Cannabinoids in Pain
and Palliative Care

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Phytochemical and genetic analyses of ancient cannabis from Central Asia

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\textsuperscript{4} B

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).
Fig S3B.

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 trichomes. (C) Photomicrograph of leaf fragment with high-power magnification displaying glandular trichomes. (D) Photomicrograph of leaf fragment displaying glandular trichomes.
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 investigations
    – Removed from US Pharmacopoeia in 1942
# Controlled Substances Act 1970

<table>
<thead>
<tr>
<th>Category</th>
<th>Schedule I</th>
<th>Schedule II</th>
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</thead>
<tbody>
<tr>
<td>Potential for abuse</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Accepted medical use</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Safety</td>
<td>Lack of accepted safety for use under medical supervision</td>
<td>Abuse of drug may lead to future psychological or physical dependence</td>
</tr>
</tbody>
</table>
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
Cannabinoids 101

• A group of $C_{21}$ terpenophenolic compounds uniquely produced by cannabis
• Endogenous cannabinoids e.g. anandamide are termed endocannabinoids
• Synthetic cannabinoids e.g. HU-210 have been developed
• Phytocannabinoids suggested to designate $C_{21}$ compounds produced by cannabis
Non-THC Cannabinoids

- Cannabidiol (CBD)
- Cannabinol (CBN)
- Cannabichromene (CBC)
- Cannabigerol (CBG)
- Delta-8-THC (Δ⁸-THC)
- Tetrahydrocannabivirin (THCV)
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
- CBD possesses sedative properties, reduces anxiety and other unpleasant psychological side effects of pure THC
Non-THC Components of Marijuana

- ∆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
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
CANNABINOID RECEPTORS: G-PROTEIN COUPLING
CB₁ 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

- Anandamide
- Di-homo-γ-linolenoyl ethanolamide
- Docosatetraenoyl ethanolamide
- 2-Arachidonyl-Glycerol
Endogenous Cannabinoid System

CB2 Receptor
- Immune function
- Cell proliferation
- Inflammation
- Pain

CB1 Receptor
- Appetite
- Immune function
- Muscle control
- Pain
- IOP

CBx Receptor
- Cognition
- Emesis
- Neuroexcitability
- Reward
- Thermoregulation

VR1 Receptor
- Pain
- Vasodilation

Synthesis → Endocannabinoids → Cellular uptake, Metabolism

Signal Transduction

Martin 2004
Manipulation of Endogenous Cannabinoid System

**Activation**
- CB₁ Receptor agonist
- CB₂ Receptor agonist
- Enhanced EC synthesis
- Decreased EC metabolism
- Transporter blocker
- Altered signaling pathway

**Inhibition**
- CB₁ Receptor antagonist
- CB₂ Receptor antagonist
- Decreased EC synthesis
- Increased EC metabolism
- Transporter activator
- Altered signaling pathway

Martin 2004
Anandamide Inactivation Pathway

Presynaptic Neuron

THC

CB Receptor

AEA

Neurotransmitters

2-AG

CB Receptor

THC

AEA

GABA & Glutamate Receptors

Inhibitors

SB-FI-26

CBD

FABP

ABA

FAAH, AEA Breakdown

AEA (Anandamide) FAAH (fatty acid amide hydrolase)
FABP (human fatty acid binding protein), CB (cannabinoid receptor)

Dale Deutsch, Biochemistry and Cell Biology, Stony Brook University
http://www.stonybrook.edu/commcms/biochem/research/faculty/deutsch.html
Symptom Management Challenges Associated with Cancer and Its Treatments

THC 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-HT₃ antagonists
Oncologists’ THC Survey

• 1000 responses from randomly selected members of American Society of Clinical Oncology surveyed in 1990
  – 44% had recommended marijuana to at least one patient
  – Marijuana believed to be more effective than dronabinol by 44%; dronabinol more effective by 13%

» Doblin et al JCO 1991
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…
Oral Delta-9 THC: An Approved Drug

FOR THE TREATMENT OF ANOREXIA ASSOCIATED WITH WEIGHT LOSS IN PATIENTS WITH AIDS

A significant appetite improvement was achieved at week 4 of a 6-week study. Trends toward improved body weight and mood, and decreases in nausea were also seen during the same 6-week study, but these results were not statistically significant.

MARIOL was well tolerated. Side effects were generally mild and resolved by dosage reduction. The most frequent adverse reactions included euphoria (13%), dizziness (7%), thinking abnormal (7%), sinusitis (6%), somnolence (6%). Although no drug-drug interactions were discovered during clinical trials of MARIOL, cannabinoids may interact with other drugs, including amphetamines, atropine, and antihistamines.

MARIOL has the potential for abuse. The same care in prescribing and accounting for MARIOL should be used as for other Schedule II drugs. Prescriptions should be limited to the amount necessary for the period between visits.

A Patient Assistance Program is available. For information call: 1-800-278-8051.

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
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)
Pharmacologically 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)  

• 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
Cannabis and Appetite in Cancer

- Two clinical trials of dronabinol in cancer-related anorexia
  - 54 adults, placebo-controlled RCT: THC better
  - 459 adults randomized to dronabinol, megestrol or both: THC (49% ↑ appetite, 3% ↑ wt) inferior to megestrol (75% ↑ appetite, 11% ↑ wt) and combined Rx offered no added benefit

- Two trials (N=12 and 149) in HIV wasting with similar results

Reviewed in Ben Amar, J of Ethnopharmacology 2006
Cannabinoids and Pain

- Elevated levels of the CB1 receptor - like the opioid - are found in areas of the brain that modulate nociceptive 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
Marijuana 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 ≤ 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
Figure 2. Flow of participants through the trial.
Experimental Pain Model

Pain Model Timeline: Days 1 and 5

Time (min)
-105 -95 -65 -60 -25 -15 0 15 25 55 65 95 105

LTS1  Forearm  Heat  Forearm  Capsaicin  VAS  Map1  VAS2  RK1  LTS2  VAS4  RK2  LTS3  VAS5  RK3  LTS4  VAS6  RK4  LTS5

↓ Smoke
## Baseline Characteristics by Study Arm

<table>
<thead>
<tr>
<th></th>
<th>Placebo N=25</th>
<th>Cannabis N=25</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td>23 males (2 MTF TG)</td>
<td>20 males (1 MTF TG)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>Mean = 47 ± 7</td>
<td>Mean = 49 ± 6</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td>11 AA, 9 white</td>
<td>9 AA, 12 white</td>
</tr>
<tr>
<td><strong>HIV</strong></td>
<td>14 years</td>
<td>15 years</td>
</tr>
<tr>
<td><strong>CD4+</strong></td>
<td>442/mm³</td>
<td>453/mm³</td>
</tr>
<tr>
<td><strong>HIV RNA</strong></td>
<td>&lt; 400 14</td>
<td>&lt; 400 18</td>
</tr>
</tbody>
</table>
## Baseline Characteristics by Study Arm

<table>
<thead>
<tr>
<th></th>
<th>Placebo N=25</th>
<th>Cannabis N=25</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neuropathy 6 years</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>Meds</td>
<td>14</td>
<td>12</td>
</tr>
<tr>
<td>Both</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Current ART</td>
<td>22</td>
<td>17</td>
</tr>
<tr>
<td>BL Pain</td>
<td>52.0</td>
<td>53.8</td>
</tr>
</tbody>
</table>
Baseline Pain Medications

- Gabapentin
- Opioids
- Other
- None

Graph shows the comparison between two categories, labeled as 'P' and 'C'.
Results: Neurology RCT

Abdams 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
HIV Neuropathy Crossover RCT

- 28 HIV patients
- Placebo or active cannabis, dose escalation between 1-8% THC
- Inhaled 4 x/d for 5 d, then 2 week washout before cannabis or placebo
- 46% with > 30% pain reduction vs 18% placebo; NNT=3.5
Cannabis Effect on Neuropathic Pain in Complex Regional Pain Syndrome

- 38 patients with central and peripheral neuropathic pain
- Randomized to high-dose, low-dose or placebo cannabis
- Linear analgesic dose response observed for both doses
- Effect not anxiolytic; reduces core nociception and emotional response to pain equally

Cannabis Effect on Post-traumatic and Postsurgical Neuropathic Pain

- Randomized, double-blind, 4-period crossover study enrolled 23 participants
- Inhaled 0, 2.5, 6 or 9.4% THC cannabis 25 mg tid for 5 days; 9 day rest between doses
- Average daily pain intensity significantly lower on 9.4% THC cannabis (5.4) than on 0% (6.1) ($p = 0.023$; difference = 0.7, 95% CI 0.02–1.4)
- Improved quality of sleep also noted

Ware et al CMAJ 2010
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 scale
  – Average ↓ 2.6 in the 5 responders
  – NNT=5

Lynch et al, J Pain Symptom Management, 2013
<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quantity</th>
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<tbody>
<tr>
<td>Ext. Hyoscyamus</td>
<td>2-3 gr.</td>
</tr>
<tr>
<td>Ext. Conium</td>
<td>1-2 gr.</td>
</tr>
<tr>
<td>Ext. Ignatia</td>
<td>1-2 gr.</td>
</tr>
<tr>
<td>Ext. Opium</td>
<td>1-3 gr.</td>
</tr>
<tr>
<td>Ext. Aconite Leaves</td>
<td>1-4 gr.</td>
</tr>
<tr>
<td>Ext. Cannabis Ind.</td>
<td>1-5 gr.</td>
</tr>
<tr>
<td>Ext. Stramon. Seed</td>
<td>1-5 gr.</td>
</tr>
<tr>
<td>Ext. Bellad. Leaves</td>
<td>1-6 gr.</td>
</tr>
</tbody>
</table>

**John Wyeth & Brother, Inc.**

Philadelphia

Guaranteed under The Food and Drug Act, June 29, 1906.
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

- Cannabinoids interact with kappa and delta receptors in production of pain relief.
- Analgesic effects of opioids mediated by mu receptors, but may be enhanced by cannabinoid effects.
- Cannabinoid:opiod interaction may occur at the level of their signal transduction mechanisms:
  - Receptor activation for both leads to decreased cAMP production via G protein activation.
  - Some evidence that cannabinoids might increase production or release of endogenous opioids.
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

<table>
<thead>
<tr>
<th>morphine</th>
<th>oxycodone</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>42.9 (33-55)</td>
<td>47.1 (28-61)</td>
</tr>
<tr>
<td>62 mg bid (10-200)</td>
<td>53 mg bid (10-120)</td>
</tr>
<tr>
<td>34.8 (29.4, 40.1)</td>
<td>43.8 (38.6, 49.1)</td>
</tr>
</tbody>
</table>
Pain Characteristics

- Musculoskeletal NOS 7
- Post-traumatic 4
- Arthritis 2
- Peripheral neuropathy 2
- Cancer 1
- Fibromyalgia 1
- Migraine 1
- Multiple sclerosis 1
- Sickle cell disease 1
- Thoracic outlet syndrome 1
a. Morphine

Abrams et al, Clinical Pharmacology & Therapeutics 2011
b. Oxycodone

Mean Oxycodone Level By Study Day

- Day 1
- Day 5

Oxycodone plasma level (mg/ml)

Hour

Abrams et al., Clinical Pharmacology & Therapeutics 2011
# Pain by Study Day

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

*p<0.001

Abrams et al, Clinical Pharmacology & Therapeutics 2011
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 trends 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.
Oleores. Capsc. 1-20 gr.
Peppermint Oil q. s.
Dose 1 to 4 Tablets
872196A
SHARP & DOHME
BALTIMORE
IOM: Efficacy of Cannabinoid Drugs

• The accumulated data indicate a potential therapeutic value for cannabinoid drugs
  – Pain relief
  – Control of nausea and vomiting
  – Appetite stimulation

• THC therapeutic effects best established

• Effects of cannabinoids generally modest; usually there are more effective medications
Challenging Symptoms in Palliative Care

- Anorexia
- Weight loss $\Rightarrow$ cachexia
- Nausea and vomiting
- Moderate to severe pain
- Anxiety
- Depression
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 mood a potentially useful tool in palliative medicine?
IOM: Use of Smoked Marijuana

- The goal of clinical trials of smoked marijuana would not be to develop it as a licensed drug, but as a first step towards the development of non-smoked, rapid-onset cannabinoid delivery systems.
- This may take years; in the meantime there are pts with debilitating sx for whom smoked marijuana may provide relief.
IOM: Efficacy of Cannabinoid Drugs

• **Recommendation:** Clinical trials of cannabinoid drugs for symptom management should be conducted with the goal of developing
  – rapid onset
  – reliable
  – safe

• delivery systems

Joy et al eds. Marijuana and Medicine 1999
Vaporization of Cannabis
Vaporization

- THC vaporizes at a lower temperature than it burns
- Vaporizer heats cannabis to 155° C, below the burning point of combustible plant
- Vapors are cooler, purer and probably less toxic than smoke
- May be more psychoactive as less of THC content has been burned off

* Gieringer 1996
Vaporization Conclusions

• Vaporization of cannabis is a safe and effective mode of delivery
  – Plasma THC levels are comparable
  – Physiologic effects are comparable
  – Expired carbon monoxide is decreased
• Participants had a clear preference for vaporization over smoking as a delivery system for the cannabis used in this trial
• Vaporization of cannabis could be used as a delivery system in clinical effectiveness trials

Abrams et al, Clin Pharm and Therapeutics 2011
The Safety of Cannabis

• No deaths have been reported from OD
  – Estimate 800 cigarettes required to kill (death secondary to CO not cannabinoid poisoning)
  – By comparison, 300 ml of vodka or 60 mg of nicotine would be lethal
  – Unlike opioid receptors, dearth of brainstem cannabinoid receptors

• Addictive potential and minor withdrawal syndrome less than or equal to caffeine
### The Safety of Cannabis

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  - Estimate 800 cigarettes required to kill (death secondary to CO not cannabinoid poisoning)
  - By comparison, 300 ml of vodka or 60 mg of nicotine would be lethal
  - Unlike opioid receptors, dearth of brainstem cannabinoid receptors
- **Addictive potential and minor withdrawal syndrome less than or equal to caffeine**

### Addictive Potential Comparison

<table>
<thead>
<tr>
<th>Substance</th>
<th>Ever Used (%)</th>
<th>Became Dependent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobacco</td>
<td>76%</td>
<td>32%</td>
</tr>
<tr>
<td>Heroin</td>
<td>2%</td>
<td>23%</td>
</tr>
<tr>
<td>Cocaine</td>
<td>16%</td>
<td>17%</td>
</tr>
<tr>
<td>Alcohol</td>
<td>92%</td>
<td>15%</td>
</tr>
<tr>
<td>Anti-anxiety drugs</td>
<td>13%</td>
<td>9%</td>
</tr>
<tr>
<td>Marijuana</td>
<td>46%</td>
<td>9%</td>
</tr>
</tbody>
</table>
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 mood and sleep a potentially useful tool in palliative medicine?
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
"Smoke two joints, and call me in the morning."
Date

To Whom It May Concern:

This patient and I have discussed the risks and benefits of medical marijuana use as a treatment for the following condition(s) related to cancer:

- [ ] Nausea
- [ ] Vomiting
- [ ] Weight Loss
- [ ] Anorexia
- [ ] Pain
- [ ] Other

If________________________ chooses to use medical marijuana therapeutically, I will continue to monitor and provide advice on his/her condition and progress.

I am a medical provider licensed to practice in the State of California. I understand that the dispensary may contact me to verify the information contained in this letter. Please feel free to contact me at the direct practice phone number below. Valid for one year from date above.
<table>
<thead>
<tr>
<th>Product</th>
<th>Size</th>
<th>Price</th>
<th>Price</th>
<th>Price</th>
<th>THC</th>
<th>CBD</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Green Dragon Indoor</td>
<td>-</td>
<td>$45</td>
<td>$85</td>
<td>$290</td>
<td>17%</td>
<td>1%</td>
<td>An energetic, interactive, &amp; mind blowing sativa high. Delicious flavor &amp; aroma.</td>
</tr>
<tr>
<td>Green Dragon (GH) Outdoor</td>
<td>Gram</td>
<td>$14</td>
<td>$35</td>
<td>-</td>
<td>14%</td>
<td>1%</td>
<td>An energetic, interactive, &amp; mind blowing sativa high. Delicious flavor &amp; aroma.</td>
</tr>
<tr>
<td>Stella Blue CBD (OD) Outdoor</td>
<td>Gram</td>
<td>$15</td>
<td>$40</td>
<td>$270</td>
<td>6%</td>
<td>10%</td>
<td>A blend of all the Sativa strains that we cultivate in house.</td>
</tr>
<tr>
<td>Sour Pineapple Indoor</td>
<td>Eighth</td>
<td>$35</td>
<td>-</td>
<td>-</td>
<td>15%</td>
<td>Pending</td>
<td>A sativa cross of Sour Diesel and Pineapple Kush with a nice, fragrant citrus aroma.</td>
</tr>
<tr>
<td>Chocolope Haze Indoor</td>
<td>Eighth</td>
<td>$55</td>
<td>$105</td>
<td>-</td>
<td>16%</td>
<td>Pending</td>
<td>Classic flavors of Chocolate Thai Sticks with delicious frutiness of Cannaloape Haze. It produces a comical, yet dreamy high.</td>
</tr>
<tr>
<td>Kona Bomb Indoor</td>
<td>Eighth</td>
<td>$45</td>
<td>$85</td>
<td>-</td>
<td>14%</td>
<td>Pending</td>
<td>A bright and cerebral sativa with euphoric overtones.</td>
</tr>
<tr>
<td>Red Congo</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>This is a placeholder for products that</td>
</tr>
</tbody>
</table>
Proposition 215: Compassionate Use

• Passed with 56% support November 1996
• Allows for right to possess and cultivate marijuana for medical purposes
  – where medical use has been deemed appropriate and recommended by a physician
• For use in “treatment of cancer, anorexia, AIDS, spasticity, glaucoma, arthritis, migraine or any other illness for which marijuana provides relief”
Lou Dobb’s Quick Vote

- Do you believe the federal government should prosecute doctors who prescribe medical marijuana?
  - June 6, 2005  N=4638

- National surveys in 2010 found that 75% respondents believe patients should have access to marijuana for medical purposes
• 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
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.