Marijuana: Is It Medicine Yet?

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Donald I. Abrams, MD Disclosure

- Scientific Advisor to:
  - AXIM Biotechnologies, Inc
  - Cannformatics
  - INSYS Therapeutics
  - Intec Pharma
  - Lumen
  - Maui Wellness Group
  - Scriptyx
  - Tikun Olam USA
  - VIVO Cannabis
  - Whistler Therapeutics

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Journal of Experimental Botany
www.jxb.oxfordjournals.org

RESEARCH PAPER

Phytochemical and genetic analyses of ancient cannabis from Central Asia

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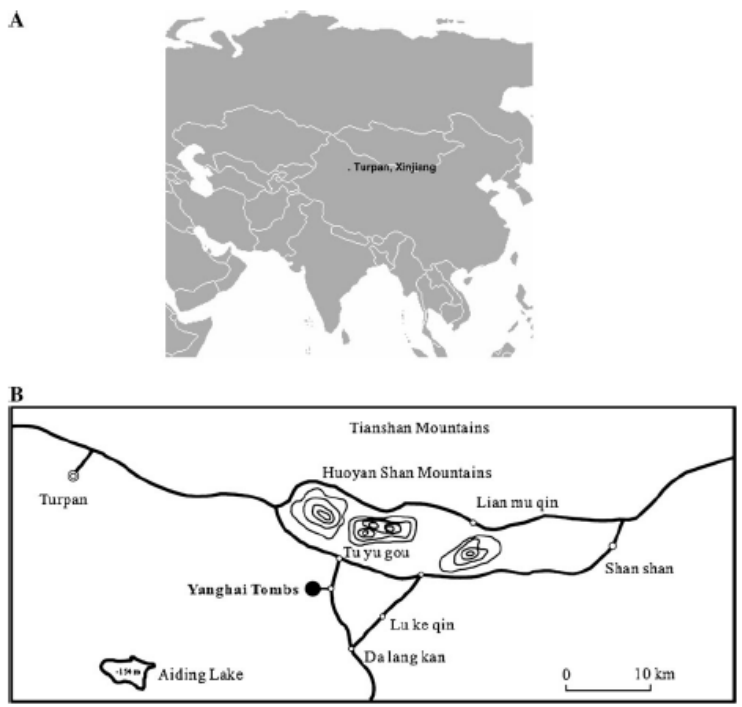
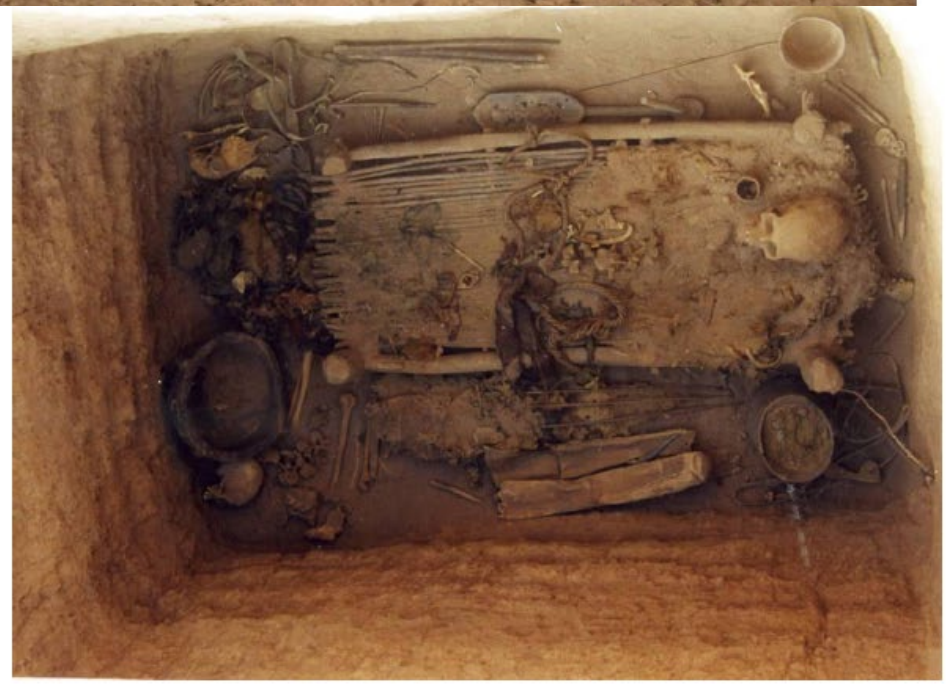


Fig. 1. Area maps. (A) Map of Turpan, Xinjiang, China and its location in Central Asia. (B) Map of Yanghai Tombs site and surrounding area (adapted from Xinjiang Institute of Cultural Relics and Archaeology, 2004).



Russo et al, J Exp Bot 2008

Russo et al, J Exp Bot 2008

Fig S5. Containers in which cannabis was stored in tomb (previously published in Mandarin

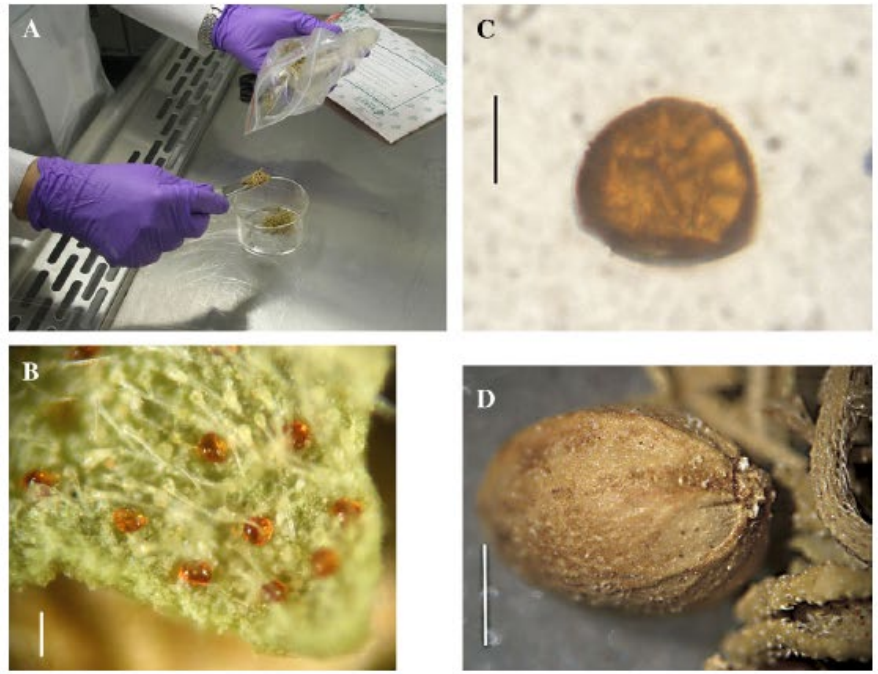


Fig. 2. Photomicrographs of ancient cannabis. (A) Photograph of the whole cannabis sample being transferred in laminar flow hood. (B) Photomicrograph of leaf fragment at low power displaying non-glandular and amber sessile glandular trichomes. Note retention of chlorophyll and

Cannabis as Medicine

- Cannabis (marijuana, hemp) is one of the oldest known psychoactive plants
- First reported use as medicine > 3000 years ago
- Introduced into Western medicine in 1840’s by Dr. W.B. O’Shaughnessy
- Promoted for putative analgesic, sedative, anti-inflammatory, antispasmodic and anticonvulsant properties

Additional products available in 1906 manufactured by Eli Lilly, Wyeth, Sharp & Dohme

Cannabis as Medicine

- Interest waned in early 1900's with advent of opiates, barbiturates, chloral hydrate, aspirin and syringes
- First federal restrictions in 1937 with Marihuana Tax Act ($1/oz for medical use, $100/oz for recreational users)
- AMA virtually alone in opposing act
    - Believed objective data re: harmful effects were lacking
    - Act would impede future clinical investig
- Removed from US Pharmacopoeia in

Harry Jacob Anslinger, zealous mas-

Stakeholder Meeting for the
National Academies' Report:

The Health Effects of Cannabis and Cannabinoids:

The Current State of Evidence and Recommendations for Research

The National Academies of
SCIENCES · ENGINEERING · MEDICINE

Schedule I Substances

- Marijuana
- Heroin
- LSD
- Mescaline
- Other hallucinogenic amphetamine derivatives
- Methaqualone
- Illicit fentanyl derivatives
- Gamma hydroxybutyrate (GHB)

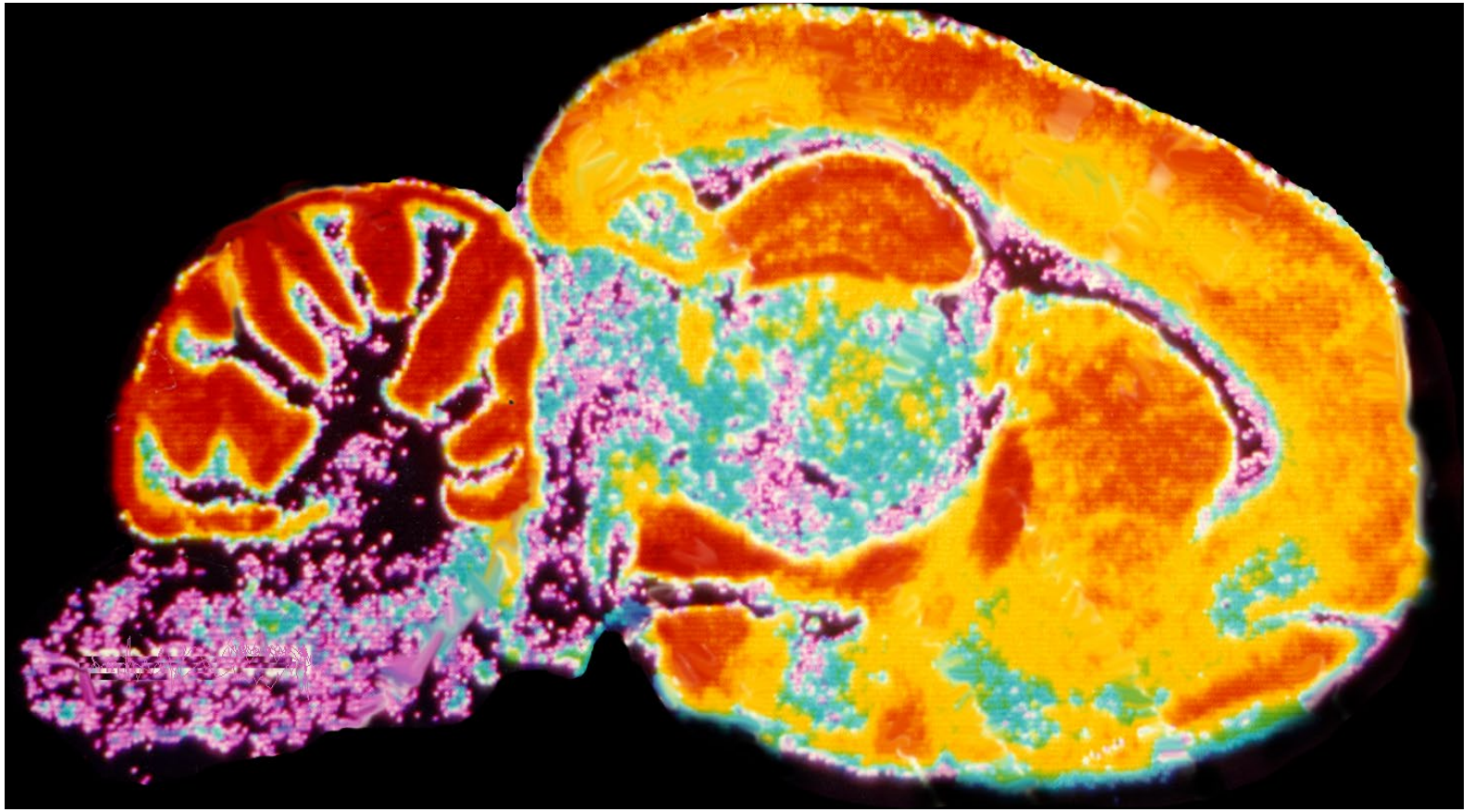
Cannabis as Medicine

- Contains over 400 chemical compounds
- Highest concentration of bioactive compounds in resin exuded from flowers of female plants
- Main psychoactive component believed to be delta-9-THC
- At least 70 other cannabinoids identified in pyrolysis products
- delta-8-THC similar in potency but only in small concentration

Cannabinoid Receptors

- CB_1 and CB_2 receptors identified
- Receptors coupled to G-proteins and inhibit adenylate cyclase
- CNS responses mediated via CB_1 (largest concentration in basal ganglia and cerebellum)
- Activation CB_1 receptor:
    - inhibits N-type voltage-gated Ca channels
    - increases K conductance in hippocampal neurons
    - increases prostaglandin production

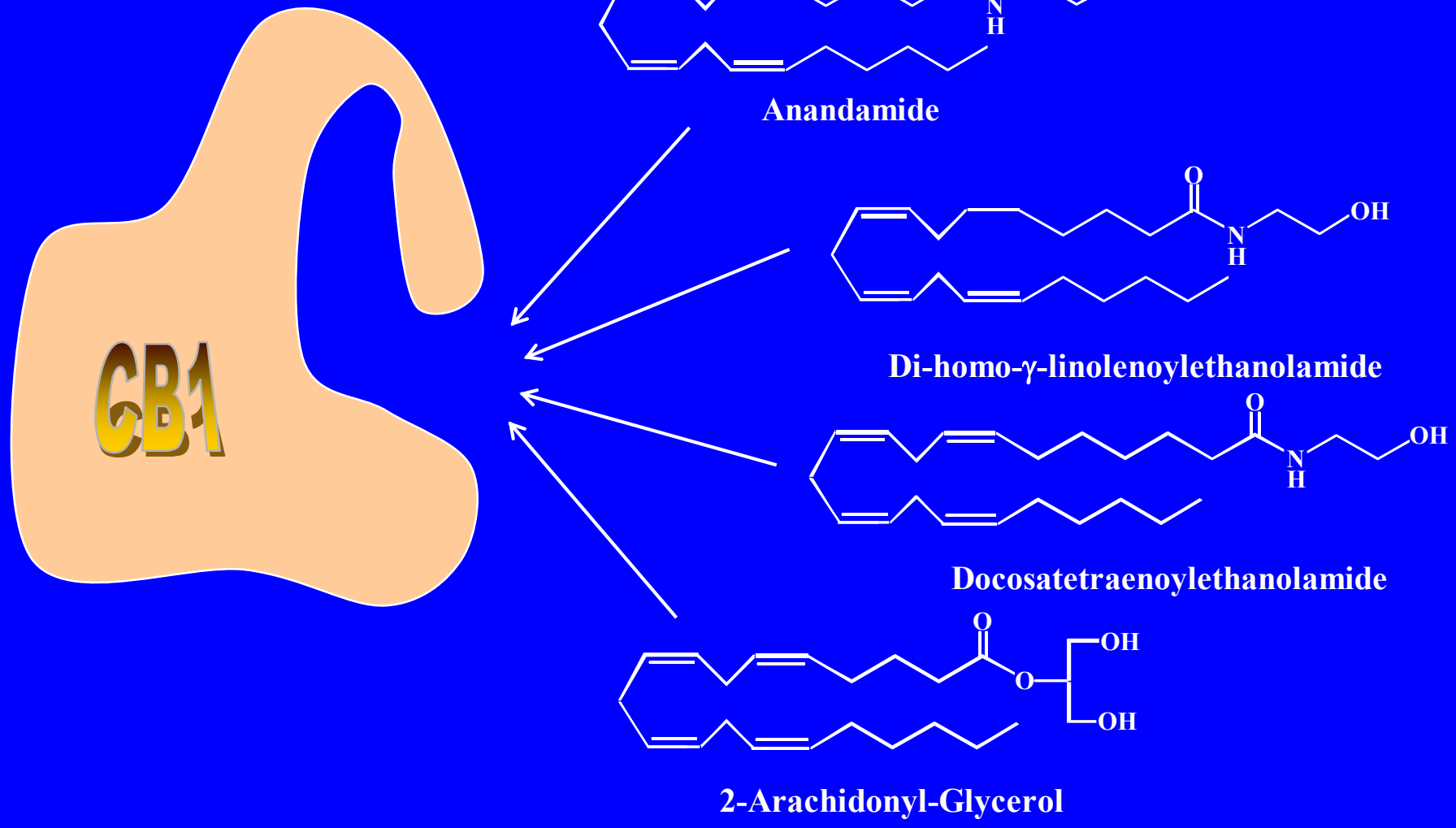
CB_1 Receptor Regional Distribution in Rat Brain



Cannabinoid Receptors

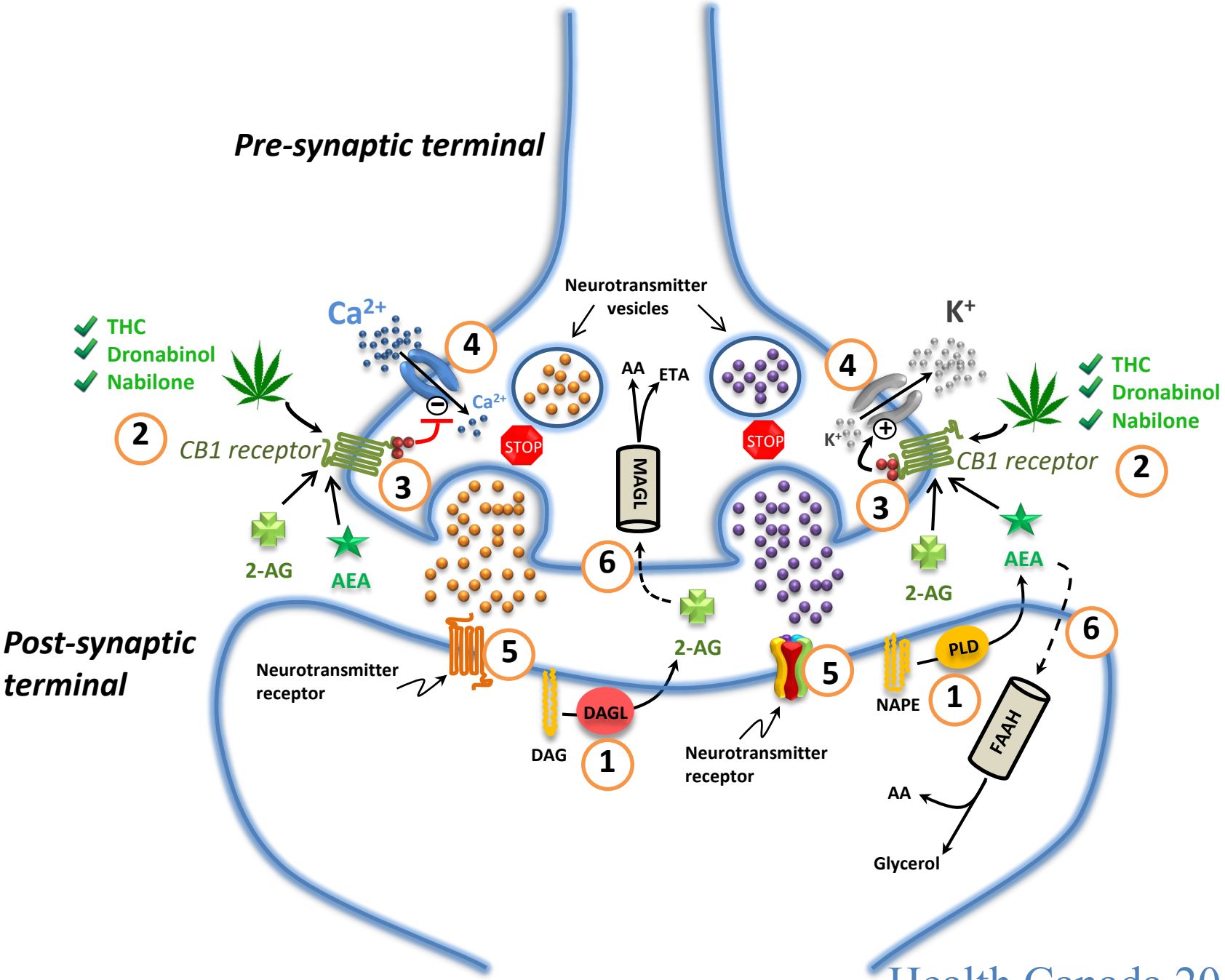
- CB_2 receptor not expressed in the brain
- Originally detected in macrophages and marginal zone of the spleen
- Largest concentration in peripheral blood present in B-cells and NK cells

Endocannabinoids



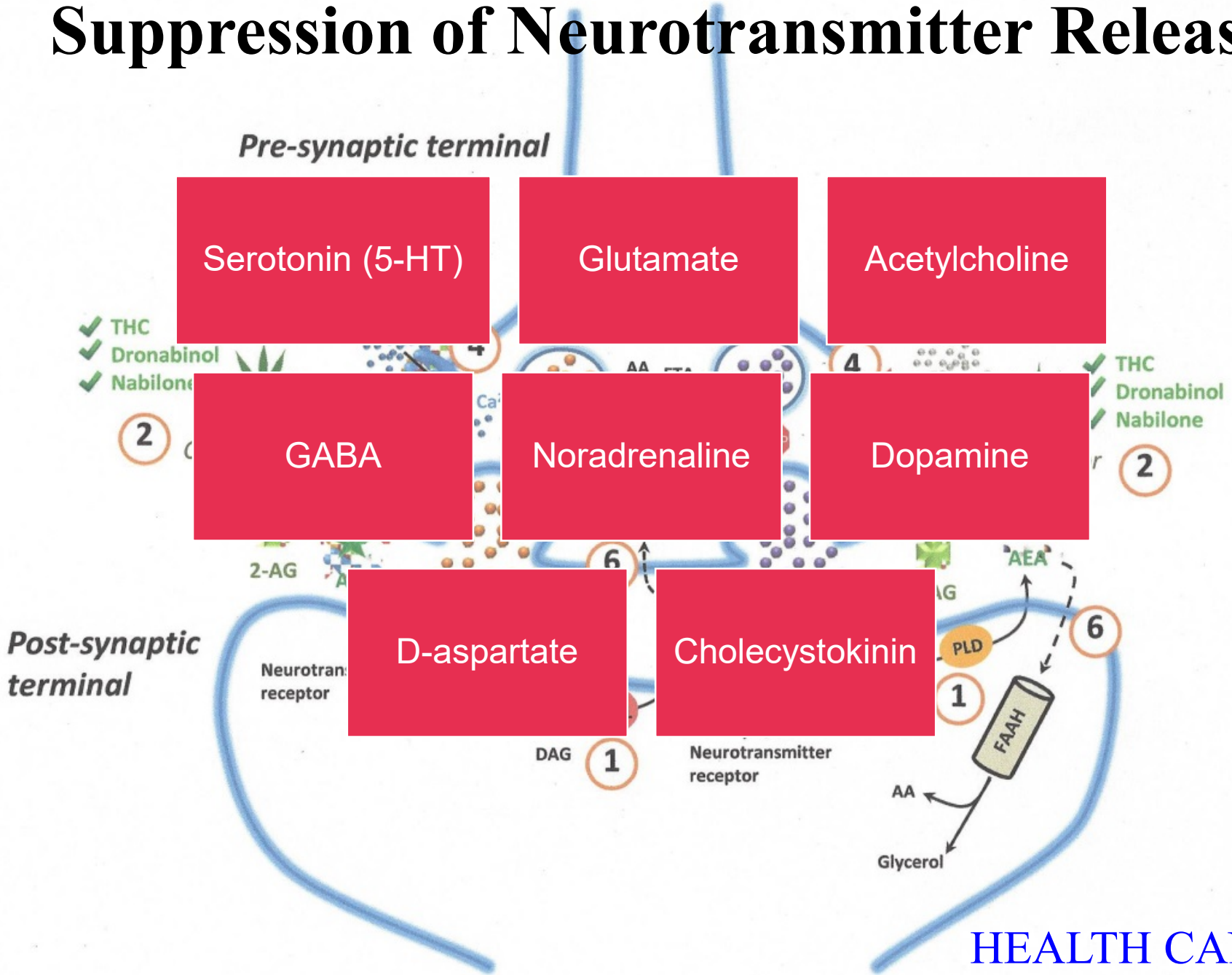
CB_1 Receptor Activation

- Overall effect is suppression of neurotransmitter release at both excitatory and inhibitory synapses
- Inhibition occurs through a retrograde signaling mecahnism
  - ECs are synthesized and released from post-synaptic neurons
  - Diffuse backward across the synaptic cleft and bind to CB_1 receptors on the pre-synaptic terminals



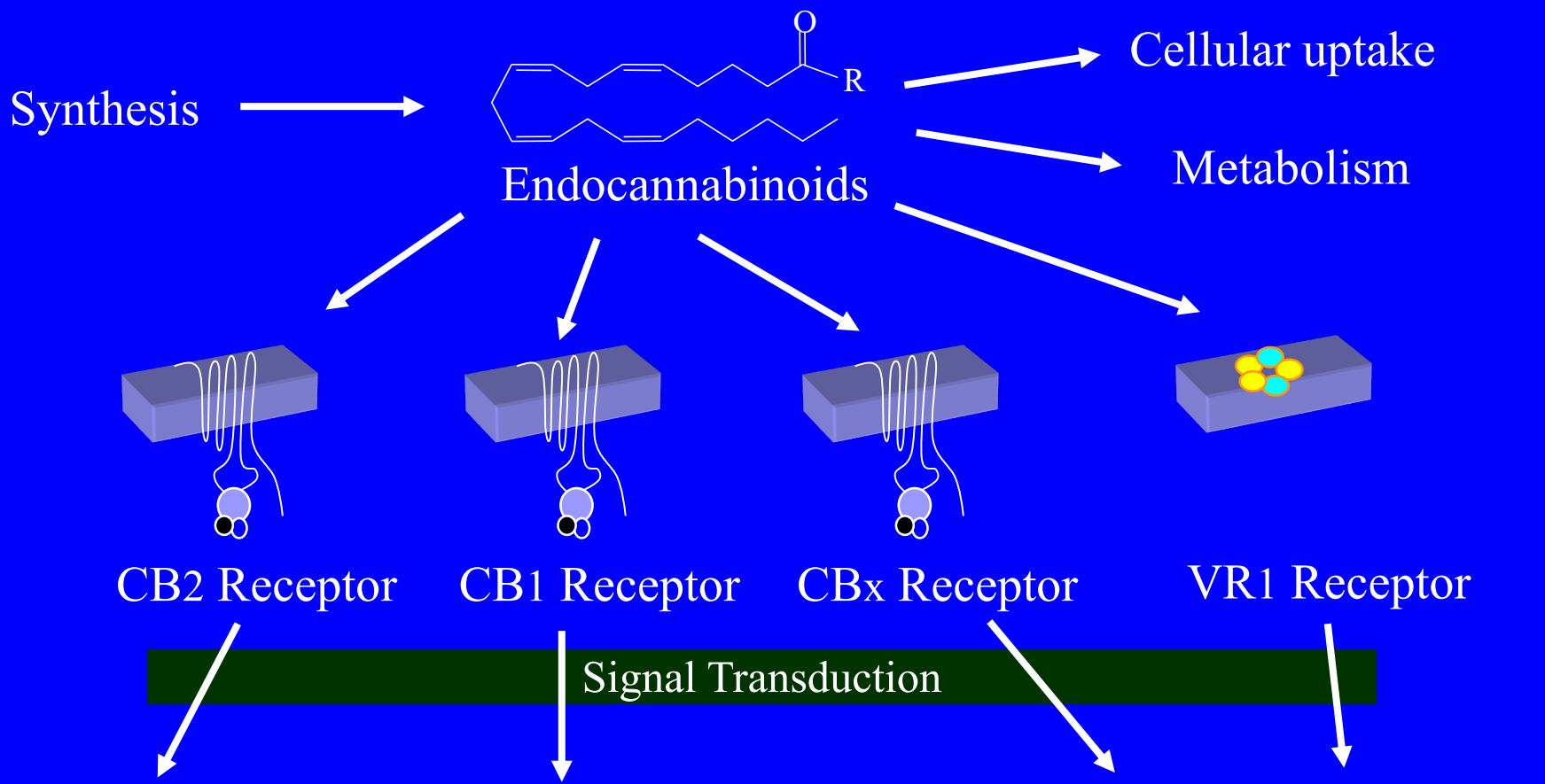
Health Canada 2016

Suppression of Neurotransmitter Release



HEALTH CANADA

Endogenous Cannabinoid System



Martin 2004

What About Cannabidiol (CBD)?

- Modulates the pharmacokinetics of THC
  - Very low affinity for CB1 and CB2 receptors
    - Slight affinity for CB receptors as an antagonist
  - May modulate downstream signal transduction
  - Potent cytochrome P450 3A11 inhibitor thus blocking formation of 11-OH metabolite
- Pre-administration of CBD may potentiate THC effects (PK mechanism)
- Simultaneous co-administration may result in attenuation of some THC effects (PD mechanism)

CBD Effects

- Beneficial effects of the non-psychotropic cannabinoid is derived from *in vitro* and animal studies
- Few, if any, clinical studies of these substances exist
- *In vitro* and animal studies do suggest many potential therapeutic applications

CBD Effects

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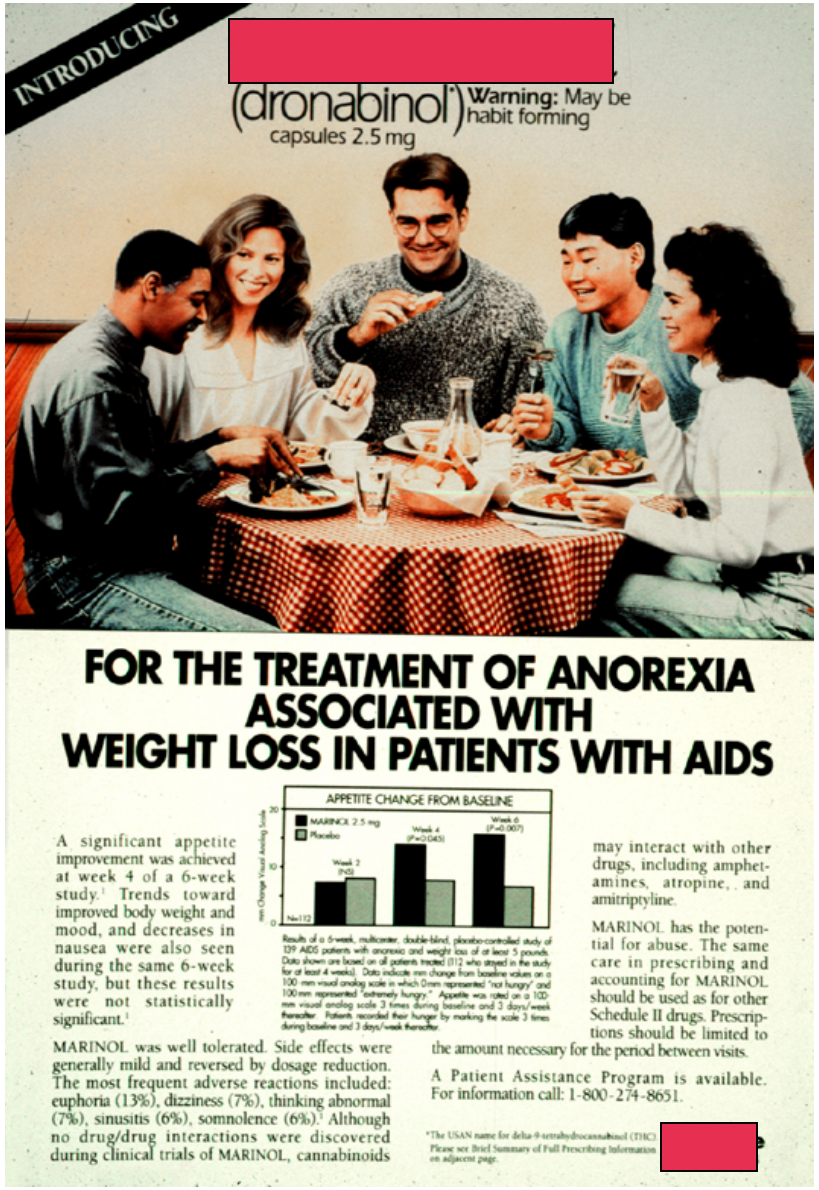
- Few, if any, clinical studies of these substances exist
- *In vitro* and animal studies do suggest many potential therapeutic applications
- Anti-inflammatory
- Analgesic
- Anti-nausea
- Anti-emetic
- Anti-psychotic
- Anti-ischemic
- Anxiolytic
- Anti-epileptiform

Non-THC Components of Cannabis

- ∆9-tetrahydrocannabinol (THC) is the primary active ingredient of cannabis
- Secondary compounds may enhance the beneficial effects of THC
- Other cannabinoid and non-cannabinoid compounds may reduce THC-induced anxiety, anticholinergic effects and immunosuppression
- Terpenoids and flavonoids may increase cerebral blood flow, enhance cortical activity, kill respiratory pathogens and provide anti-inflammatory activity

Oral Delta-9 THC: An Approved Drug



Approved in 1986 for N&V from chemoRx; AIDS anorexia in 1992

Oral THC Pharmacology

- Low (6-20%) and variable bioavailability
- Peak [plasma] within 1-6 hr; may remain elevated for several hrs
- Initially oxidized in liver to 11-OH-THC, a potent psychoactive metabolite
- Further oxidation of 11-OH-THC leads to elimination products (urine and feces)
- Terminal half life 20-30 hrs

Smoked THC Pharmacology

- Rapidly absorbed into blood stream and redistributed
- Considerable amount of dose lost in smoke and destroyed by pyrolysis
- Peak blood levels achieved at end of smoking, decline rapidly over 30 minutes
- Smoking achieves higher peak concentration but shorter duration of effect
- Smaller amts 11-OH-THC formed

Stakeholder Meeting for the
National Academies' Report:

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SCIENCES · ENGINEERING · MEDICINE

Summary of Statement Task

- Develop a comprehensive, in-depth review of existing evidence regarding the health effects (both harms and benefits) of cannabis and cannabinoids use

- Make short- and long-term recommendations regarding a research agenda to identify the most critical research questions and advance the cannabis and cannabinoid research agenda

Study Approach

Committee member expertise included:

- substance abuse
- cardiovascular health
- general epidemiology
- immunology
- pharmacology
- pulmonary health
- neurodevelopment
- oncology
- pediatrics
- public health
- systematic review methodology
- and others…

Between June and December 2016, the committee held 5 in-person meetings and 1 virtual meeting

The committee held 2 open session meetings

Study Approach

- Adopted key features of a systematic review process
- Conducted an extensive search of relevant databases (e.g., Medline, Embase, the Cochrane Database of Systematic Reviews, PsycINFO)
  - Initial search resulted in more than 24, 000 articles
  - Committee considered more than 10,000 abstracts to determine relevance for the report
- Primacy given to recently published systematic reviews and high-quality primary research that studied one or more of the committee's 11 prioritized health endpoints

Study Approach

- Standardized language to categorize the weight of evidence

- 5 levels of evidence:
  - CONCLUSIVE
  - SUBSTANTIAL
  - MODERATE
  - LIMITED
  - NO or INSUFFICIENT

Conclusive or Substantial Evidence of Effect

- For this level of evidence, there are many (or several) supportive findings from good-quality studies with no credible opposing findings. A firm conclusion can be made, and the limitations to the evidence, including chance, bias, and confounding factors, can be ruled out with reasonable confidence.

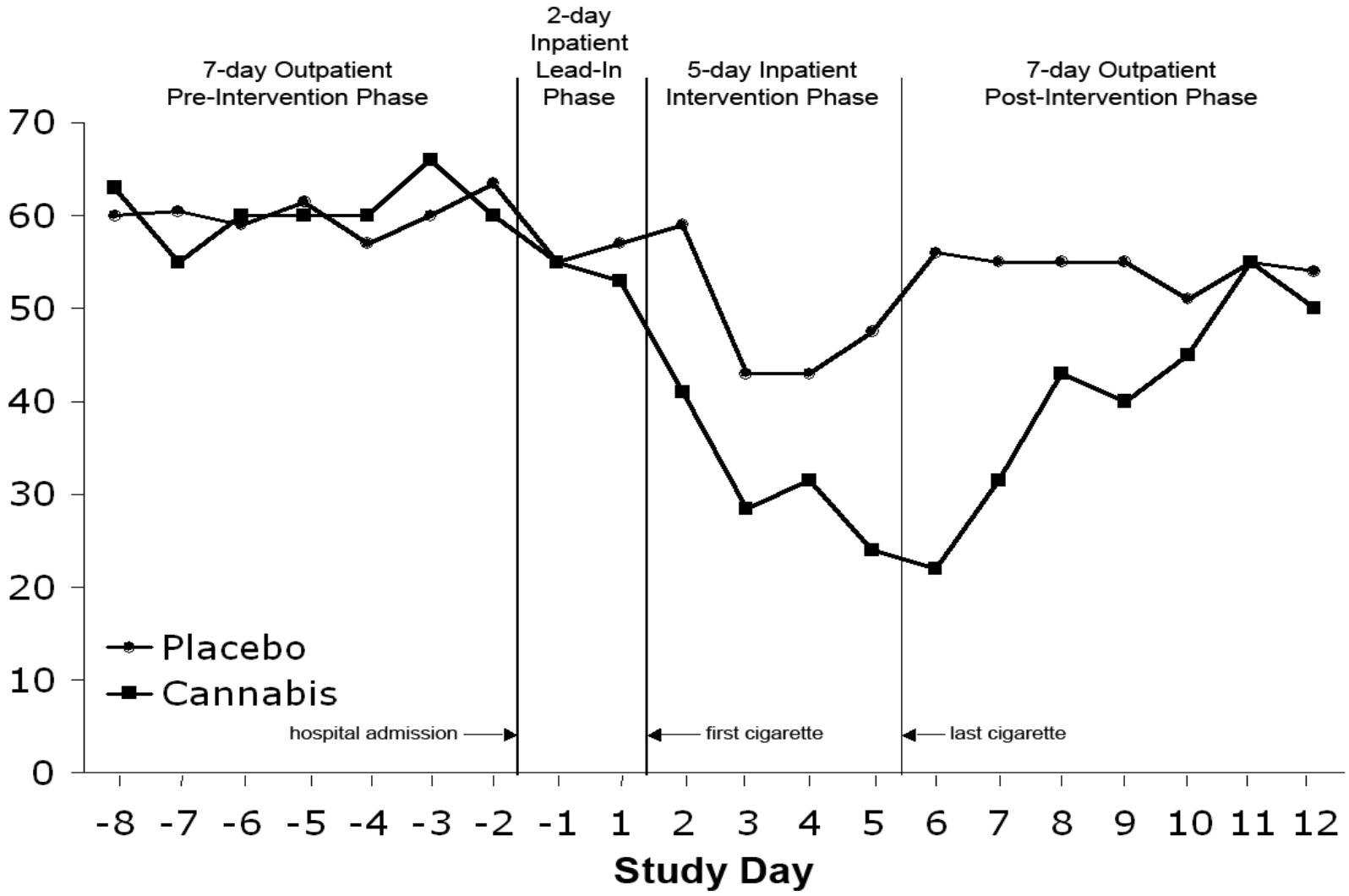
  - For the treatment for chronic pain in adults (cannabis)
  - Antiemetics in the treatment of chemotherapy-induced nausea and vomiting (oral cannabinoids)
  - For improving patient-reported multiple sclerosis spasticity symptoms (oral cannabinoids)

A Tale of Two Systematic Reviews of Cannabinoids in Chronic Pain

- Whiting JAMA'15
- 28 studies (2454 pts) 13 nabiximols, 5 inhaled
- >30% ↓ pain favored active over placebo (OR 1.41 [0.99-2.00])
- Moderate quality evidence of benefit in neuropathic and cancer pain

- Nugent AIM '17
- 27 trials of "plant-based" cannabis preparations
- Low strength evidence for alleviation of neuropathic pain
- Insufficient evidence in other pain populations

Results: Neurology RCT



Abrams et al Neurology 2007

HIV Neuropathy Meta-Analysis of Individual Patient Data

- Pooled individual patient treatment effects from 5 RCTs
- Involved 178 participants with 405 specific effects
- Evidence synthesis provides evidence that inhaled cannabis results in short-term reductions in chronic neuropathic pain for 1 in every 5-6 patients treated (NNT 5.6; 3.4-14)

Andreae et al, J Pain 2015

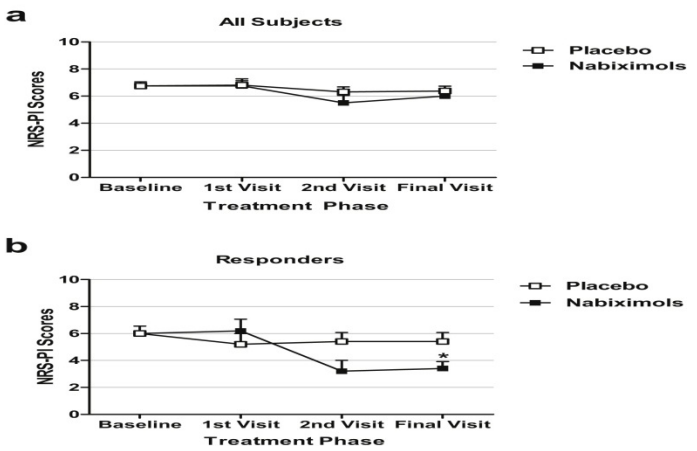
Cannabis in Diabetic Neuropathy

- Randomized, double-blind, placebo-controlled crossover study in 16 pts
- Vaporized placebo or 1%, 4% or 7% THC administered each once in 4 single dosing sessions
- There was a significant difference in spontaneous pain scores between doses ($P<.001$) in a dose response fashion

Wallace et al, J Pain 2015

Nabiximols in Chemotherapy-Induced Peripheral Neuropathy

- Nabiximols has been shown to be effective in relief of pain associated with multiple sclerosis, cancer and rheumatoid arthritis
- 16 patients with CIPN randomized to nabiximols or placebo in crossover pilot study
- Overall, no significant difference between groups
  - 5 pts reported > 2 point ↓ on 0-10 scale
  - Average ↓ 2.6 in the 5 responders
  - NNT=5



Lynch et al, J Pain Symptom Management, 2013

GELATINE-COATED

NEURALGIC, Idiopathic

(Brown-Séquard)

Ext. Hyoscyamus	2-3 gr.
Ext. Conium	2-3 gr.
Ext. Ignatia	1-2 gr.
Ext. Opium	1-2 gr.
Ext. Aconite Leaves	1-3 gr.
Ext. Cannabis Ind.	1-4 gr.
Ext. Stramon. Seed	1-5 gr.
Ext. Bellad. Leaves	1-6 gr.

JOHN WYETH & BROTHER, Inc.

PHILADELPHIA

0665233

Guaranteed under The Food and

Cannabinoid: Opioid Interactions

- Share several pharmacologic properties:
  - Antinociception
  - Hypothermia
  - Sedation
  - Hypotension
  - Inhibition of intestinal motility and locomotion

- Initially thought to act on same pathways to produce their pharmacologic actions

Cannabinoid: Opioid Interactions

- In mice and rats, THC greatly enhances analgesic effect of morphine in a synergistic fashion
- Increased potency of other mu opioids (hydromorphone and oxymorphone) seen with oral-Δ-9-THC in mouse models
- Possibility of enhanced and persistent analgesic effect at lower opioid doses

Welch and Cichewicz, multiple refs

Cannabinoid: Opioid Interaction Trial: Objectives

- Evaluate effect of vaporized cannabis on blood levels of prescribed opioids:
  - Sustained release morphine
  - Sustained release oxycodone
- Determine the short-term side-effects of co-administration of cannabis and opioids
- Assess effect of vaporized cannabis on level of chronic pain

Funded in part by NIDA and NIH CRC grants

Cannabinoid: Opioid Interaction Trial: Design

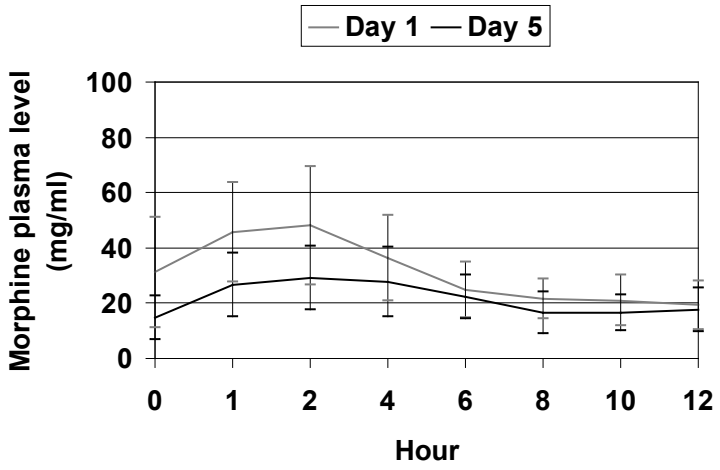
- 5-day inpatient study in Clinical Research Center at SFGH
- 12-hour blood sampling on day 1 on stable daily dose of opioid analgesic
- Vaporization of 3.2% THC cannabis commences at 8 pm day 1; then three times daily at 8am, 2pm, 8pm
- After 8am vaporization on day 5, plasma sampled for 12 hours for opioid and THC levels
- Subjects complete drug effects questionnaire re: pain and other symptoms during PK draws

Participant Characteristics

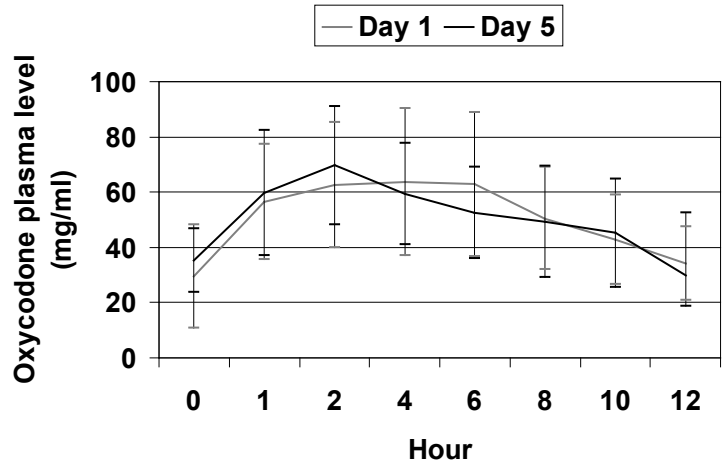
Morphine		Oxycodone
10	Number Enrolled	11
4	Women	6
8	Caucasian	9
42.9 (33-55)	Age	47.1 (28-61)
62 mg bid (10-200)	Opioid Dose	53 mg bid (10-120)
34.8 (29.4, 40.1)	Pain Score day 1	43.8 (38.6, 49.1)

Plasma Opiate Levels by Study Day

a. Morphine



b. Oxycodone



Abrams et al, Clinical Pharmacology & Therapeutics 2011

Pain by Study Day

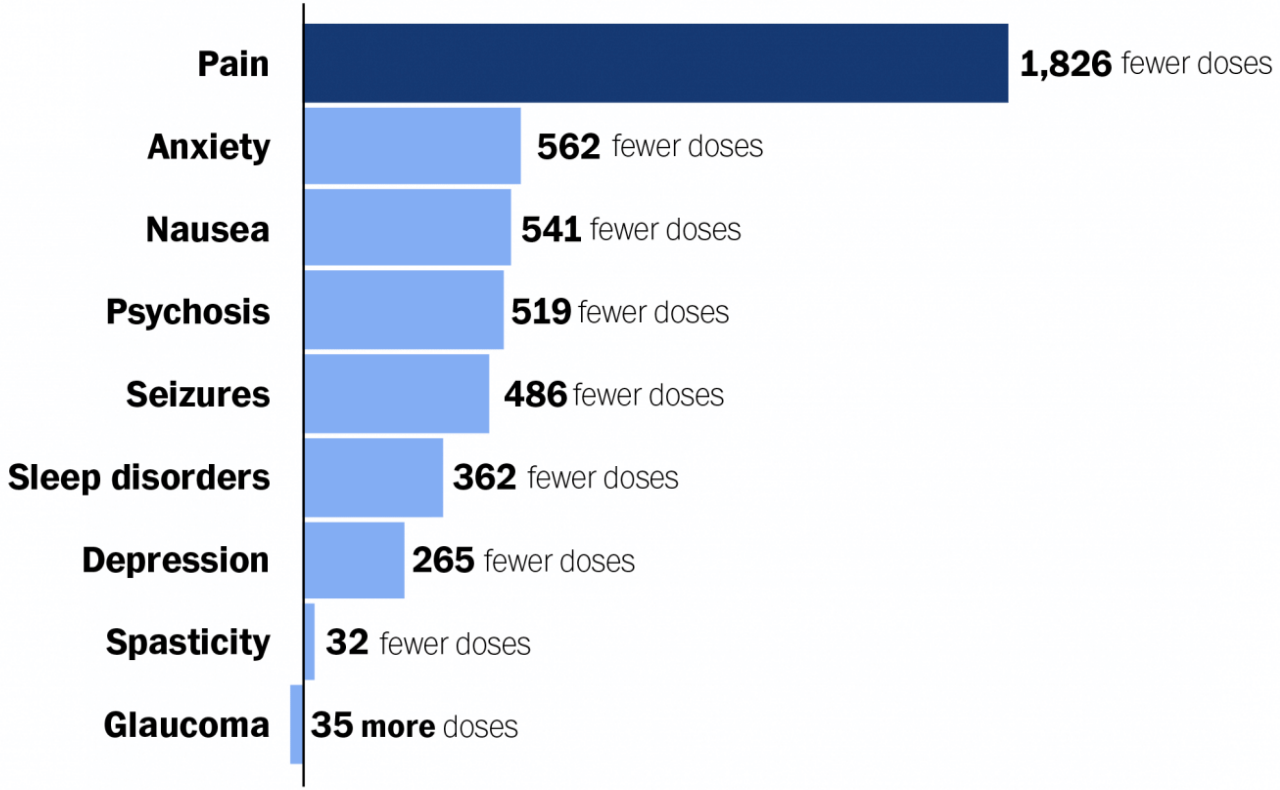
	n	**Day 1** Mean (95% CI)	**Day 5** Mean (95% CI)	**Difference** Mean (95% CI)*
Overall	21	39.6 (35.8, 43.3)	29.1 (25.4, 32.8)	**-10.7 (-14.4, -7.3)**
Morphine	10	34.8 (29.4, 40.1)	24.1 (18.8, 29.4)	**-11.2 (16.5, -6.0)**
Oxycodone	11	43.8 (38.6, 49.1)	33.6 (28.5, 38.6)	**-10.3 (14.8, -5.8)**

*__p<0.001__ Abrams et al, Clinical Pharmacology & Therapeutics 2011

POISON
No. 100 969
CHOCOLATE-COATED
TABLETS
CHLORODYNE
HALF STRENGTH
MORPH. HYDROCHL.
1-12 gr.
Ext, Cannabis 1-8 gr.
Nitroglycerin 1-600 gr.
Ext. Hyoscyam. 1-4 gr.
Oleores. Capsc. 1-20 gr.
Peppermint Oil q s.
Dose 1 to 4 Tablets
87196A
SHARP & DOHME
BALTIMORE

Fewer Pills Prescribed in Medical States

- Difference between annual drug doses prescribed per physician in medical marijuana states, and in states without medical marijuana laws, by drug category.



Bradford and Bradford, Health Affairs, July 2016

Conclusive or Substantial Evidence of Effect

- For this level of evidence, there are many (or several) supportive findings from good-quality studies with no credible opposing findings. A firm conclusion can be made, and the limitations to the evidence, including chance, bias, and confounding factors, can be ruled out with reasonable confidence.

  - For the treatment for chronic pain in adults (cannabis)
  - Antiemetics in the treatment of chemotherapy-induced nausea and vomiting (oral cannabinoids)
  - For improving patient-reported multiple sclerosis spasticity symptoms (oral cannabinoids)

ASCO Guidelines

"The Expert Panel recommends FDA-approved cannabinoids dronabinol or nabilone to treat nausea and vomiting that is resistant to standard antiemetic therapies. Evidence remains insufficient to recommend marijuana in this setting."

asco.org/supportive-care-guidelines

Hi Dr Abrams,

“I am contacting you to see about getting an extension of the

medicinal marijuana letter you issued me last year which expired on March 21st.

Although I did not use it until my last 5 sessions of chemo (me getting over the stigma of its use), it did what no other drug could do, completely solve the severe nausea I had.

It allowed me to play with my children, attend their sports and school functions, and just function very normally in day to day activities.

I cannot thank you enough for giving me that option!

I am currently on a chemo vacation, after a clean scan and the only time I use medical marijuana now is when I have trouble sleeping. I would like to continue to use it for that purpose instead of relying on pharmaceutical options like zolpidem etc.”

Moderate Evidence of Effect

- For this level of evidence, there are several findings from good- to fair-quality studies with very few or no credible opposing findings. A general conclusion can be made, but limitations, including chance, bias, and confounding factors, cannot be ruled out with reasonable confidence.

  - Improving short-term sleep outcomes in individuals with sleep disturbance associated with obstructive sleep apnea syndrome, fibromyalgia, chronic pain, and multiple sclerosis (cannabinoids, primarily nabiximols)

No or Insufficient Evidence

"For this level of evidence, there are mixed findings, a single poor study, or health endpoint has not been studied at all. No conclusion can be made because of substantial uncertainty due to chance, bias, and confounding factors."

No or Insufficient Evidence

- Cancers, including glioma (cannabinoids)
- 34 *in vitro* and/or *in vivo* experimental studies and one pilot human trial included:
  - All but one study showed that cannabinoids selectively kill tumor cells
  - Antitumor activity
    - Antiproliferative effects (cell cycle arrest)
    - Decreased viability
    - Cell death via toxicity, apoptosis, necrosis, autophagy
  - Antiangiogenic effects
  - Antimigratory effects

Machado Rocha et al, 2014

The First Human Trial

- 9 patients with recurrent GBM treated with 20-40 ug THC intra-tumorally per day x 15d
- Treatment was well tolerated
- Effect on survival no different from chemo
- In vitro, THC inhibited the proliferation and decreased viability of GBM cells from biopsies
    - Guzman 2006
- Later demonstrated that CBD enhanced the inhibitory effects of THC on GBM cell proliferation and survival
    - Marcu 2010

Additional Completed Trial

- A safety study of Sativex (12) compared with placebo (9), with dose dense temozolomide in recurrent GBM
  - 83% one year survival c/w 53% (p=0.042)
  - Median survival 550 days c/w 369 in placebo
    - GW Pharmaceuticals press release February 2017
- Pure CBD as a single agent for solid tumors
  - Phase 2 efficacy study in 60 patients with progressive disease after standard therapies at Hadassah Medical Organization
  - Closed after 3 GBM, 1 other, with no response
    - Personal communication Yakir Rotenberg June 2016

No or Insufficient Evidence

- Cancer-associated anorexia cachexia syndrome and anorexia nervosa (cannabinoids)
  - Randomized double-blind study of 469 adults with advanced cancer and weight loss
    - Dronabinol 2.5 mg bid — Appetite ↑ 49%, Wt ↑ >10%: 3%
    - Megestrol 800 mg qd — Appetite ↑ 75%, Wt ↑ >10%: 11%*
    - Combination — Appetite ↑ 66%, Wt ↑ >10% :8%
      - Jatoi, J Clin Oncol 2002
  - Smaller RCT of dronabinol in cancer patients demonstrated enhanced chemosensory perception in the treatment group
    - Food tasted better, appetite improved and calories ↑
      - Brisbois et al, Annals of Oncology 2011

No or Insufficient Evidence

- Cancers, including glioma (cannabinoids)
- Cancer-associated anorexia cachexia syndrome and anorexia nervosa (cannabinoids)
- Symptoms of irritable bowel syndrome (dronabinol)
- Epilepsy (cannabinoids)
- Spasticity in patients with paralysis due to spinal cord injury (cannabinoids)
- Symptoms associated with amyotrophic lateral sclerosis (cannabinoids)

CBD for Epilepsy

- Two case series reported; no control groups:
  - Open-label, expanded access program of Epidiolex® in 162 pts with severe intractable childhood seizures
    - Median monthly seizure frequency decreased from 30.0 to 15.8 over 12-week treatment period (Rosenberg/Devinsky 15, 16)
  - Unblinded Israeli experience with 74 pts receiving 20:1 CBD:THC oil for an average of 6 months:
    - 75-100% reduction 18%
    - 50-75% reduction 34%
    - 25-50% reduction 12%
    - < 25% reduction 26%
    - Aggravation 7%

CBD for Epilepsy: Finally an RCT

- Double-blind, placebo-controlled trial of 120 children and young adults with Dravet syndrome
  - Cannabidiol oral solution 20 mg/kg or placebo
  - Standard antiepileptic treatment continued
- Median frequency of monthly seizures decreased from:
  - 12.4 to 5.9/mo on CBD
  - 14.9 to 14.1 on placebo (P=0.01)
- Patients with at least a 50% decrease was:
  - 43% with CBD
  - 27% with placebo (P=0.08)
- Seizure-free:
  - 5% CBD,
  - 0% placebo (P=0.08)
- Adverse events (diarrhea, vomiting, fatigue, fever, somnolence) more frequent in CBD

Devinsky, NEJM 2017

No or Insufficient Evidence

- Chorea and certain neuropsychiatric symptoms associated with Huntington's disease (oral cannabinoids)
- Motor system symptoms associated with Parkinson's disease or the levodopa-induced dyskinesia (cannabinoids)
- Dystonia (nabilone and dronabinol)
- Achieving abstinence in the use of addictive substances (cannabinoids)
- Mental health outcomes in individuals with schizophrenia or schizophreniform psychosis (cannabidiol)

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"SMOKE TWO JOINTS, AND CALL ME IN THE MORNING."

Dosing of Medicinal Cannabis

- Dosing of botanicals always complex
  - Plant products vary in potency
  - Contain varying amounts of components
- Difficult to standardize dose of inhaled medicine
- Individual variation in response to cannabis
  - Prior experience
  - ? Pharmacogenomics

Cannabis Dose Guidelines

- Multiple variables dictate that dosing be highly individualized
- A patient-determined self-dosing model is recommended
- Self titration model acceptable in view of the plant and host variables and the low toxicity of cannabis
- Gabapentin an example of another drug with relatively low toxicity and high dosing limits titrated to effect

Carter et al IDrugs 2004

Cannabis-Induced Euphoria

- Often described as a “side-effect” of Rx
- Is it really an “adverse experience”, particularly in the terminal patient ?
- Is a single treatment that increases appetite, decreases nausea and vomiting, relieves pain and improves sleep and mood a potentially useful tool in oncology and palliative medicine?

Mail ●●○○○ 7:41 PM
7x7.com

Alisa Scerrato (via Hoodline)

The Apothecarium Takes Pot Shops to Glam New Heights, Expands to Marina and Berkeley

By David Downs | Oct 13, 2016

Mail ●●○○○ 7:41 PM
7x7.com

The Apothecarium Takes Pot Shops to Glam New Heights, Expands to Marina and Berkeley

By David Downs | Oct 13, 2016

THE GREEN CROSS
Volcano DIGIT
Mighty
Green Cross
San Francisco
Proposition 65 WARNING:
Smoke from cannabis contains chemicals known to the State of California to cause cancer.

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Smoke from cannabis
contains chemicals known
to the State of California
to cause cancer.
PAX
027
SUN-GROWN HUMBOLDT BLUE DREAM (SD)
THC 19.5% CBD 0.1%
SUN GROWN
CW RESULTS
SUN-GROWN HEADBAND (SD)
THC 19.1% CBD 0.1%
SUN-GROWN RIPPER HAZE
CW RESULTS COMING SOON
SUN-GROWN DO
THC 18.9

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Green Dragon Indoor	–	–	$ 45 Eighth	$ 85 Quarter	$ 290 Ounce	Sativa	**THC 17%** CBD 1%	An energetic, interactive, & mind blowing sativa high. Delicious flavor & aroma.
Green Dragon (GH) Outdoor	–	$ 14 Gram	$ 35 Eighth	–	–	Sativa	**THC 14%** CBD 1%	An energetic, interactive, & mind blowing sativa high. Delicious flavor & aroma.
Stella Blue CBD (OD) Outdoor	–	$ 15 Gram	$ 40 Eighth	$ 75 Quarter	$ 270 Ounce	Sativa	**THC 6%** CBD 10%	A blend of all the Sativa strains that we cultivate in house.
Sour Pineapple Indoor	–	–	$ 35 Eighth	–	–	Sativa	**THC 15%** CBD Pending	A sativa cross of Sour Diesel and Pineapple Kush with a nice, fragrant citrus aroma.
Chocolope Haze Indoor	–	–	$ 55 Eighth	$ 105 Quarter	–	Sativa	**THC 16%** CBD Pending	Classic flavors of Chocolate Thai Sticks with delicious fruitiness of Cannalope Haze. It produces a comical, yet dreamy high.
Kona Bomb Indoor	–	–	$ 45 Eighth	$ 85 Quarter	–	Sativa	**THC 14%** CBD Pending	A bright and cerebral sativa with euphoric overtones.
Red Congo			$	$	$			This is a placeholder for products that

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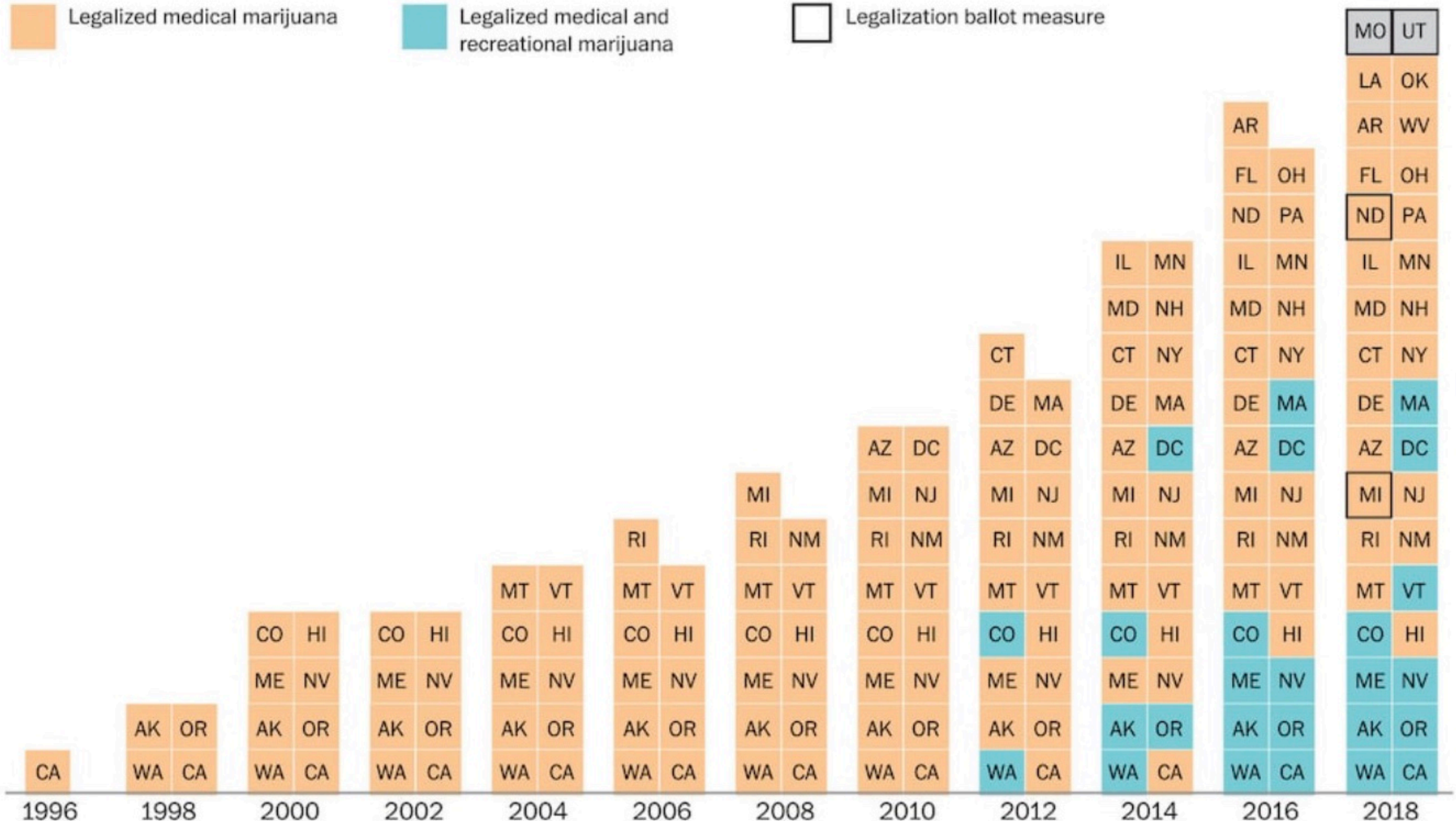
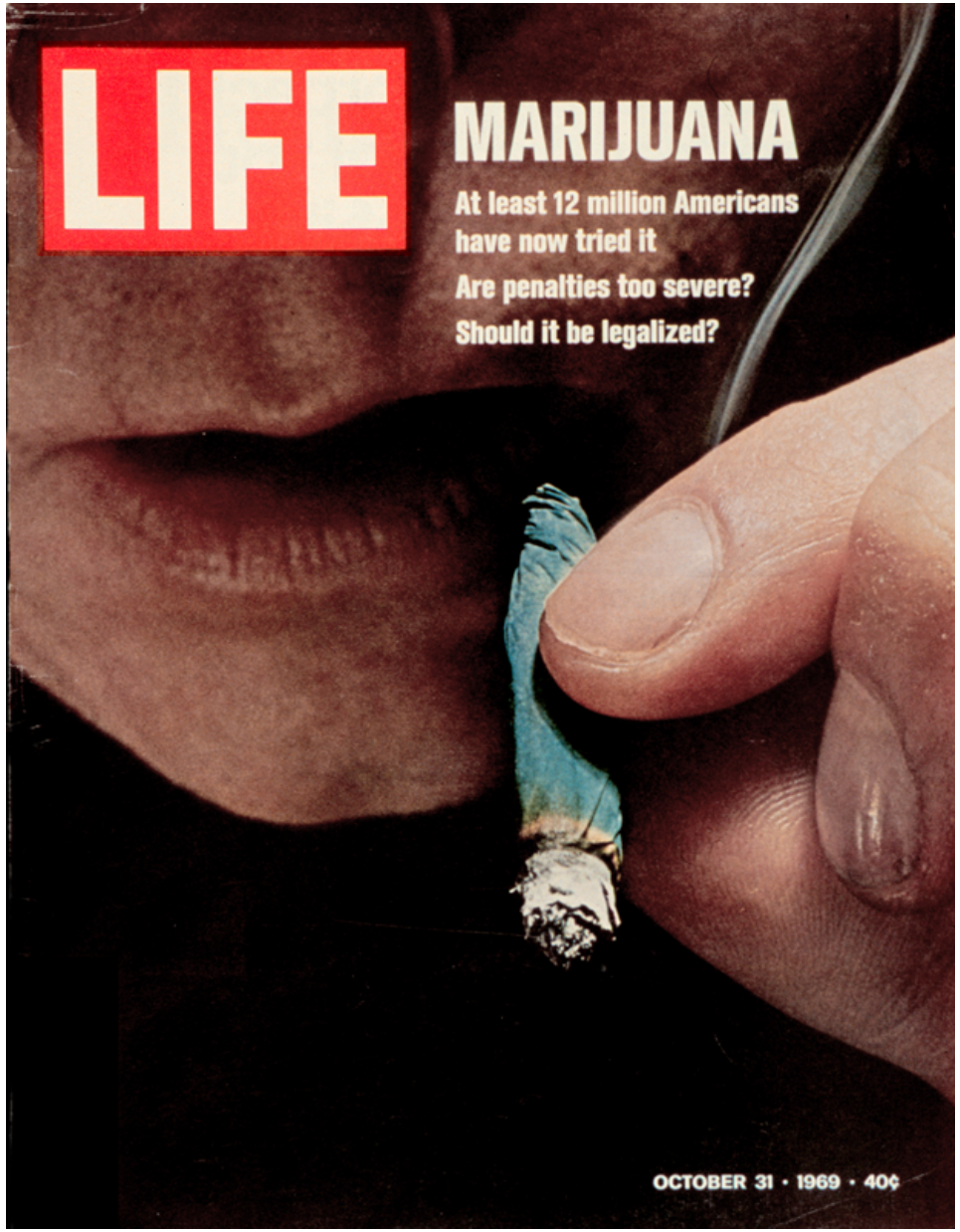
100%

The States Where It's Legal To Smoke Marijuana



Seed
Soil
Sun
That's cannabis, the California Way
Only individuals with legally recognized Medical Cannabis Identification Cards or a verifiable,
written recommendation from a physician for medical cannabis may obtain cannabis from medical cannabis dispensaries.
flowkana
NOW IN SELECT
DISPENSARIES


LIFE
MARIJUANA
At least 12 million Americans have now tried it
Are penalties too severe?
Should it be legalized?
OCTOBER 31 · 1969 · 40¢

History Of Medicine

- 2000 B.C. - Here, eat this root.
- 1000 A.D. - That root is heathen. Here, say this prayer.
- 1850 A.D. - That prayer is superstition. Here, drink this potion.
- 1940 A.D. - That potion is snake oil. Here, swallow this pill.
- 1985 A.D. - That pill is ineffective. Here, take this antibiotic.
- 2000 A.D. - That antibiotic is artificial. Here, eat this root.