NEW MEXICO MEDICAL CANNABIS CONFERENCE
The Plant | The People | The Purpose

Cannabis In Cancer Care:
What We Know and What We Don't

Donald I. Abrams, M.D.
Chief, Hematology-Oncology
Zuckerberg San Francisco General
Professor of Clinical Medicine
University of California San Francisco

Disclosure

- I have nothing to disclose
- Although I did go to college in the ‘60’s
- And I will be discussing off-label use
  - Of an illegal substance

HEALTH AND MEDICINE

Cannabis May Have Eased Breast Cancer Symptoms of Siberian Ice Princess

October 17, 2014 | by Lisa Winter

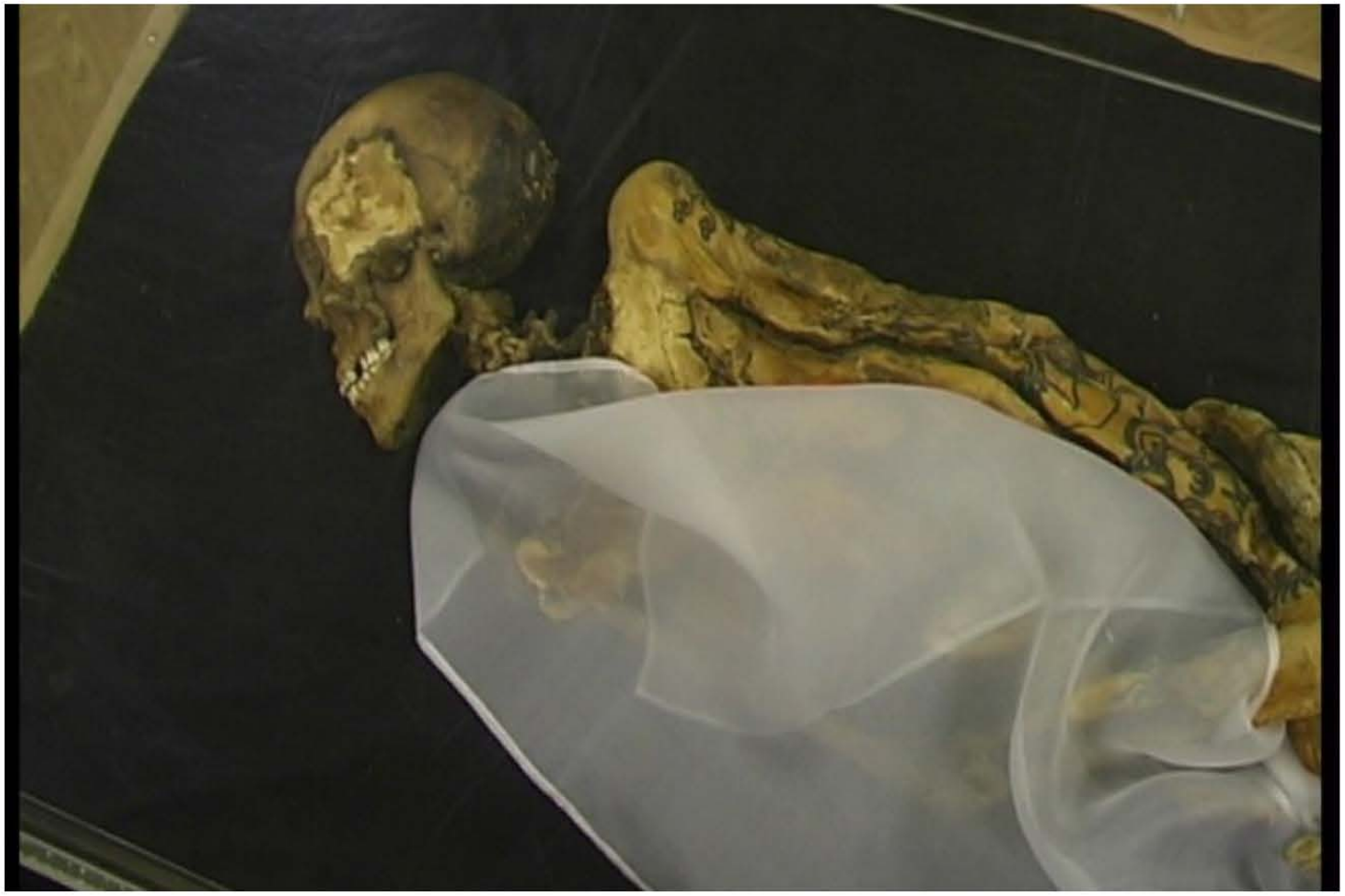

photo credit: Kobsev via Wikimedia Commons

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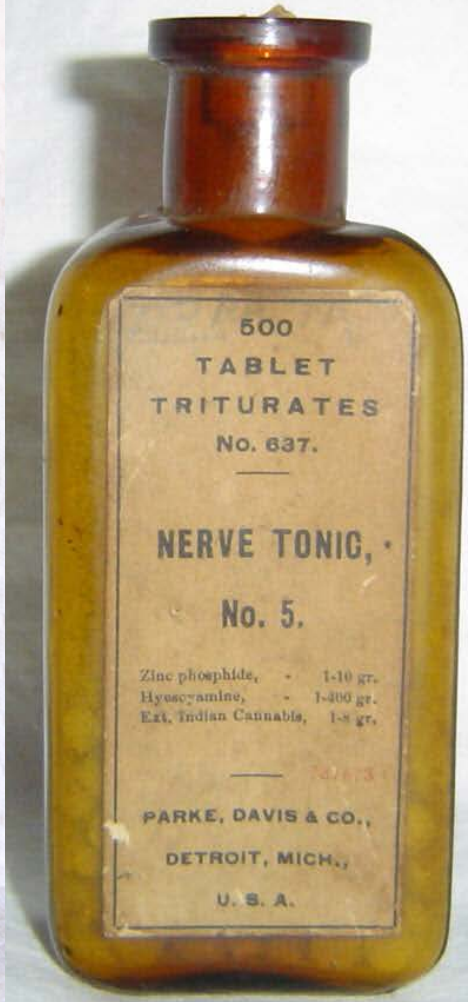
Chemistry

Cannabis as Medicine

- Marijuana (cannabis, 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 investigations
  - Removed from US Pharmacopoeia in 1942

Harry Jacob Anslinger, zealous mas-

Schedule I Substances

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

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Cannabis as Medicine

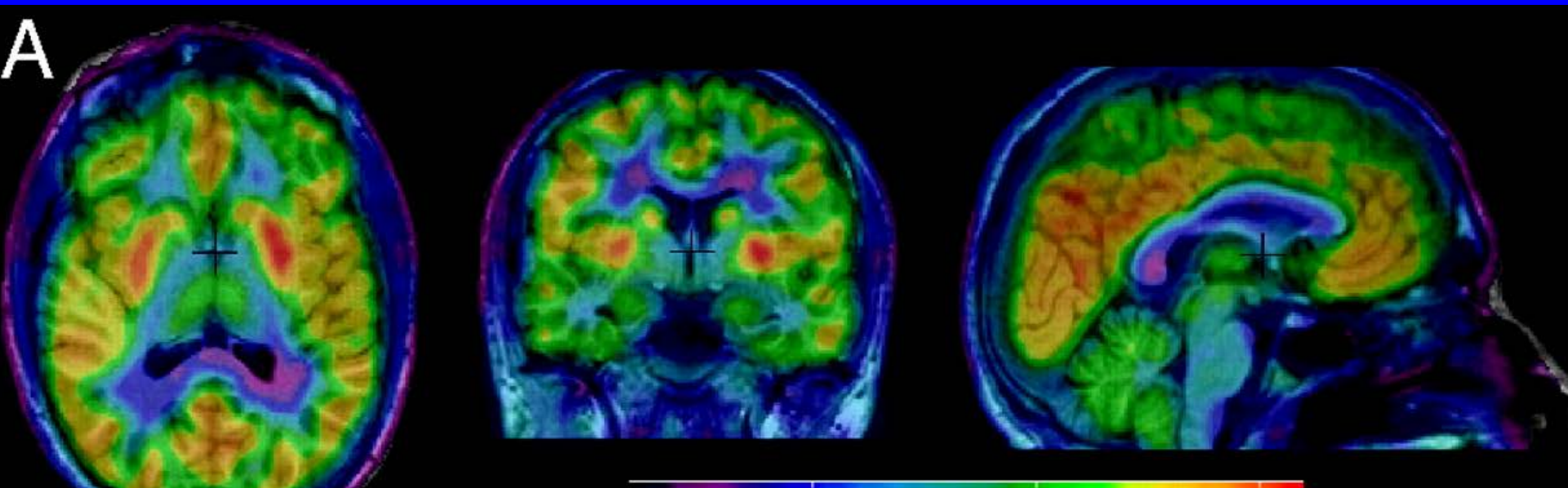
- Contains over 400 chemical compounds
- Highest concentration of bioactive compounds in resin exuded from flowers of female plants
- Main psychoactive component believed to be delta-9-THC
- At least 70-100 other cannabinoids identified in combusted products
- delta-8-THC similar in potency but only in small concentration

Cannabinoid Receptors

- CB_1 and CB_2 receptors identified
- Receptors encoded by separate genes on separate chromosomes; share 48% amino acid identity
- G-protein coupled receptors that inhibit adenylyl cyclase on activation
  - Decreases cyclic AMP and protein kinase A activity
  - Inhibition of Ca^{++} influx through various Ca^{++} channels
  - Stimulation of inwardly rectifying K^{+} channels and mitogen-activated protein kinase cascades

Cannabinoid$_1$ Receptor

- CB_1 receptors identified throughout central and peripheral nervous system
  - Density highest in cingulate gyrus, frontal cortex, hippocampus, cerebellum and basal ganglia
- CB1 receptors present in virtually all organs and tissues of the body



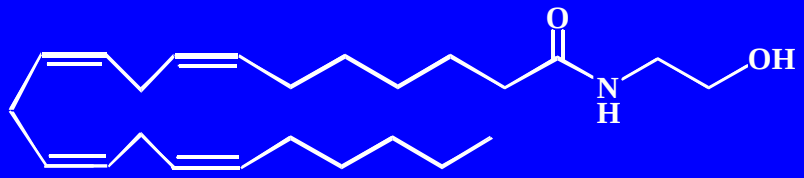
Cannabinoid$_2$ Receptor

- CB_2 receptor originally detected in macrophages and marginal zone of the spleen
- Largest concentration in peripheral blood present in B-cells and NK cells
- Also found in bone and to a lesser degree in liver and nerve cells

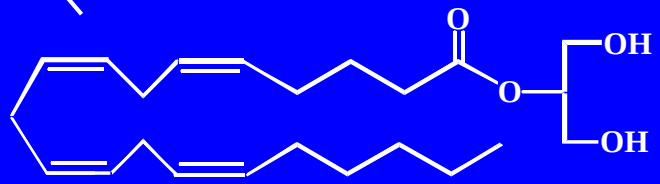
Endocannabinoids

Anandamide

Di-homo-γ-linolenoylethanolamide



Docosatetraenoylethanolamide



2-Arachidonyl-Glycerol

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

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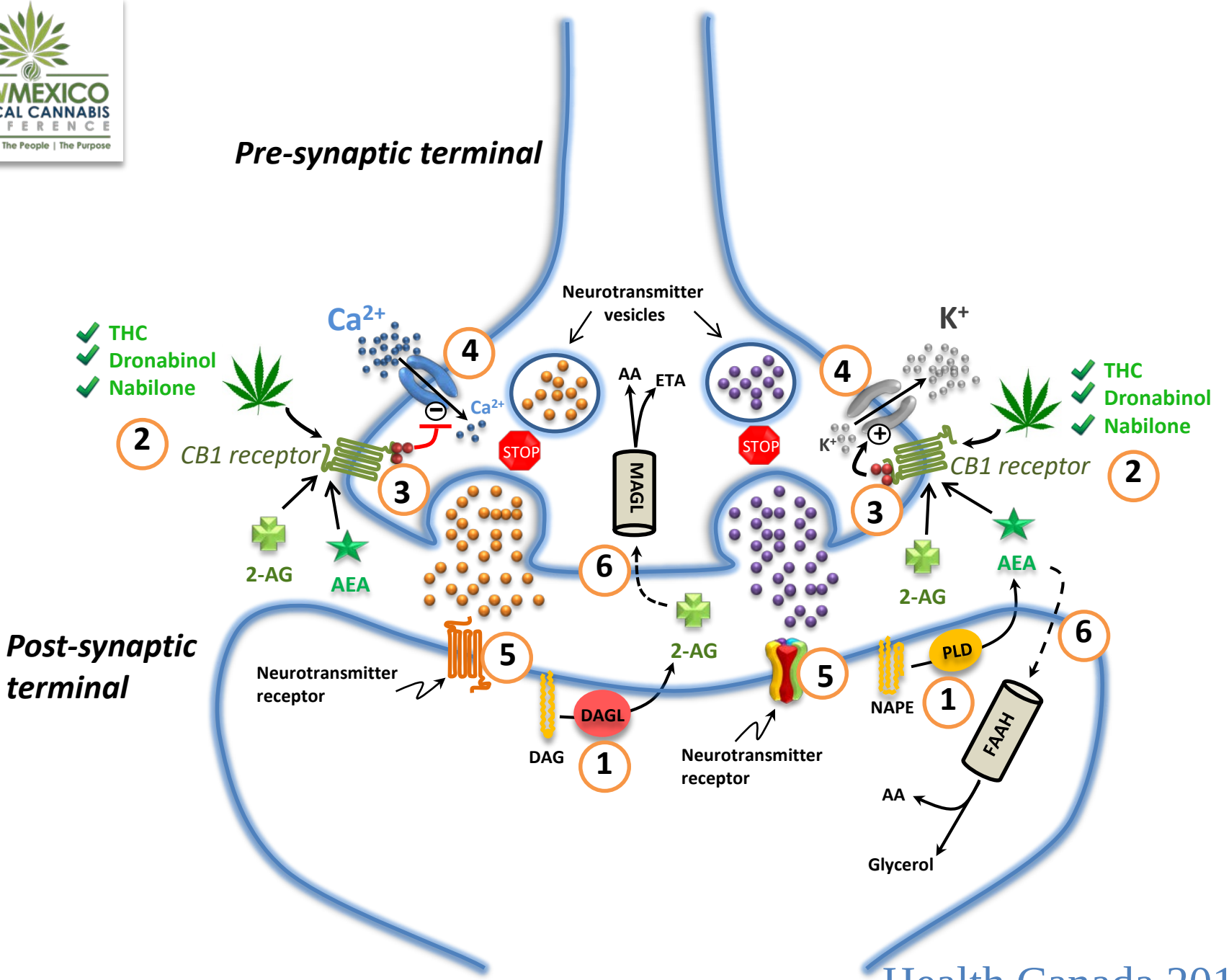
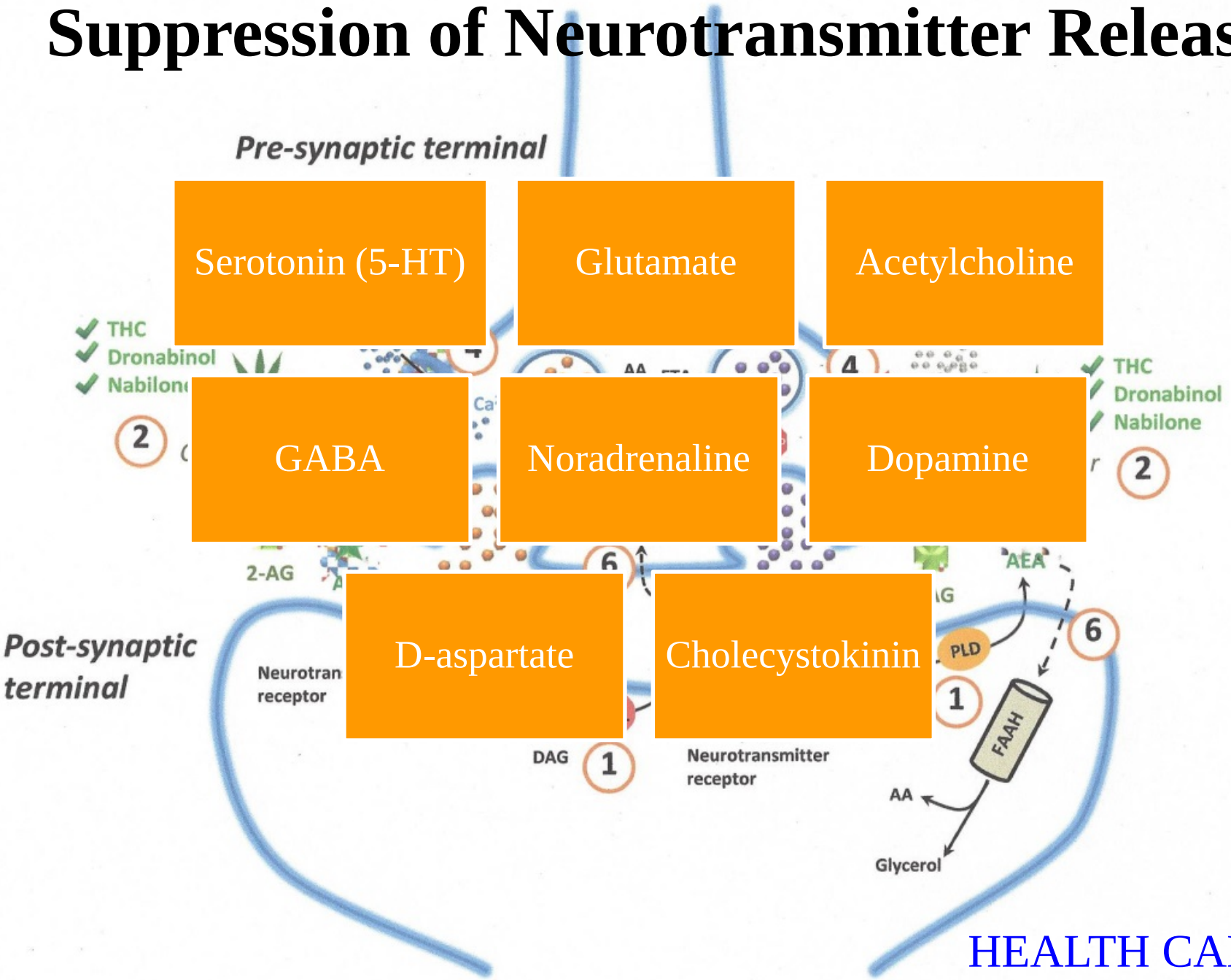


Health Canada 2016

Suppression of Neurotransmitter Release



HEALTH CANADA

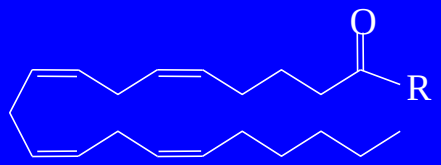
What About Cannabidiol (CBD)?

- 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:THC Ratios

- CBD-mediated attenuation of THC-induced effects observed when CBD:THC is ≥ 8:1
- CBD-mediated potentiation of THC-induced effects seen when CBD:THC is ~2:1
- In rats and mice!
  - » Zuardi 2012
- There is NO information in scientific or medical literature on the effects of varying CBD:THC ratios in the Rx of medical disorders

Endogenous Cannabinoid System



Synthesis

Endocannabinoids

Cellular uptake

Metabolism

CB2 Receptor

CB1 Receptor

CBx Receptor

VR1 Receptor

Signal Transduction

Immune function
Cell proliferation
Inflammation
Pain

Appetite
Immune function
Muscle control
Pain
IOP
Cognition
Emesis
Neuroexcitability
Reward
Thermoregulation

Pain
Vaso-
dilation

Pain
Inflammation

Oral Delta-9 THC: An Approved Drug

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

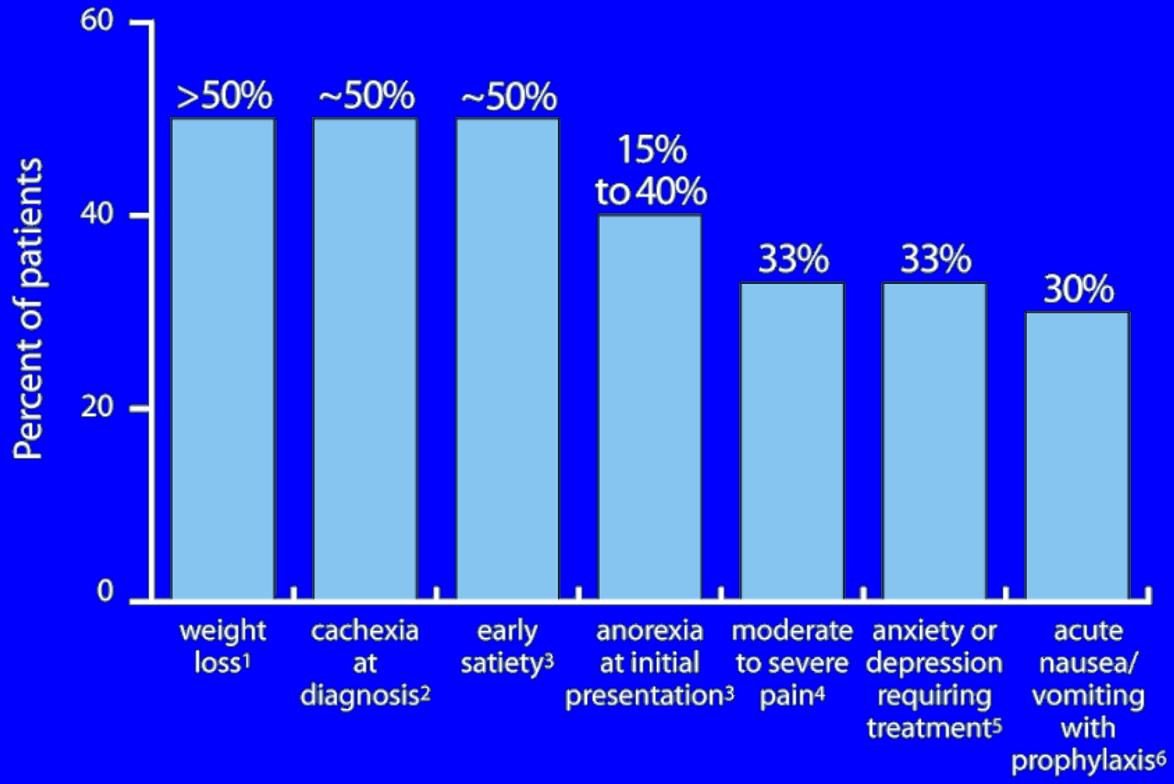
Oral THC Pharmacology

- 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

Inhaled 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

Symptom Management Challenges Associated with Cancer and Its Treatments



1. Arnold SM, et al. In: DeVita VT, et al, eds. *Cancer: Principles & Practice of Oncology*. 2001.
2. Damsky D. *Clin J Onc Nursing*. 2002;6(4):235-238.
3. Body JJ. *Curr Opin Oncol*. 1999;11:255-260.
4. Foley KM. In: DeVita VT, et al, eds. *Cancer: Principles & Practice of Oncology*. 2001.
5. Massie MJ, et al. In: DeVita VT, et al, eds. *Cancer: Principles & Practice of Oncology*. 2001.
6. Carlson RH. *Oncology Times*. 2001;23(3):19-23.

Cannabinoids and Appetite

- Anandamide in low concentrations in mice leads to a potent enhancement of appetite
- CB1 receptors implicated in food intake control n.b. lateral hypothalamus and limbic system locations
- CB1 knockout mice eat less than wild type litter mates
- CB1 receptors involved in motivational/reward aspects of eating

Cannabinoids and Appetite

- Endocannabinoids enhance reward effects via mesolimbic dopaminergic systems
  - System may be involved in suckling
  - Milk has high levels of 2-AG
  - CB1 antagonist given to mice at 24hrs causes them to stop suckling and die
- Phase II clinical trial of CB1 antagonist in obesity encouraging (3-4 kg ↓ in 2wks)

Pharmacological Blockade of the eCB System

Pharmacologically induced deficiency of the eCB system by SR141716 or AM251 may lead to:

- suppressed feeding and weight loss Freedland et al. (2000) Pharmacol Biochem Behav; Rowland et al. (2001) Psychopharmacology
- increased anxiogenic-like behavior Haller et al. (2004) Behav Pharmacol; Navarro et al. (1997) Neuroreport
- attenuated responsiveness to rewarding stimuli (e.g., ethanol, sucrose, heroin, nicotine) Arnone et al. (1997) Psychopharmacology; Cohen et al. (2002) Behav Pharmacol; De Vries et al. (2003) Psychopharmacology
- reduced sensitivity to the reinforcing effects of electrical brain stimulation Deroche-Gamonet et al. (2001) Psychopharmacology
- increased duration of wakefulness, hyperarousal and vigilance Santucci et al. (1996) Life Sci

→ Similarities with melancholic depression

Courtesy of Dr. Patrik Roser

Pharma … of the eCB

Pharmacol… …f the eCB system by SR1417

- suppresse… …l. (2000) Pharmacol Biochem Behav; Rowland et al. (200…
- increased … …4) Behav Pharmacol; Navarro et al. (1997) Neuroreport
- attenuate… …nuli (e.g., ethanol, sucrose, h… …cology; Cohen et al. (2002) Behav Pharmacol; De Vrie…
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Dr. Patrik Roser

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diet-blog.com

d DIETS TIPS MYTHS TOO >

Acomplia: Miracle Diet Pill?

By Jim F

It looks like the weight loss drug Acomplia will never see the light of day.

Despite the success of its second trial, the FDA didn't approve the drug and in 2009 Sanofi-Aventis gave up their pursuit as it was banned throughout Europe due to health risks.

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Cannabinoids and Appetite

- 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

Cannabis and Chemotherapy N & V

- Interest in 70's prompted by anecdotal reports when available antiemetics were inadequate
- In randomized trials, oral THC better than placebo and equivalent or superior to prochlorperazine
- Smoked THC appeared superior to oral
- THC<metoclopramide<5-HT_3 antagonists

Cannabinoids in CINV

- Meta-analysis of 30 randomized trials of oral nabilone, oral dronabinol or IM levonantradol; no cannabis trials
  - 1366 patients involved
  - Cannabinoids were more effective than phenothiazines and metoclopramide
  - NNT for nausea control = 6
  - NNT for vomiting = 8
    - » Tramer et al, BMJ 2001
- Similar results from later meta-analysis of 15 studies of nabilone and 14 of dronabinol
  - » Ben Amar et al, J Ethnopharm 2006

Cannabis in CINV

- Only 3 controlled cannabis trials in CINV
  - In 2, cannabis only available after dronabinol failed
  - Third was a randomized double-blind, placebo-controlled, cross-over trial in 20 cancer patients
    - 25% reported positive antiemetic response
    - 35% preferred dronabinol, 20% preferred smoked and 45% had no preference
      - » Ben Amar et al, J Ethnopharm 2006
- Phase II trial of nabiximols added to standard antiemetics in 16 pts showed 4.8 sprays/day more effective than placebo
  - » Duran et al, J Clin Pharm 2010

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.

Cannabinoids and Pain

- Elevated levels of the CB1 receptor - like the opioid - are found in areas of the brain that modulate nocioceptive processing
- CB1 and CB2 agonists have peripheral analgesic actions
- CBs may also exert anti-inflammatory effects
- Analgesic effects not blocked by opioid antagonists

THC and Analgesia

- Intravenous THC exerts potent antinociceptive effects
- Cannabinoid-induced analgesia appears linked to opioid system
- In cancer trial, oral THC 20 mg was comparable to codeine 120 mg but with marked psychological effects
- Cannabinoids also effective in a rat model of neuropathic pain

Cannabis in HIV Neuropathy

- HIV-related painful distal symmetric polyneuropathy is a common problem
- Current therapy for HIV neuropathy pain is inadequate
  - Opioids generally ineffective
  - Anticonvulsants in common use currently
  - Anecdotal reports of marijuana's efficacy
- Cannabinoids effective in preclinical models of neuropathic pain

Supported in part by UC CMCR and NIH GCRC funds

Cannabis in painful HIV-associated sensory neuropathy

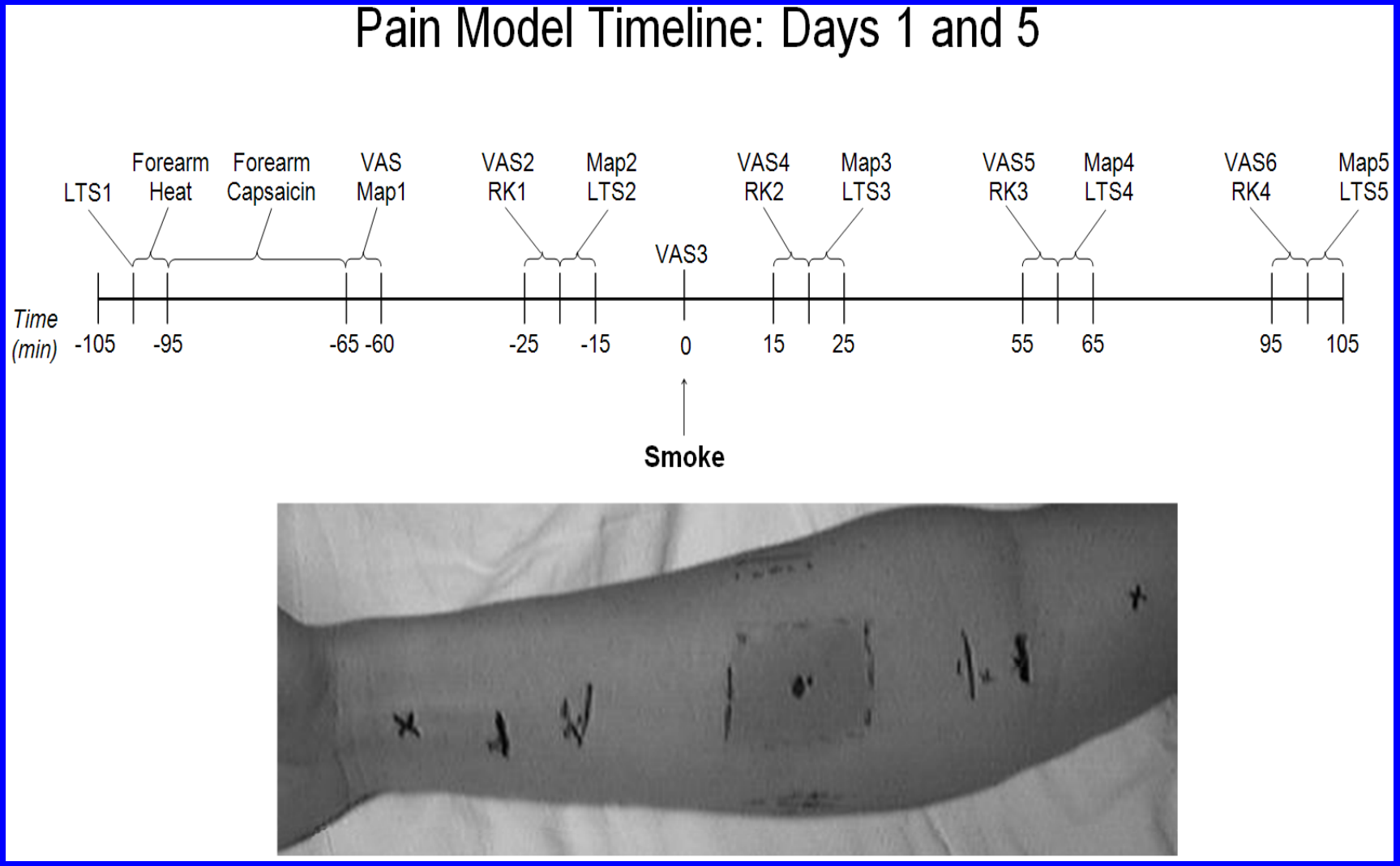
A randomized placebo-controlled trial

D.I. Abrams, MD; C.A. Jay, MD; S.B. Shade, MPH; H. Vizoso, RN; H. Reda, BA; S. Press, BS; M.E. Kelly, MPH; M.C. Rowbotham, MD; and K.L. Petersen, MD

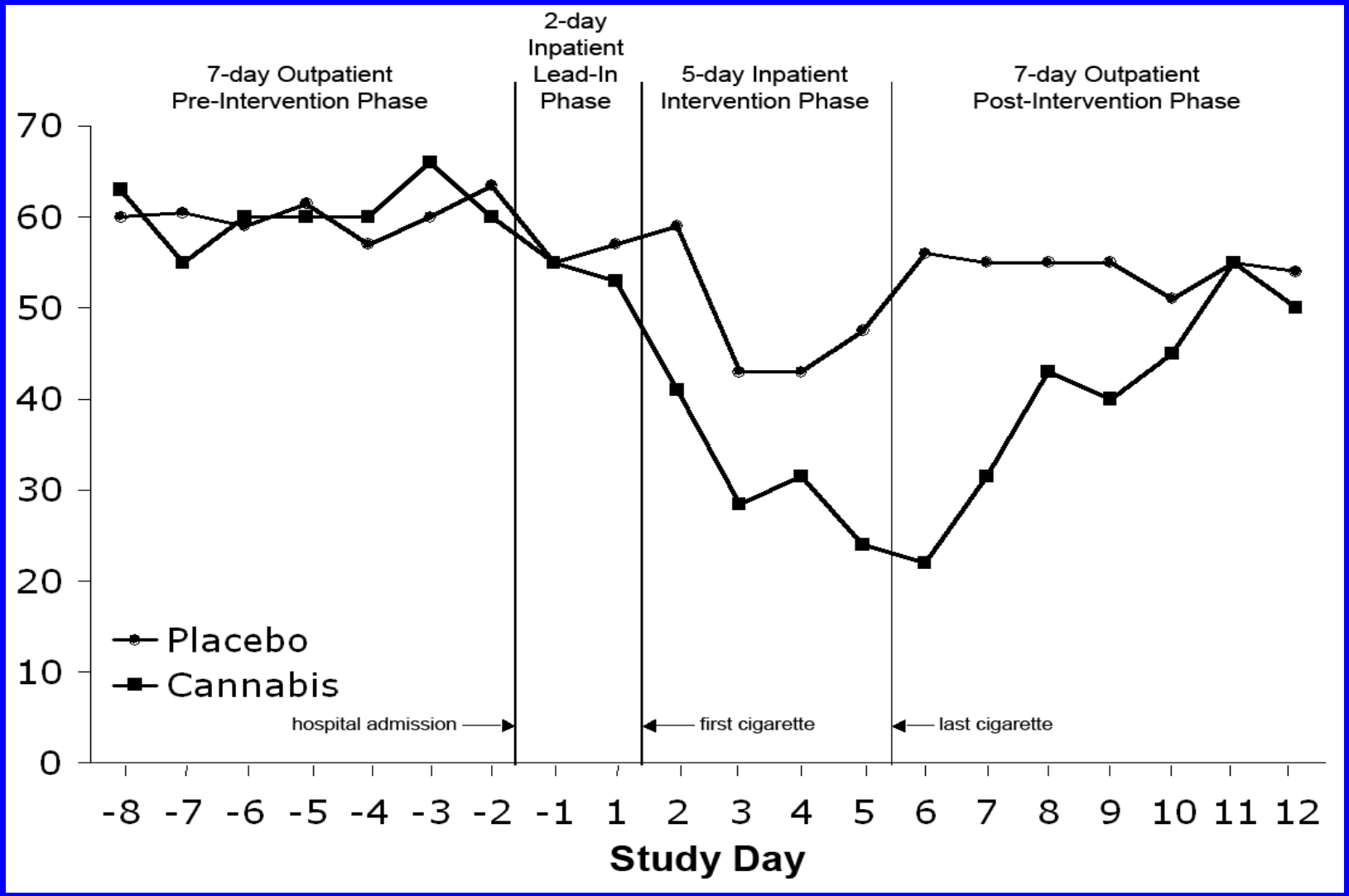
Abstract—*Objective:* To determine the effect of smoked cannabis on the neuropathic pain of HIV-associated sensory neuropathy and an experimental pain model. *Methods:* Prospective randomized placebo-controlled trial conducted in the inpatient General Clinical Research Center between May 2003 and May 2005 involving adults with painful HIV-associated sensory neuropathy. Patients were randomly assigned to smoke either cannabis (3.56% tetrahydrocannabinol) or identical placebo cigarettes with the cannabinoids extracted three times daily for 5 days. Primary outcome measures included ratings of chronic pain and the percentage achieving >30% reduction in pain intensity. Acute analgesic and anti-hyperalgesic effects of smoked cannabis were assessed using a cutaneous heat stimulation procedure and the heat/capsaicin sensitization model. *Results:* Fifty patients completed the entire trial. Smoked cannabis reduced daily pain by 34% (median reduction; IQR = −71, −16) vs 17% (IQR = −29, 8) with placebo ($p = 0.03$). Greater than 30% reduction in pain was reported by 52% in the cannabis group and by 24% in the placebo group ($p = 0.04$). The first cannabis cigarette reduced chronic pain by a median of 72% vs 15% with placebo ($p < 0.001$). Cannabis reduced experimentally induced hyperalgesia to both brush and von Frey hair stimuli ($p \leq 0.05$) but appeared to have little effect on the painfulness of noxious heat stimulation. No serious adverse events were reported. *Conclusion:* Smoked cannabis was well tolerated and effectively relieved chronic neuropathic pain from HIV-associated sensory neuropathy. The findings are comparable to oral drugs used for chronic neuropathic pain.

NEUROLOGY 2007;68:515–521

Experimental Pain Model

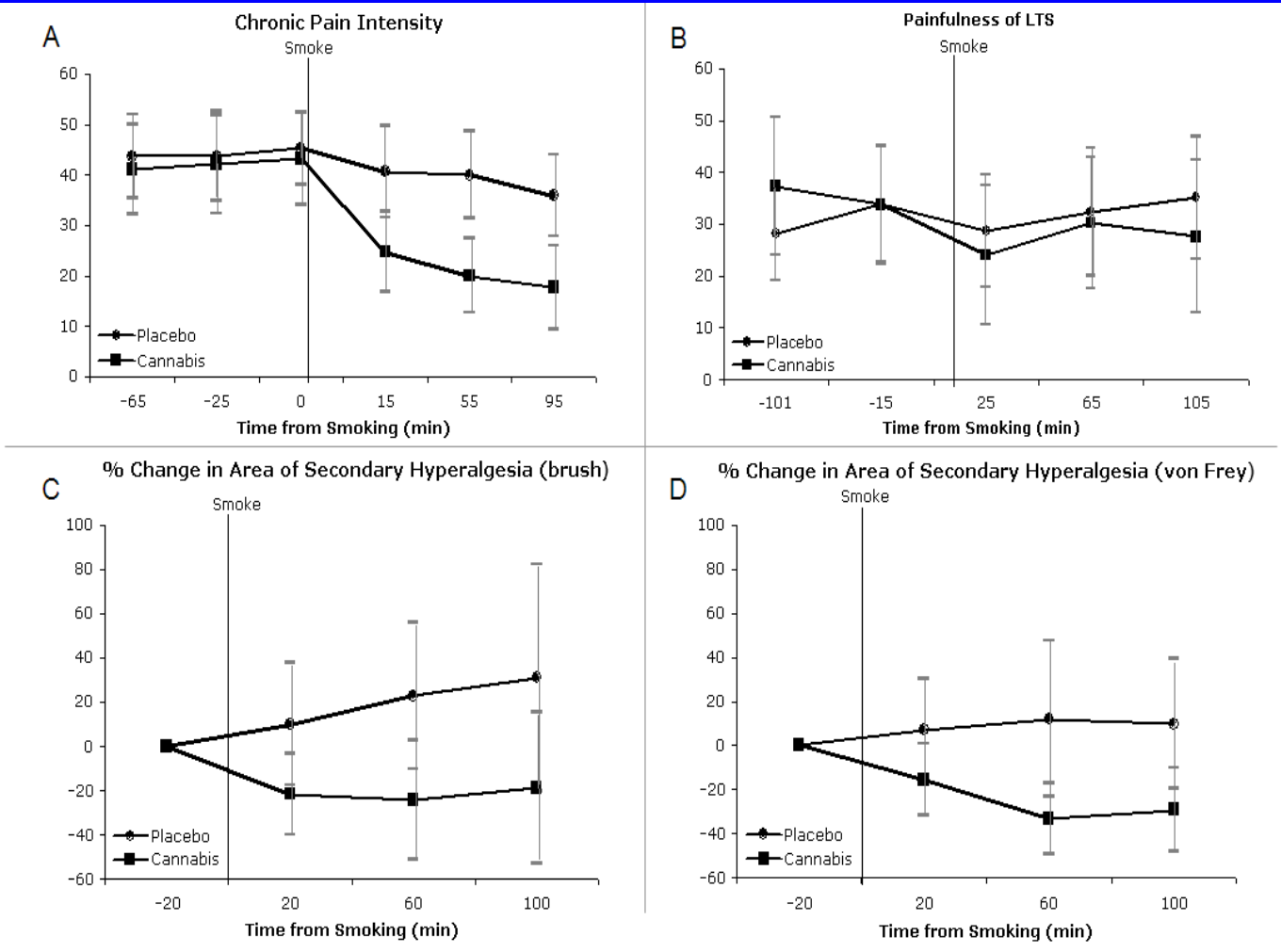


Results: Neurology RCT



Abrams et al Neurology 2007

Results: Neuropathy RCT



Abrams et al Neurology 2007

Neuropathy RCT: Conclusions

- Smoked cannabis is an effective treatment in patients with painful HIV-related peripheral neuropathy
- Smoked cannabis was also effective in attenuating central sensitization produced by a standardized experimental pain model
- The magnitude of pain reduction from smoked cannabis is comparable to that reported in trials of gabapentin for painful HIV-related neuropathy

Abrams et al Neurology 2007

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

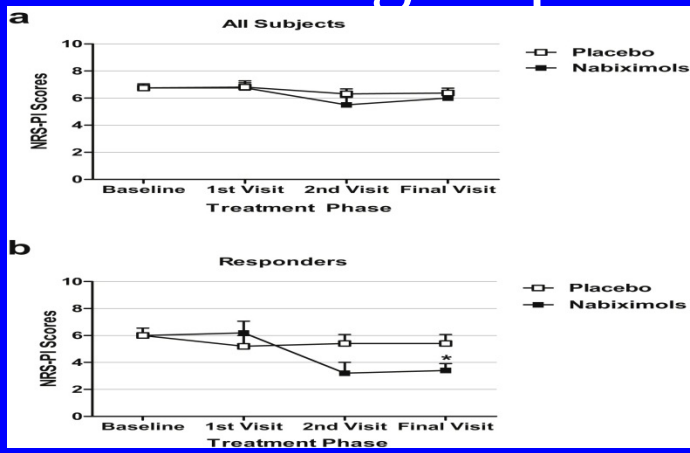
Guaranteed under The Food and

Cannabinoids in Chemotherapy-Induced Peripheral Neuropathy

- Activation of CB1 and CB2 receptors suppresses development of vincristine-induced PN in rats
  - » Rahn et al, Br J Pharmacol 2007
- In mice receiving daily cisplatin, anandamide plus a FAAH inhibitor attenuated CIPN
  - » Khasabova et al, J of Neuroscience 2012
- In mice injected with paclitaxel, CBD pre-treatment aborts CIPN
  - » Ward et al, Br J Pharmacol 2014

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
  - Average ↓ 2.6 in the 5 responders
  - NNT=5



Lynch et al, J Pain Symptom Management, 2013

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

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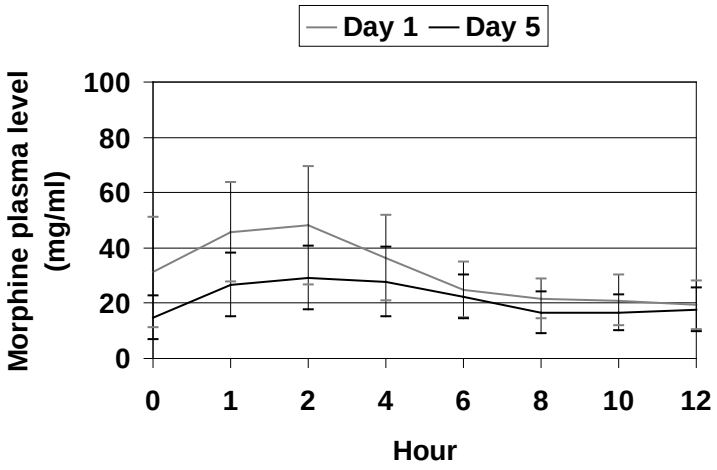
Participant Characteristics

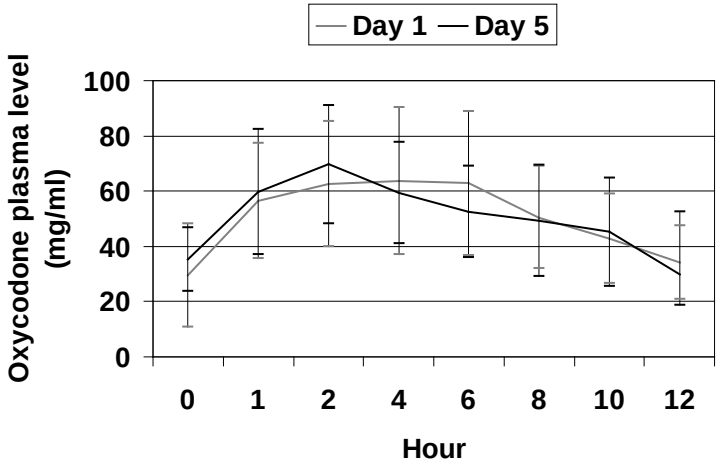
Morphine		Oxycodone
10	Number Enrolled	11
4	Women	6
8	Caucasian	9
42.9 (33-55)	Age	47.1 (28-61)
62 mg bid (10-200)	Opioid Dose	53 mg bid (10-120)
34.8 (29.4, 40.1)	Pain Score day 1	43.8 (38.6, 49.1)

Plasma Opiate Levels by Study Day

a. Morphine



b. Oxycodone



Abrams et al, Clinical Pharmacology & Therapeutics 2011

Pain by Study Day

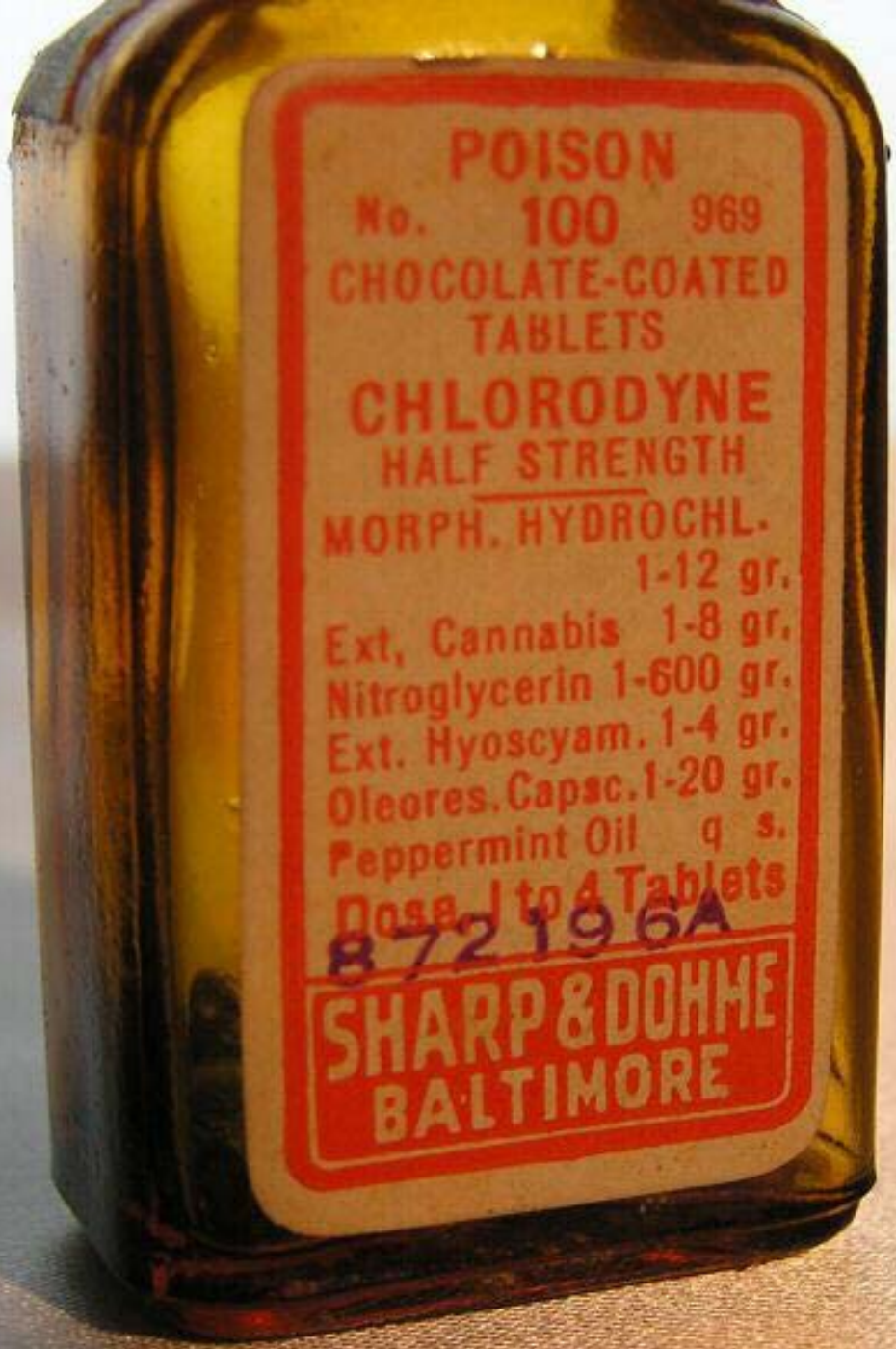
	n	**Day 1** Mean (95% CI)	**Day 5** Mean (95% CI)	**Difference** Mean (95% CI)*
Overall	21	39.6 (35.8, 43.3)	29.1 (25.4, 32.8)	**-10.7 (-14.4, -7.3)**
Morphine	10	34.8 (29.4, 40.1)	24.1 (18.8, 29.4)	**-11.2 (16.5, -6.0)**
Oxycodone	11	43.8 (38.6, 49.1)	33.6 (28.5, 38.6)	**-10.3 (14.8, -5.8)**

***p<0.001**

Abrams et al, Clinical Pharmacology & Therapeutics 2011

Cannabis:Opioid Conclusions

- Co-administration of vaporized cannabis with oral sustained release opioids is safe
- Co-administration of vaporized cannabis in subjects on stable doses of morphine or oxycodone appears to enhance analgesia
- Co-administration of vaporized cannabis t*r*ends towards lowering concentration of the opioids
  - The PK effects would be expected to reduce the analgesic effects of the opioids
  - The effect of vaporized cannabis to enhance opioid analgesia occurs by a pharmacodynamic, not a pharmacokinetic mechanism


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
872196A
SHARP & DOHME
BALTIMORE

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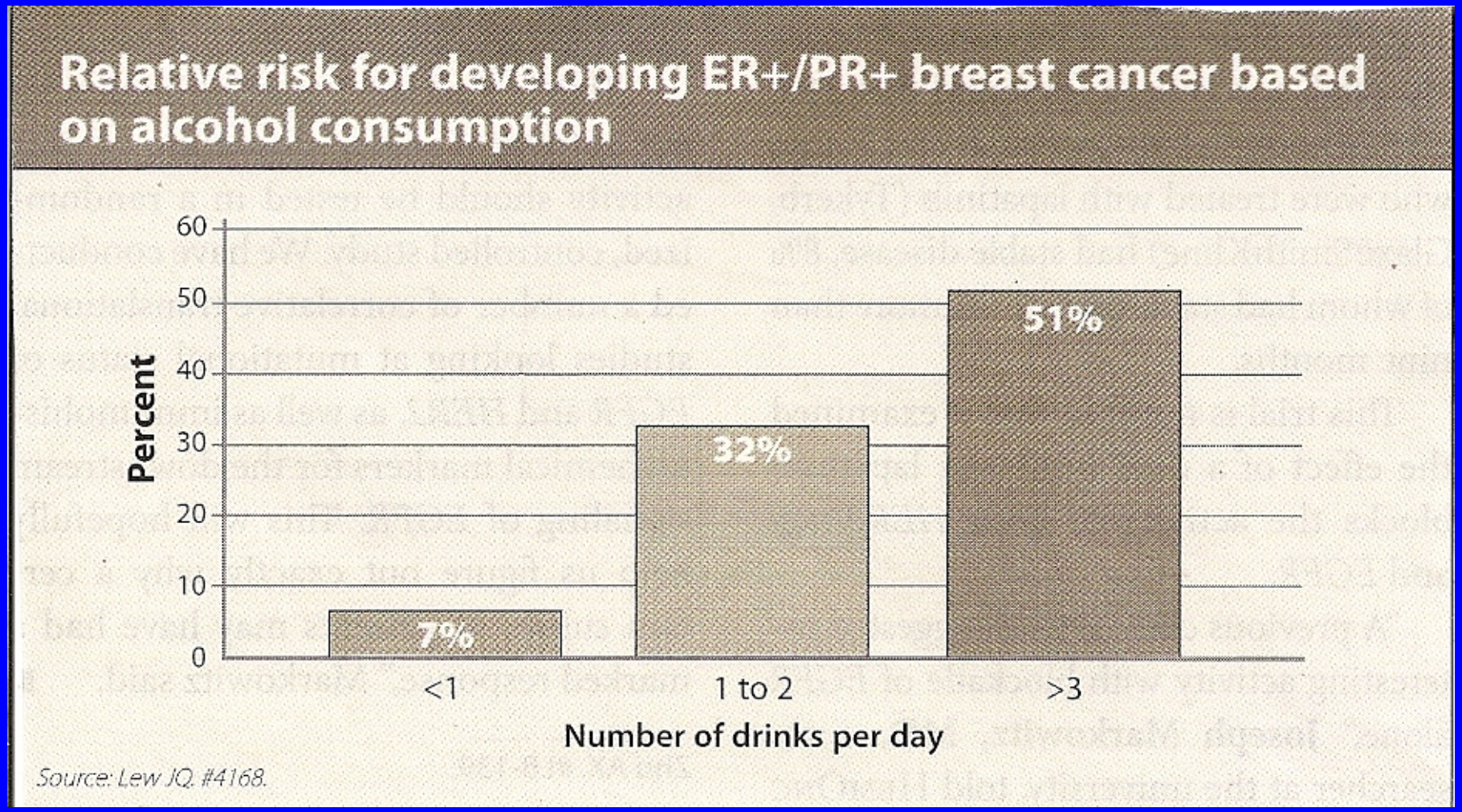
Alcohol and Breast Cancer



Lew et al HemOnc Today 2008

Smoking still takes big toll in U.S. cancer deaths

Updated: Oct 26, 2016 1:39 PM PST

(HealthDay News) -- Nearly one-third of cancer deaths among Americans aged 35 or older are caused by smoking, and the rate is much higher in the South, a new study finds.

Researchers tracking 2014 federal government data found that more than 167,000 cancer deaths among adults 35 and older in 2014 -- 28.6 percent -- were attributable to cigarette smoking.

Most of the states with the highest rates of smoking-linked cancer deaths were in the South, including nine of the top 10 ranked states for men and six of the top 10 ranked states for women, according to the study.

Some of these southern states have particularly lax anti-smoking controls in place, the researchers said.

"Not surprisingly, states with underfunded tobacco-control

© iStockphoto.com / Viesturs Kalvans

Health More>>

Join the Teal Pumpkin Project on Halloween

Poorer heart attack victims, especially women, fare worse

Does Cannabis Cause Cancer?

- National Toxicology Program of US DHHS conducted a two year rodent trial
- Mice and rats received increasing doses of THC via gavage
- Dose-related decrease of both benign and malignant tumors noted
- Animals receiving THC lived longer than those receiving vehicle alone

US Dept HHS National Toxicology Program Report 1996

Does Cannabis Cause Cancer?

- Kaiser Permanente retrospective cohort study of 65,855 men aged 15-49 seen between 1979-85 and followed thru 1993
  - In never smokers, 2 cases of lung cancer
  - In tobacco alone or tobacco plus cannabis, risk increased 10-fold over never smokers
  - In cannabis only cohort, **no** cases of lung cancer documented

Sidney et al, Cancer Causes and Control 1997

Cannabis and Lung Cancer Reviews

- 6 population or clinic-based case control studies with 2195 cases, 2985 controls
  - Little or no association between cannabis use and lung cancer incidence
    - » Zhang et al, Journal of Cancer 2015
- Another analysis included study of 49,231 Swedish conscripts followed for 40 years which showed increased risk, but did not control for concurrent tobacco use
    - » Huang et al, Cancer Epidemiology 2015

Cannabis Use and Other Cancers

- Head and neck cancer
  - Meta-analysis of 9 studies showed no significant association
    - » DeCarvalho et al, Archives of Oral Biology 2015
- Testicular cancer
  - Systematic review and meta-analysis of 3 case control studies showed increased risk of particularly non-seminomatous germ cell tumors
    - » Gurney et al, BMC Cancer 2015
- No clear associations with other cancers

Cannabis as an Anti-Cancer Agent

- In 1975 NIH investigators reported that delta-9-THC, delta-8-THC and CBD inhibited Lewis lung adenocarcinoma cell growth in vitro and in mice
- Increasing body of preclinical evidence suggests cannabinoids may have anti-cancer activity
- Anti-oxidant and anti-inflammatory effects may contribute as well
- Possibility of anti-tumor activity via cannabinoid receptors inducing apoptosis and impairing tumor vascularization

Cannabinoids and Cancer

- Multiple tumor cell lines inhibited *in vitro*
- Cannabinoid administration to nude mice curbs growth of various tumor xenografts
  - Lung, breast, colorectal and pancreas carcinoma
  - Skin carcinoma
  - Melanoma
  - Thyroid epithelioma
  - Lymphoma
  - Glioma

» Velasco et al, Neuropharmacology 2004

Cannabinoids and Cancer

- Cannabinoids induce apoptosis in mouse gliomas
- Cannabinoids administration in mouse models differentiates tumor vascular hyperplasia
  - Associated with reduced expression of VEGF and VEGF receptors (inhibition of tumor angiogenesis)
- Cannabinoids decrease the activity of matrix metalloproteinase-2; hence may also modify glioma invasiveness (inhibition of metastasis)
- Despite above, normal glial cells unaffected

Velasco et al, Neuropharmacology 2004

Gliomas Systematic Review

- 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, J Neurooncology 2014

The Lone 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

Cannabinoid Receptors in Human Tumors

- Gliomas: CB1 and CB2 expressed; CB2 in high grade
- Colon: CB2 associated with poor prognosis in III/IV
- Hepatocellular: Increased CB1 and CB2 associated with improved prognosis/survival
- Pancreatic: Both overexpressed c/w nl tissue
- Breast: CB2 correlates with HER2+; correlation between CB2 and aggressiveness
- Prostate: Both overexpressed and correlated with poor outcome
- Non-small cell Lung: CB1 in 24%, CB2 in 55%

Ladin et al, Frontiers in Pharmacology, 2016

Ongoing Clinical Trials

- A safety study of Sativex compared with placebo (both with dose dense temozolomide) in recurrent glioblastoma
  - N=20
  - Estimated completion September 2016
- Pure cannabidiol as a single agent for solid tumors
  - Phase 2 efficacy study in 60 patients with progressive disease after standard therapies
  - Hadassah Medical Organization; closed July 2015

ClinicalTrials.gov

Cannabis and Cannabinoids (PDQ®)

Last Modified: 12/14/2011

Overview

This complementary and alternative medicine (CAM) information summary provides an overview of the use of *Cannabis* and its components as a treatment for people with cancer -related symptoms caused by the disease itself or its treatment.

This summary contains the following key information:

- *Cannabis* has been used for medicinal purposes for thousands of years.
- By federal law, the possession of *Cannabis*, also known as marijuana, is illegal in the United States.
- The U.S. Food and Drug Administration has not approved *Cannabis* as a treatment for cancer or any other medical condition.
- Chemical components of *Cannabis*, called cannabinoids, activate specific receptors found throughout the body to produce pharmacologic effects, particularly in the central nervous system and the immune system.
- Commercially available cannabinoids, such as dronabinol and nabilone, are approved for the treatment of cancer-related side effects.
- Cannabinoids may have benefits in the treatment of cancer-related side effects.

Many of the medical and scientific terms used in this summary are hypertext linked (at first use in each section) to the NCI Dictionary of Cancer Terms, which is oriented toward nonexperts. When a linked term is clicked, a definition will appear in a separate window. All linked terms and their corresponding definitions will appear in a glossary in the printable version of the summary.

Reference citations in some PDQ CAM information summaries may include links to external Web sites that are operated by individuals or organizations for the purpose of marketing or advocating the use of specific treatments or products. These reference citations are included for informational purposes only. Their inclusion should not be viewed as an endorsement of the content of the Web sites, or of any treatment or product, by the PDQ Cancer CAM Editorial Board or the National Cancer Institute.

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Cannabis-Induced Euphoria

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

Cannabis in Supportive Care

- 211 Israeli cancer patients seeking cannabis licenses were interviewed at baseline
- 131 had a second interview 6-8 wks later
  - 25 had stopped treatment after < one week
    - More CNS involvement
    - Less CINV, anorexia or weight loss
  - 106 who continued clearly a biased sample
    - All cancer or treatment related side effects significantly improved
      - Nausea, vomiting, mood disorders, fatigue, wt loss, anorexia, sexual function, sleep, itching and pain ($P<0.001$)
      - 43% reduced pain meds, 33% reduced antidepressants
        - » Bar-Sela et al, Evidence-Based Comp + Alt Med, 2013

The NEW ENGLAND JOURNAL of MEDICINE
May 30, 2013

CLINICAL DECISIONS
INTERACTIVE AT NEJM.ORG

Medicinal Use of Marijuana — Polling Results

Jonathan N. Adler, M.D., and James A. Colbert, M.D.

- Readers responded to the case of Marilyn, a 68 yo with metastatic breast cancer, seeking cannabis to alleviate symptoms
- 1446 votes cast from 72 countries and 56 states and provinces in North America (1063 total)
- “We were surprised by the outcome of polling and comments with 76% of all votes in favor of the use of marijuana for medicinal purposes- even though marijuana use is illegal in most countries”

WebMD Physician Survey 2014

- WebMD/Medscape survey of 1544 MDs from more than 12 specialties in 48 states
  - 68% say it can help with certain Rx and conditions
  - 67% say it should be a medical option for patients
  - 56% support making it legal nationwide
    - 50% in states where it is not legal say it should be legal
    - 52% in states considering new law say it should be legal
- Oncologists and hematologists show highest level of support among specialists (82%)

www.webmd.com April 2, 2014

Cannabis and Chemotherapy

- No adverse effect of cannabis tea with irinotecan or docetaxel
  - » Engels et al, Oncologist 2007
- Cannabinoids with chemotherapy acts synergistically to reduce tumor growth in mice
  - THC plus temozolamide effective in glioma xenografts even in temozolamide-resistant tumors
  - Adding CBD enhanced effect even with lower THC
    - » Torres et al, Mol CA Therapy 2011
- Gemcitabine combined with different cannabinoids reduces viability of pancreatic cancer cells
  - » Donadelli et al, Cell Death Disease 2011

NEWMEXICO MEDICAL CANNABIS CONFERENCE
The Plant | The People | The Purpose

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.