reflective of marijuana smoking employed a puff volume of 70 ml, a duration of 2 s, and a 30 s interval. These conditions are referred to as “extreme” and differ from the Health Canada “intense” tobacco smoking conditions, which employ a puff volume of 55 ml

Marijuana: Predictable delivery? Smoked or Ingested Marijuana



Does Smoked Marijuana fulfill FDA Dose Requirements?

- Not standardized
- No quality control
- Dose not regulated
- Dosage forms not regulated
- Smoked, vaporized, baked products, teas

Clinical Trials: MS, cancer, HIV-AIDS appetite

Multiple Sclerosis: spasticity or pain

TRIALS	#	# PATIENTS	RESULTS
THC	3	30	2/3 subjective
THC + CB	7	> 700	mixed
Smoke		1	Reduced spasticity
Smoke		10	Impaired posture, balance
Smoke		1	Reduced nystagmus
Sativex	1	337	No significant effect on pain

Cancer and HIV-AIDS Appetite

TRIAL	#	PATIENTS	RESULTS
THC	5	>300	Improved appetite
THC vs Megace synthetic derivative of progesterone	1	52	Megace more effective

Clinical Trials: Pain

- Cancer (44): THC better than placebo;
  1 trial compared with other pain killer
- Dental extraction (10):THC better than placebo
  - not as good as Valium
- HIV: SMOKE (143/523) questionnaire to patients who used marijuana, self-reported improvement
- HIV Neuropathic Pain: SMOKE experienced marijuana users also on opoids; 7 reported improvement over placebo cigarettes
- Neuropathic pain: SMOKE

Clinical Trials: Nausea, glaucoma

Nausea

THC: (n=1366) 30 RCT better than placebo

Glaucoma

Smoked or ingested THC: side effect profile prominent: hypotension, rapid heart rate, euphoria, dysphoria, changes in pupil size, increased tear production, conjunctival hyperemia

Clinical Trials: other

Primary dystonia

Nabilone (n=15): no improvement

Tourette's

THC (n=36): reduced tics

Psychosis/schizophrenia

CB1 antagonist (n=481): no improvement

Obesity

Rimonabant (n>5,500) weight reduction (nausea, anxiety, diarrhea

Clinical Trials: Brain disorders

Parkinson's disease

CB_1 antagonist (n=24): no improvement

Nabilone (n=7): - *not psychoactive* - reduces dyskinesia

(Sieradzan KA, et al., Cannabinoids reduce levodopa-induced dyskinesia in Parkinson's disease: a pilot study. Neurology. 2001 Dec 11;57(11):2108-11.)

Alzheimer's Disease

Dronabinol (n=6): reduced agitation

(Walther S, Mahlberg R, Eichmann U, Kunz D. Delta-9-tetrahydrocannabinol for nighttime agitation in severe dementia. Psychopharmacology (Berl). 2006 May;185(4):524-8.)

Traumatic brain injury

Dexanabinol: (n=861) no improvement

(Maas AI et al., Pharmos TBI investigators. Efficacy and safety of dexanabinol in severe traumatic brain injury: results of a phase III randomised, placebo-controlled, clinical trial. Lancet Neurol. 2006 Jan;5(1):38-45.)

California

Center for Medicinal Cannabis Research

36 scientific reports were issued

less 12 abstracts or proceedings

24 publications

5 clinical studies were discontinued - could not recruit enough participants for cancer pain relief, muscle spasticity, multiple sclerosis, severe nausea and vomiting, neuropathic pain

4 were performed with patients according to ballot initiative:

all experienced marijuana users

California

Center for Medicinal Cannabis Research

- **INVESTIGATOR:** Donald Abrams, M.D.**PROJECT TITLE:** Marijuana in Combination with Opioids for Cancer Pain
- **PROJECT TYPE:** Clinical Study
- **STATUS:** **DISCONTINUED**
- **RESULTS:**

The study experienced difficulty with recruitment of participants, in part due to the 9-day hospitalization required for study participation. A variety of recruitment strategies were employed, including outreach to local oncologists, advertisements in local print media, and presentations at various related functions. None of these strategies were successful and the trial was discontinued.

California

Center for Medicinal Cannabis Research

- **INVESTIGATOR:**Mark Agius, M.D.

- **PROJECT TITLE:** Cannabis for Spasticity/Tremor in MS: Placebo Controlled Study
- **PROJECT TYPE:**Clinical Study
- **STATUS:** **FUNDING DISCONTINUED**
- **RESULTS:**This study sought to evaluate the safety and efficacy of smoked cannabis in relieving the spasticity associated with multiple sclerosis (MS) as measured by a new objective measure of spasticity.

Unfortunately, recruitment for this study proved to be difficult for many reasons, including a prohibition on driving throughout the 16 weeks participants were enrolled in the study. The study was reviewed by the CMCR Scientific Review Board and Data Safety Monitoring Board who both recommended discontinuation for lack of feasibility. No preliminary analyses of safety or efficacy were possible.

California

Center for Medicinal Cannabis Research

- **INVESTIGATOR:**Dennis Israelski, M.D.
- **PROJECT TITLE:** MMJ for HIV-associated DSPN: Adherence & Compliance Sub-Study
- **PROJECT TYPE:** Clinical Study, Sub-Study

- **STATUS:** **DISCONTINUED**
- **RESULTS:** Recruitment for this sub-study stemmed from the parent study. Methods for recruitment included: dear doctor letters, flyers, and postings on San Mateo Medical Center and Center Watch clinical trials websites. A series of focus groups were organized to get community input regarding the study.
- Changes were made to the study as a result of the focus groups with the intent **of improving recruitment, but no such improvement occurred. In total, only three patients were recruited into the sub-study, and thus did not provide enough data for analyzable results.**

California

Center for Medicinal Cannabis Research

- **INVESTIGATOR:**Suzanne Dibble, DNSc, RN
- **PROJECT TITLE:**Treating Chemotherapy-Induced Delayed Nausea with Cannabinoids
- **PROJECT TYPE:**Clinical Study

- **STATUS: DISCONTINUED**

Unfortunately, recruitment proved more difficult than anticipated and the study was discontinued. In total, 172 people were screened, but only 6 completed the study. Most people who could not participate in the study lacked a "moderate amount of nausea." This may be in large part due to recent advances in anti-nausea drug treatments. As the target for enrollment was 81 patients, the 6 who completed were not sufficient to produce analyzable results.

California

Center for Medicinal Cannabis Research

- **INVESTIGATOR:**Mark Wallace, M.D.
- **PROJECT TITLE:** Analgesic Efficacy of Smoked Cannabis in Refractory Cancer Pain
- **PROJECT TYPE:**Clinical Study

- **STATUS:** **DISCONTINUED**

- **RESULTS: Recruitment for this study was difficult.** Typical methods for recruitment, including posters, newspaper advertisements, and community referral were unsuccessful. Very few cancer pain patients were being seen in the UCSD Pain Clinic during this recruitment period. Local hospice agencies were willing to refer potential subjects, however, these subjects were often already smoking cannabis for pain control. To avoid potential complications from off-study cannabis use, these participants were not recruited. Only one subject was enrolled in the study, and was withdrawn for non-compliance with study procedures. No unexpected or unusual adverse events were noted in this subject.

When Presented With A Clinical Trial "Proving" Marijuana's Effective, What are the Caveats?

Inclusion/exclusion criteria and drop-outs

Are only experienced marijuana users eligible for testing? History of substance abuse?

Are subjects taking other pain-killers or medicines?

How many subjects in each group?

Is marijuana smoke being tested or a cannabinoid pure compound (e.g , marinol, cannabidiol). Source and purity?

Are side effects documented (e.g. cognitive impairment) by direct testing or by self-reports?

How are outcomes measured? Objectively or self-report?

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FDA ruling on marijuana

States rights: ballots, referenda, legislatures

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The future: policies and cannabinoids

Does Marijuana Fulfill FDA Criteria?

- Pure compound - NO
- Chemistry, manufacturing , and control of composition - NO
- Production methods are validated - NO
- Non-clinical pharmacology and toxicology – SOME, BUT INADEQUATE
- Human pharmacokinetics and bioavailability – NOT SYSTEMATIC
- Clinical microbiology - NO
- Clinical data: dose response, efficacy, safety - NO
- Side effect profile -NO
- Case reports, safety updates -NO

FDA Statement on Medical Marijuana

- Marijuana is listed in schedule I of the Controlled Substances Act (CSA), the most restrictive schedule.
- The Drug Enforcement Administration (DEA), which administers the CSA, continues to support that placement and FDA concurred because marijuana met the three criteria for placement in Schedule I under 21 U.S.C. 812(b)(1)
- Marijuana has a high potential for abuse has no currently accepted medical use in treatment in the United States
- Lacks accepted safety for use under medical supervision.
- There is sound evidence that smoked marijuana is harmful.
- A past evaluation by HHS agencies, FDA, SAMHSA and NIDA, concluded that no sound scientific studies supported medical use of marijuana for treatment in the United States
- No animal or human data supported the safety or efficacy of marijuana for general medical use.
- There are alternative FDA-approved medications in existence for treatment of many of the proposed uses of smoked marijuana
- A growing number of states have passed voter referenda (or legislative actions) making smoked marijuana available for a variety of medical conditions upon a doctor's recommendation.
- These measures are inconsistent with efforts to ensure that medications undergo the rigorous scientific scrutiny of the FDA approval process and are proven safe and effective under the standards of the FD&C Act.
- Accordingly, FDA, as the federal agency responsible for reviewing the safety and efficacy of drugs, DEA as the federal agency charged with enforcing the CSA, and the Office of National Drug Control Policy, as the federal coordinator of drug control policy, do not support the use of smoked marijuana for medical purposes.

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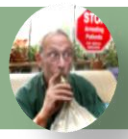


The future: policies and cannabinoids

State Laws with Legal Marijuana as medicine

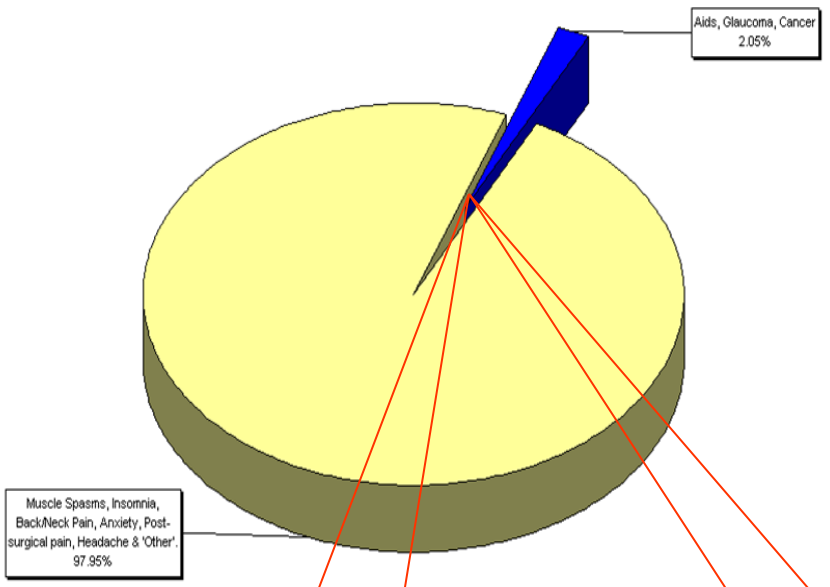
	CACHEXIA ANOREXIA	CANCER	CHRONIC PAIN	EPILEPSY	SEIZURES	GLAUCOMA	HIV-AIDS/Hep C	MULTIPLE SCLEROSIS	SPASTICITY OR CROHN'S	NAUSEA	MIGRAINE OR ALZHEIMER'
AK 1998	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	✘
CA 1996	Yes	Yes	Yes	✘	✘	Yes	Yes	✘	Yes		Yes
CO 2000	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	✘
HI 2000	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	✘
ME 1999	✘	Yes	✘	Yes	Yes	Yes	✘	Yes	Yes	Yes	✘
MT 2004	Yes	✘	Yes	Yes	Yes	✘	✘	Yes	Yes	Yes	✘
NV 2004	Yes	Yes	Yes	✘	Yes	Yes	Yes	✘	Yes	Yes	✘
NM 2007	✘	Yes	✘	Yes	✘	Yes	Yes	Yes	Yes	✘	✘
OR 1998	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
RI 2006	Yes	Yes	Yes	Yes	Yes	Yes	Yes/HepC	Yes	Yes	Yes	Yes
VT 2004	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	✘	Yes	✘
WA 1998	Yes	Yes	Yes	Yes	✘	Yes	Yes/HepC	Yes	Yes	Yes	✘
MI 2008	Yes	Yes	Yes	Yes	Yes	Yes	Yes/HepC	Yes	Yes/ALS	Yes	Yes
NJ 2010	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes/ALS	Yes	

Dose: How much can public possess?

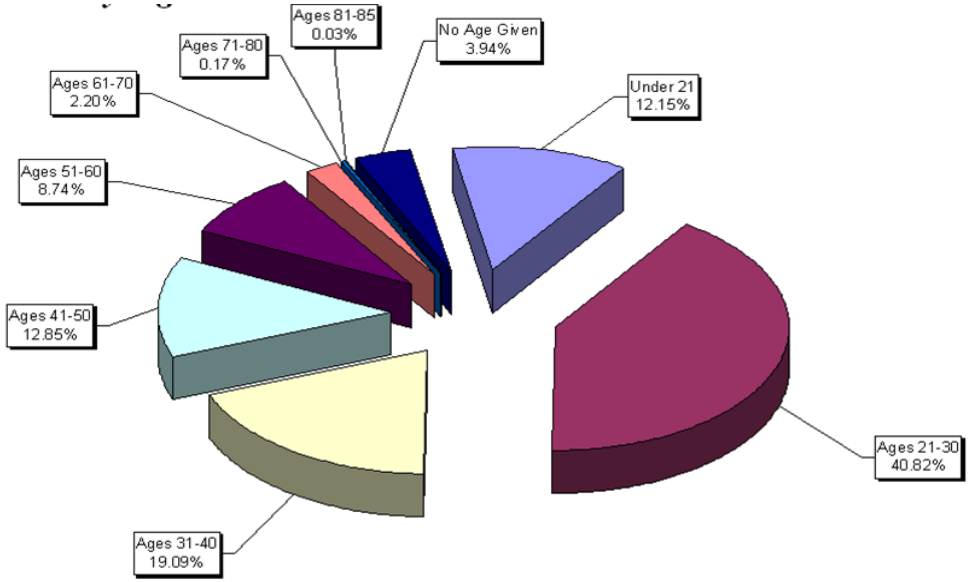
Alaska	1 oz	6 immature	3 mature
California	8 oz	12 immature	6 mature or more
Colorado	2 oz	6 plants	
Hawaii	1 oz	7 plants	3 mature
Maine	1.25 oz	6 plants	3 mature
Montana	1 oz	6 plants	
New Mexico	Adequate supply	3 months uninterrupted supply	
Nevada	1 oz	7 plants	3 mature
Oregon	24 oz	18 seedlings	6 mature
Rhode Island	2.5 oz or		12 plants
Vermont	3 oz	7 plants	
Washington	60 day supply		
Michigan	2.5 oz	12 plants	
New Jersey	2 oz		

San Diego Dispensary: Medical Marijuana

Indications



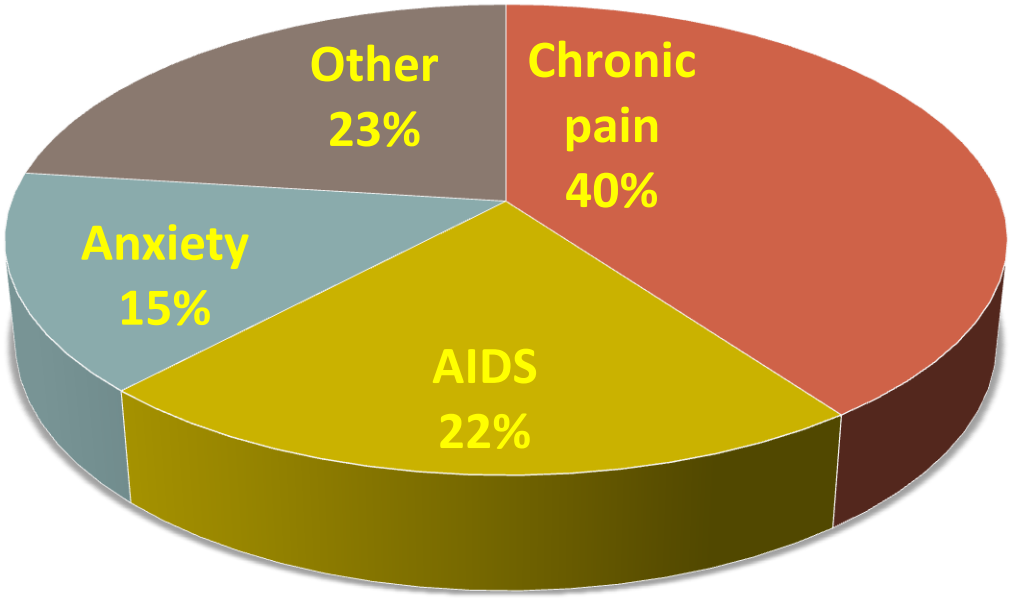
Distribution by Age



	Cachexia anorexia	Cancer	Chronic pain	Epilepsy	Seizures	Glaucoma	HIV-AIDS	Multiple sclerosis	Spasticity or Crohn's	Nausea	Migraine or Alzheimer'
CA*	yes	yes	yes	✘	✘	yes	yes	✘	yes	✘	yes

Muscle spasm, insomnia, back/neck pain, anxiety, post-surgical pain, headache, other

Reasons Given for Using Marijuana



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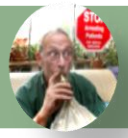
States rights: ballots, referenda, legislatures

Smoked marijuana as “medicine”: A Medical Disaster



The future: policies and cannabinoids

Marijuana as "medicine" is a medical disaster

Composition of matter: is completely unregulated purity, potency, quality, homogeneity unknown

Medical indications: For many conditions, evidence is thin or absent

Medical education: Practice of medicine increasingly is evidence-based but marijuana has no scholarly presence in medical training

Medical practice: no requirement to extract medical history or give a detailed medical exam, discuss long term treatment, effects or follow-up, provide informed consent, consult with other physicians, keep proper records that support recommending marijuana instead of safe approved alternatives, have a in good faith relationship with patient rather than a "pill mill", be able to identify substance abusers, addicted.

Marijuana Production: Dispensaries had no product liability, no product regulation , no chain of custody, no accountability.

Plants as medicines

Marijuana history and effects

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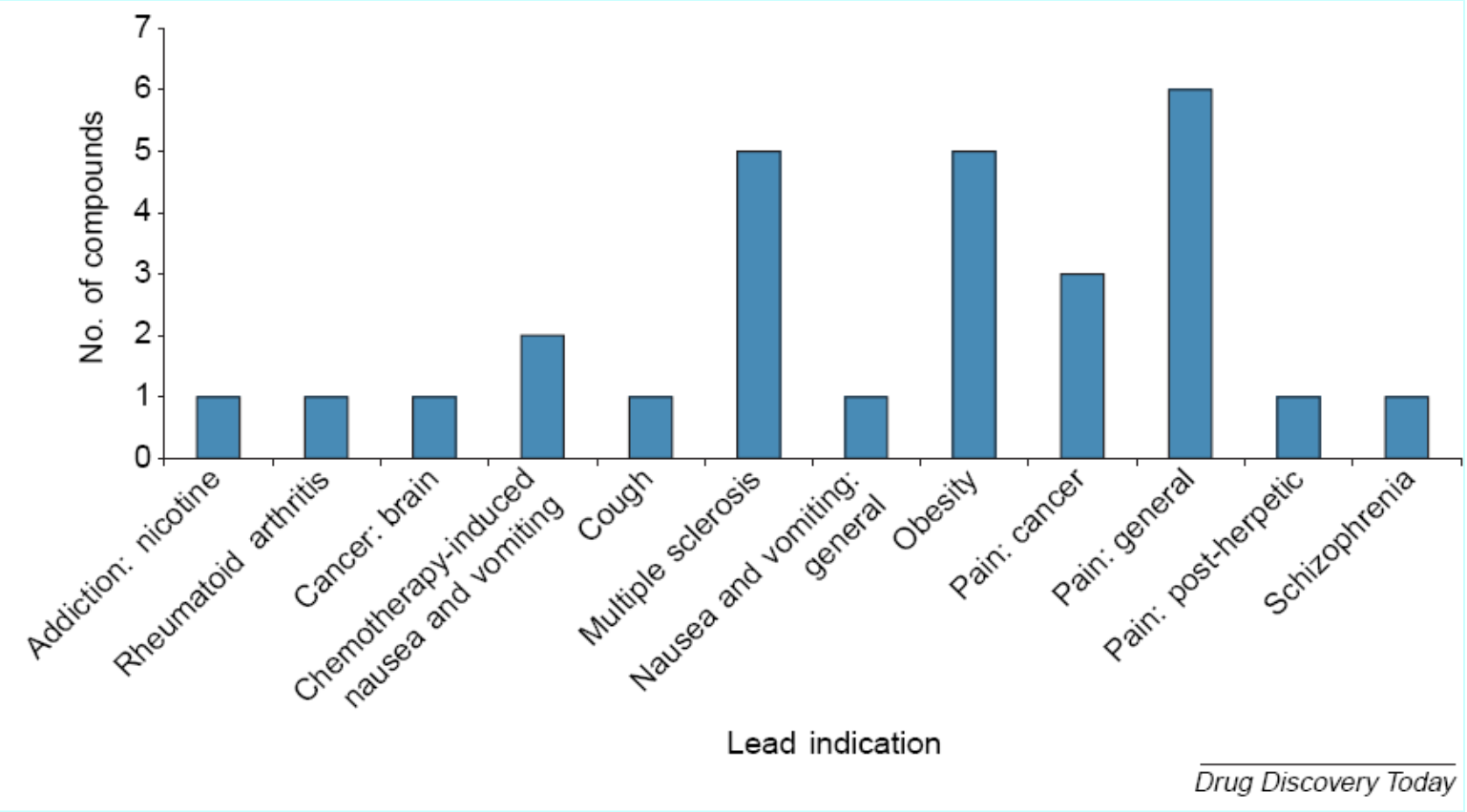
The future: policies and cannabinoids

What can jeopardize the marijuana smoke business?

- More effective non-cannabinoid medications for pain and wasting
- Pure products or drug combinations
- Drugs that increase or decrease endogenous cannabinoids
- Drugs that produce same effects but do not act at cannabinoid CB1 receptor.
- Cannabinoids that do not enter the brain but reduce peripheral pain.
- Cannabinoids that act as antagonists or at completely different receptors

Drug Discovery of Cannabinoids Lead Indications



From: Hensen B: Drug Discovery Today 10:459, 2005.

Marinol: Medicinal properties

THC, (dronabinol, Marinol), is Federally recognized as an appetite stimulant and anti-nausea/vomiting (antiemetic) agent.

It is available through special prescription to treat persons suffering from chemotherapy- or radiation-related nausea, and to treat people suffering from AIDS-related anorexia.

The FDA approved it for use:

- as an antiemetic for chemotherapy patients in 1985
- as an appetite stimulant for AIDS patients in 1992

Medicine and the Law

Good Medicine

What doctors are talking about now

Q: Should marijuana be legalized for medical use?

"Marijuana as a medicine needs to be approached as many other medicines are approached: with thoughtfully designed, randomized, controlled trials to determine safety and effectiveness. It is somewhat difficult to give a blanket, affirmative answer to the issue of legalization. The reason is that for several conditions that we have an important role in treating, there is evidence that marijuana constitutes a major risk factor for the illness. I'm actually just starting to do a study on this. It could be a risk factor, not necessarily for everyone, but for people who have a genetic or other vulnerability to the development of schizophrenic illness."

— **Theo Manschreck, M.D., president, Massachusetts Psychiatric Society**

"If Massachusetts enacts legislation that requires a physician's recommendation or prescription before an individual may legally possess or use marijuana, doctors will appear to incur the risks of civil liability for patient injuries, adverse interactions and contraindications. They stand exposed not only to civil liability and administrative investigations, but also to potential federal prosecution for distributing or recommending distribution of an illegal substance under federal law. What, if any, effective protections might be put into place by the Commonwealth if legalization is pursued is an open question."

— **Anthony E. Abeln, associate, Morrison Mahoney LLP, Boston**

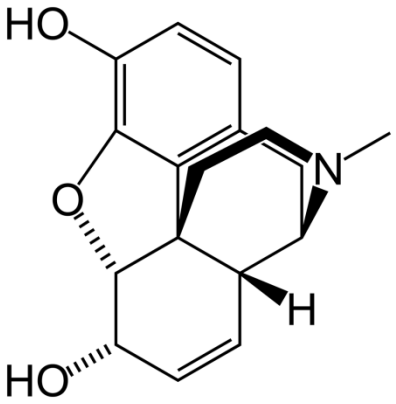
"I do not support approving marijuana for medical purposes. In 2006, the FDA reiterated that smoked marijuana does not meet existing standards of safety and efficacy for modern medicine. Chronic smoked marijuana is detrimental to health — it is teratogenic; increases the risk of pulmonary, cardiac and brain diseases; compromises cognitive function; is addictive and is implicated in psychiatric conditions. Approval will send a wrong message that cigarettes and marijuana are safe, and the process of ballot initiatives for drug approval sets a dangerous precedent by circumventing FDA standards. Also, The Institute of Medicine has declared that smoking marijuana is not modern medicine and should not be recommended generally for medical use."

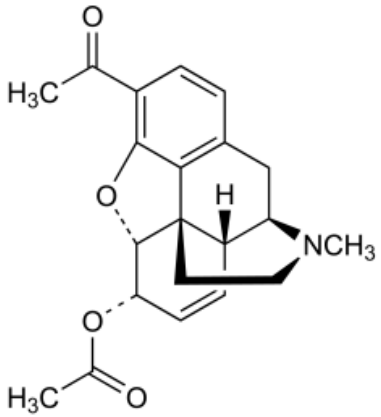
— **Bertha Madras, Ph.D., professor of psychobiology, Harvard Medical School**

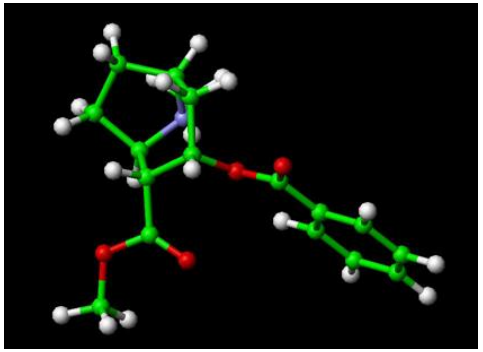
"I have no first-hand knowledge of the benefits of medical marijuana. I am aware that in other states and countries, it has been used to reduce suffering and as palliative treatment for various neurologic conditions such as multiple sclerosis, severe chronic pain, neuromuscular disorders and seizures. Instead of relying on anecdotal evidence, I would support funding for studies and clinical trials to evaluate its potential uses and benefits, as well as its risks and adverse effects. If it is legalized for medical use in this state, I would need to increase my knowledge base to be able to make informed decisions about the use of this drug/plant in cases of appropriate neurologic care."

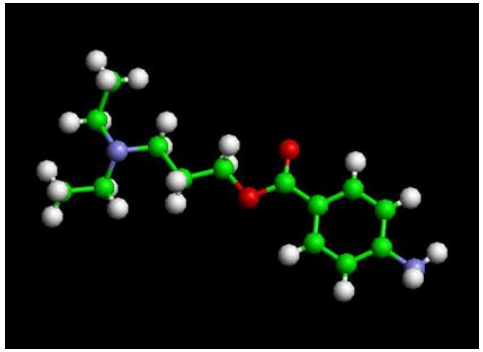
— **Alan Kurland, M.D., president, Massachusetts Neurologic Association**

Plants as sources of drugs









Conclusions

It is poor public policy and medical practice to permit marijuana to be used as a smoked medicine if it is:

- Not FDA-approved
- Ingested by smoking
- Composed of hundreds of chemicals
- Not subject to product liability regulations
- Exempt from quality control standards
- Not governed by dose, frequency of dosing, longitudinal effects
- Provided at unknown strengths of THC
- Self-prescribed and self-administered by the patient

Conclusions

It is poor medical practice to permit marijuana to be used as a smoked medicine if:

- Marinol is approved
- The scientific evidence does not achieve FDA standards for safety, efficacy
- The intoxicating effects of marijuana on cognition are unacceptable
- Long term psychological and physiological effects in sick populations are unknown
- Clinical trials require subjects to be experienced marijuana users
- Majority of trials do not provide side effect profile e.g. cognition
- Provided at unknown strengths of THC
- Self-prescribed and self-administered by the patient