Cannabis in the Treatment of Chronic Pain

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Case 1

- 50 yo Japanese-American dx'ed with adenoca colon dx'ed with ruptured appendix
  - Treated with partial colectomy and 12 cycles bevacizumab/FOLFOX
  - Developed persistent neuropathy post chemo
- PET recurrence 11/08 treated with total colectomy, capecitabine/XRT
  - FOLFIRI not given as pt has baseline 6-15 bm/day
  - Current weight 148 (normal adult weight=205)

Case 1

- Tobacco: Still 2-3/day, smoking for 30 years
- EtOH: Quit 8 years ago
- Marijuana: Positive exposure
- ROS: frequent bm's, weight loss, depression on Rx, neuropathy limits physical activity
- O/E: Thin, distressed, more comfortable lying down, abd: scars, hepar sl tender at RCM

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”

Case 1

- Cannabis of potential use in this patient for
  - Weight loss
  - Depression
  - Neuropathy
  - Possible anti-cancer effects?
    - Anti-oxidant and anti-inflammatory effects
    - Possibility of anti-tumor activity via cannabinoid receptors inducing apoptosis and impairing tumor vascularization
    - Cannabinoids decrease the activity of matrix metalloproteinase-2; hence may also modify tumor invasiveness

Cannabis in painful HIV-associated sensory neuropathy

A randomized placebo-controlled trial

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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.

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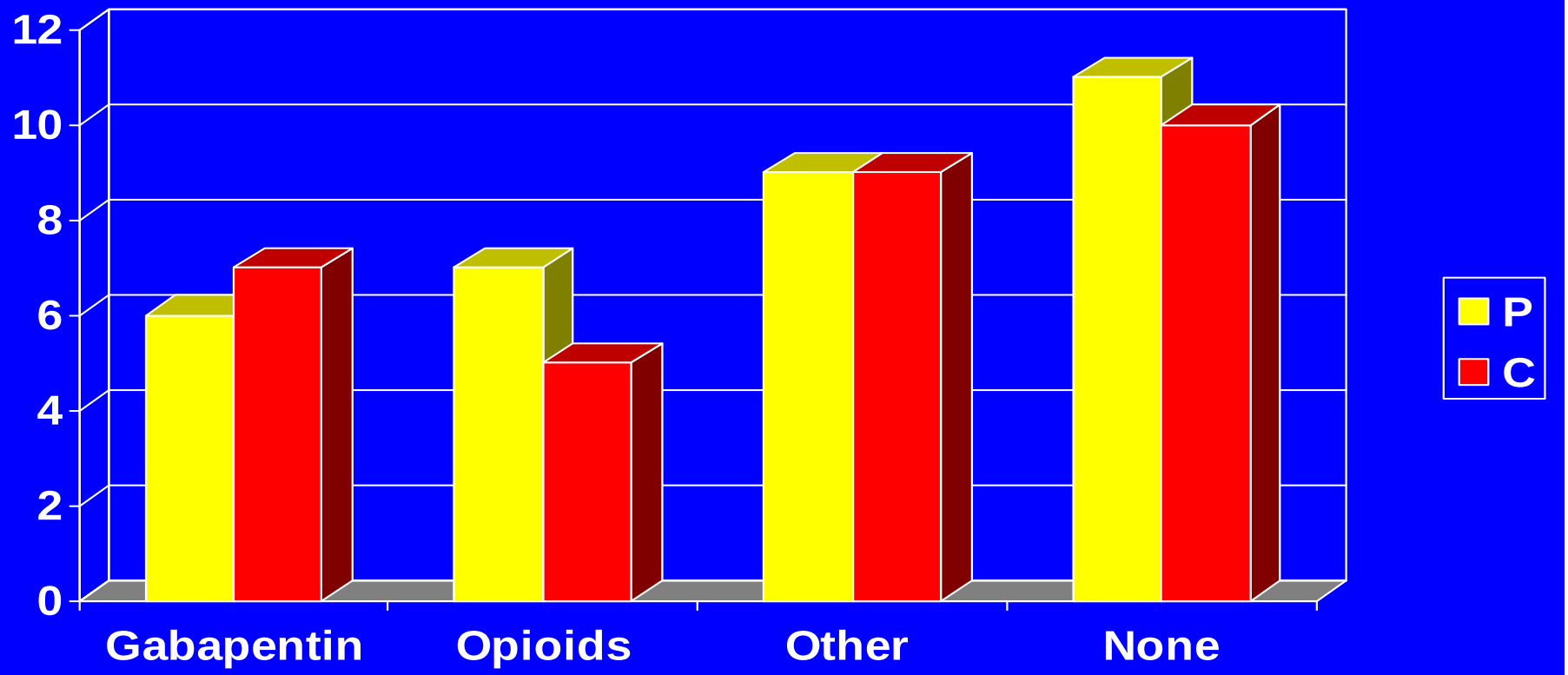
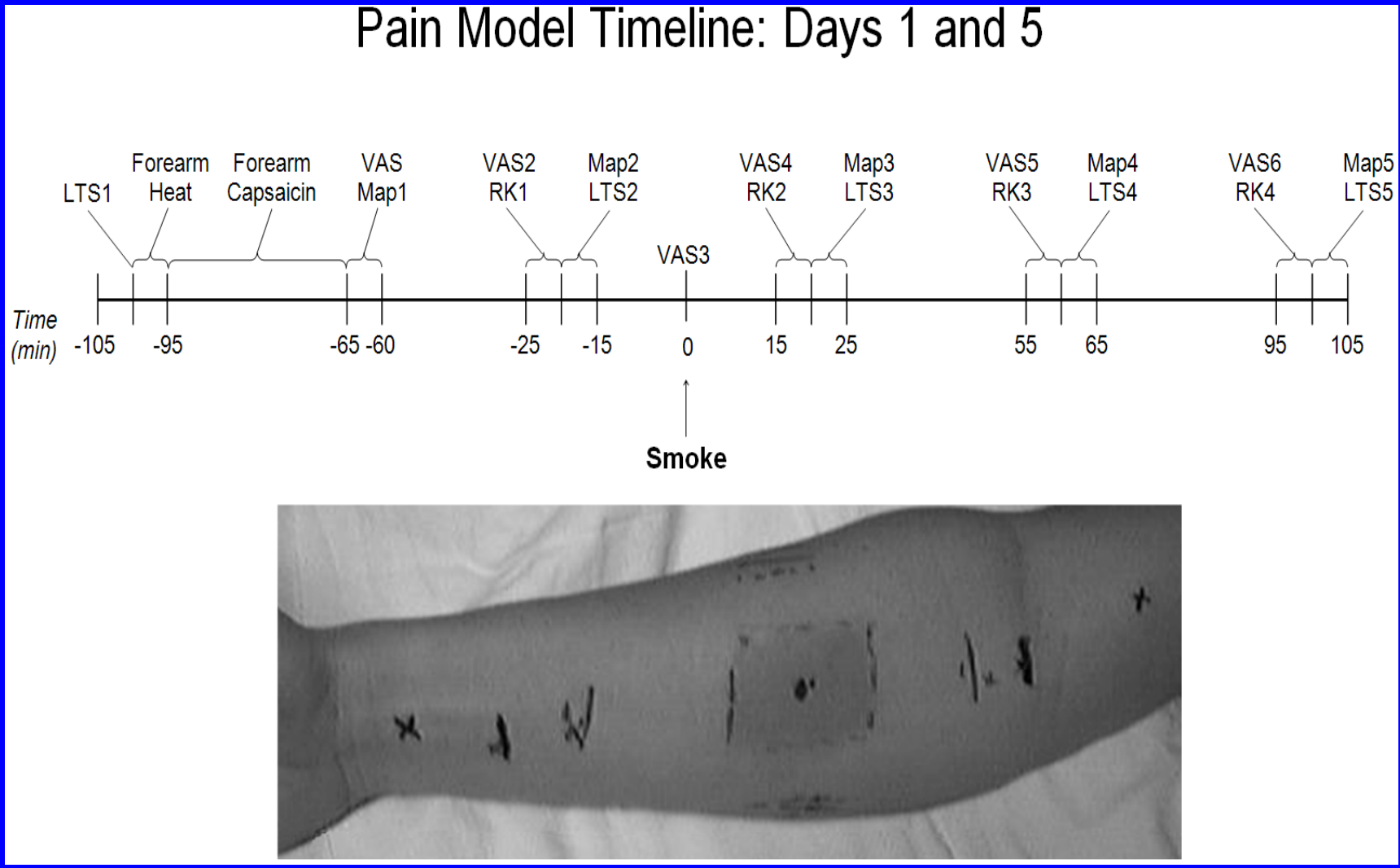
Baseline Characteristics by Study Arm

Placebo N=25		***Cannabis N=25***	
***Neuropathy* 6 years**		***Neuropathy* 6 years**	
HIV	**7**	**HIV**	**10**
Meds	**14**	**Meds**	**12**
Both	**4**	**Both**	**3**
Current ART	***22***	***Current ART***	**17**
BL Pain	**52.0**	***BL Pain***	**53.8**

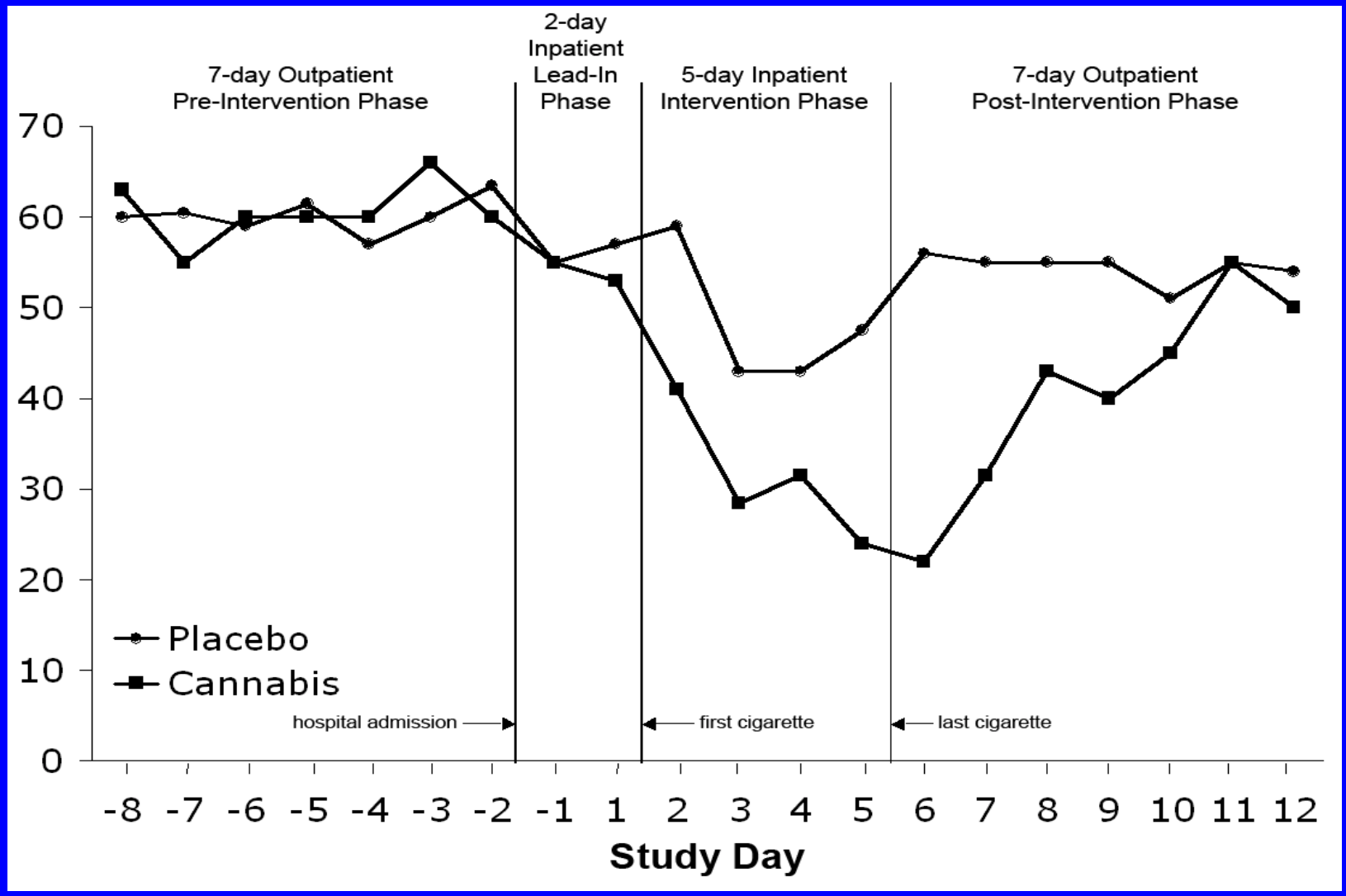
Baseline Pain Medications



Experimental Pain Model



Results: Neurology RCT



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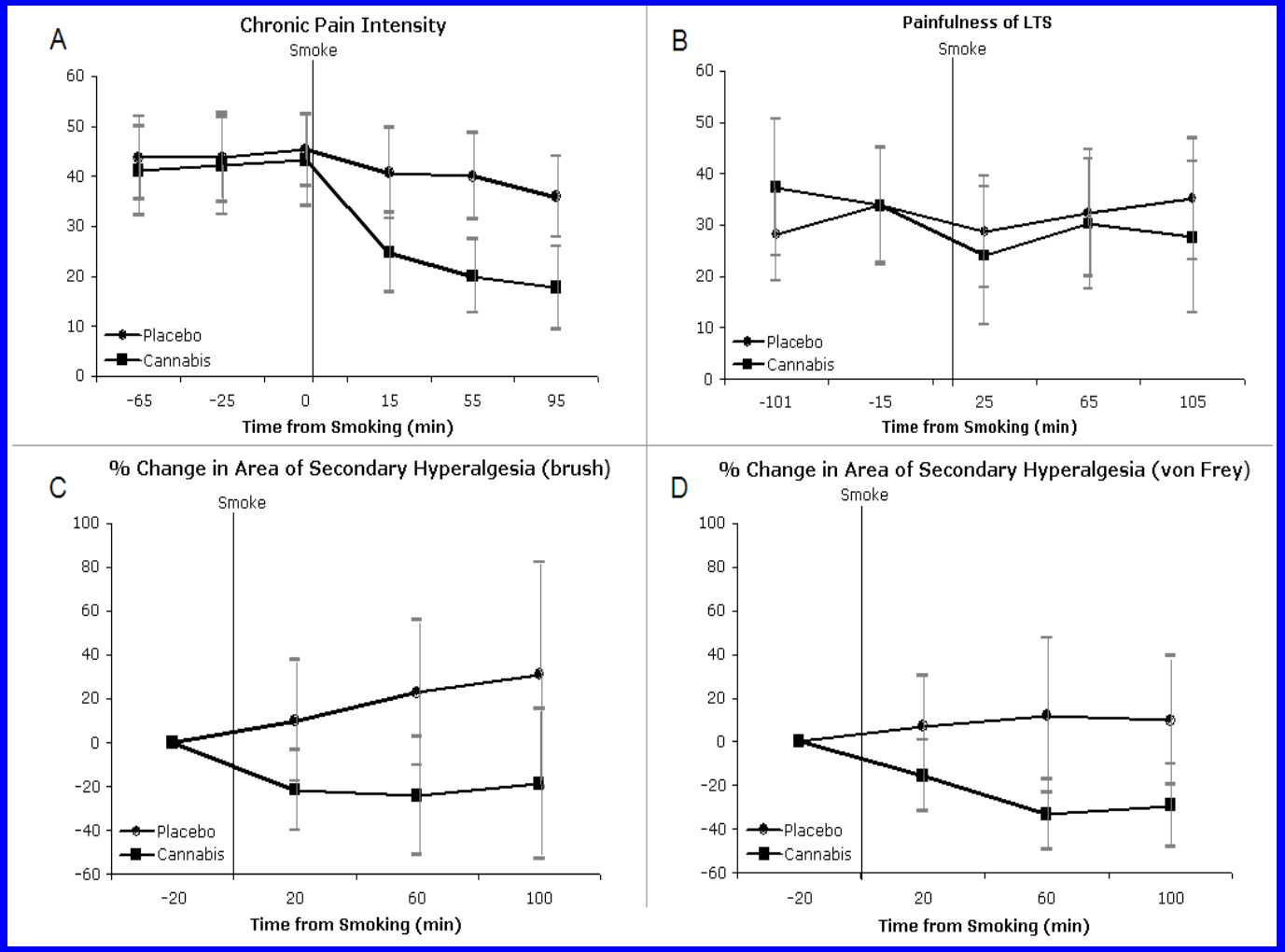
Results: Neuropathy RCT



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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

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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.

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PHILADELPHIA

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Guaranteed under The Food and

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

Vaporization

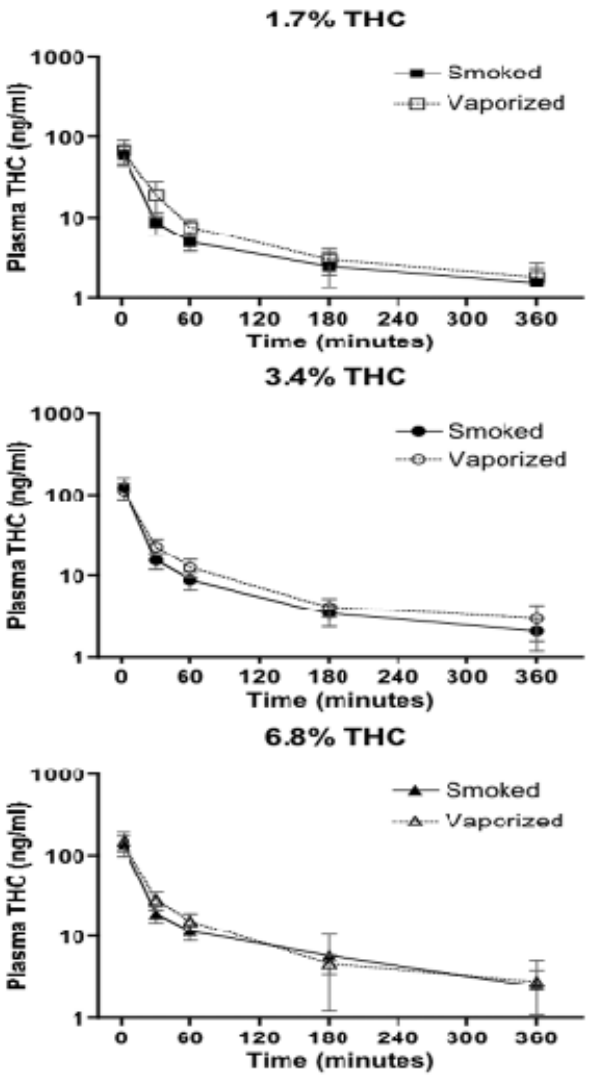
- THC vaporizes at a lower temperature than it burns
- Vaporizer heats cannabis to 155° C, below the burning point of combustible plant
- Vapors are cooler, purer and probably less toxic than smoke
- May be more psychoactive as less of THC content has been burned off

* Gieringer 1996

Volcano Device

- Maintains temperature just above point of vaporization.
- Set temperature 190 degrees Celsius.

Figure 2: THC Pharmacokinetics



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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

Case 2

- 41 yo Latino gentleman with c/o back pain and dysphagia 1/09
- CBC wnl, CT scan negative, suboptimal b/o motion
- Seen in ED May and July with persistent pain, difficulty swallowing and weight loss
- Hgb/Hct 12.3/36.5, Ba swallow with distal esophageal narrowing
- EGD 8/14: mod to pd adenocarcinoma esophagus
- Repeat CT with multiple small pulm nodules

Case 2

- 8/31 Oncology Visit
  - Persistent back pain, N&V, 20# loss/month
  - On fentanyl 200ucg. MS elixir, famotidine
  - HIV- gay, no partner, hairdresser, lives with dog with cancer; 25 pack/years, EtOH in past, +MJ
  - Twin brother and 3 other bros in NYC, estranged
  - PET ordered to assess pulmonary nodules

Case 2

- PET reveals + nodes, lytic vertebral lesions
- Feeding tube placed
- Cisplatin/irinotecan begun
- Weight down 13 kg/2 months
- Patient requests letter for medical cannabis to deal with chemotherapy side effects, anorexia, N&V and pain

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:opioid 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

Cannabinoid:Opioid Interactions

- Morphine metabolized by glucuronidation
  - Morphine-3-glucuronide
  - Morphine-6-glucuronide (active metabolite)
- If vaporized cannabis accelerates glucuronidation, lower morphine levels would result
- In capsule form, oral THC delays gastric emptying
  - If vaporized cannabis does same, time course of morphine absorption may be altered

Cannabinoid:Opioid Interactions

- Oxycodone metabolized by CYP450
  - Oxymorphone (active metabolite) via CYP2D6, undergoes glucuronidation
  - Noroxycodone (inactive metabolite) excreted unchanged in the urine
- If vaporized cannabis effects CYP 2D6 or glucuronidation, oxycodone levels may change
- If vaporized cannabis alters gastric emptying, time course of oxycodone absorption may be altered

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

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

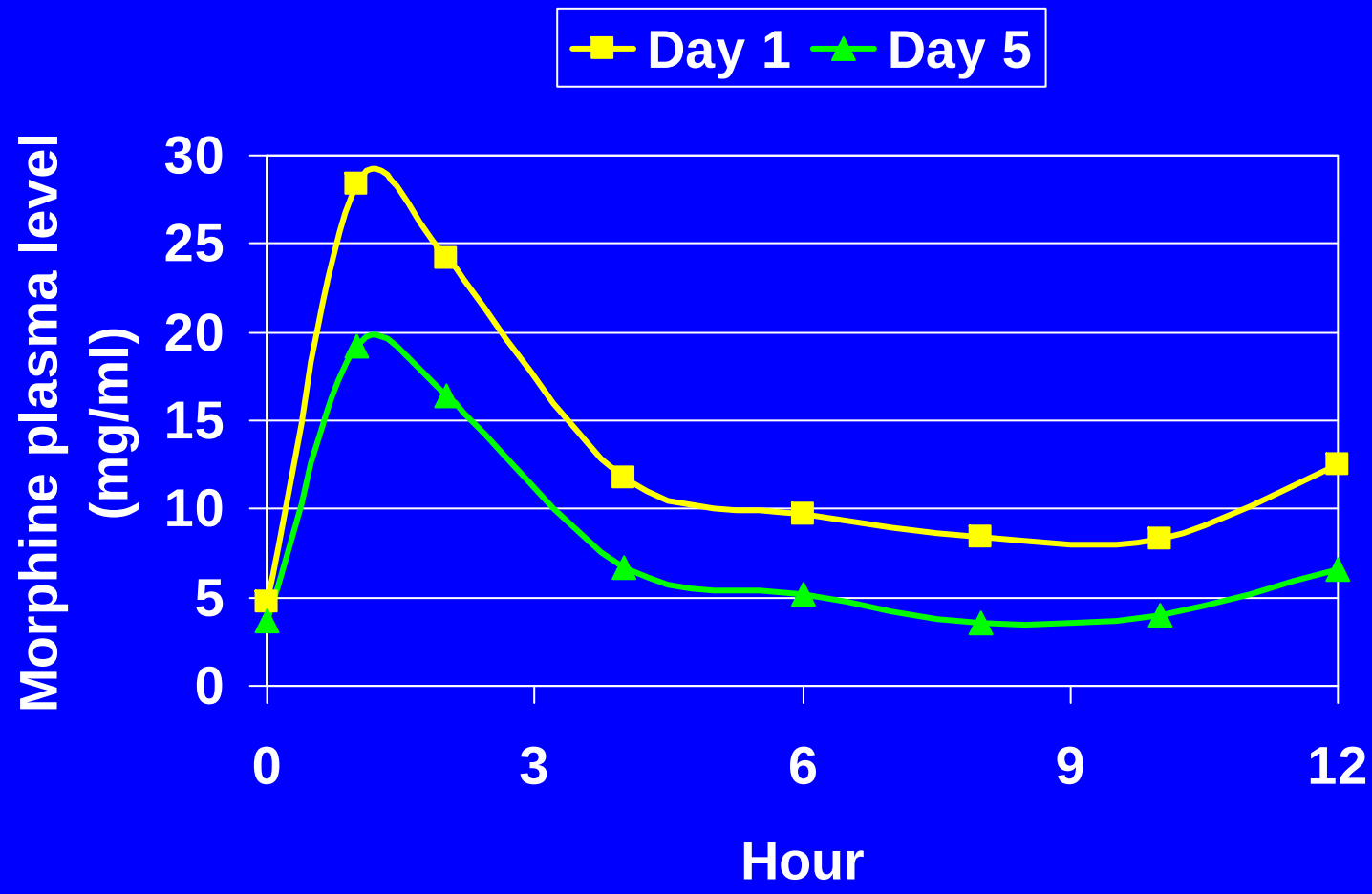
Participant Characteristics

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)

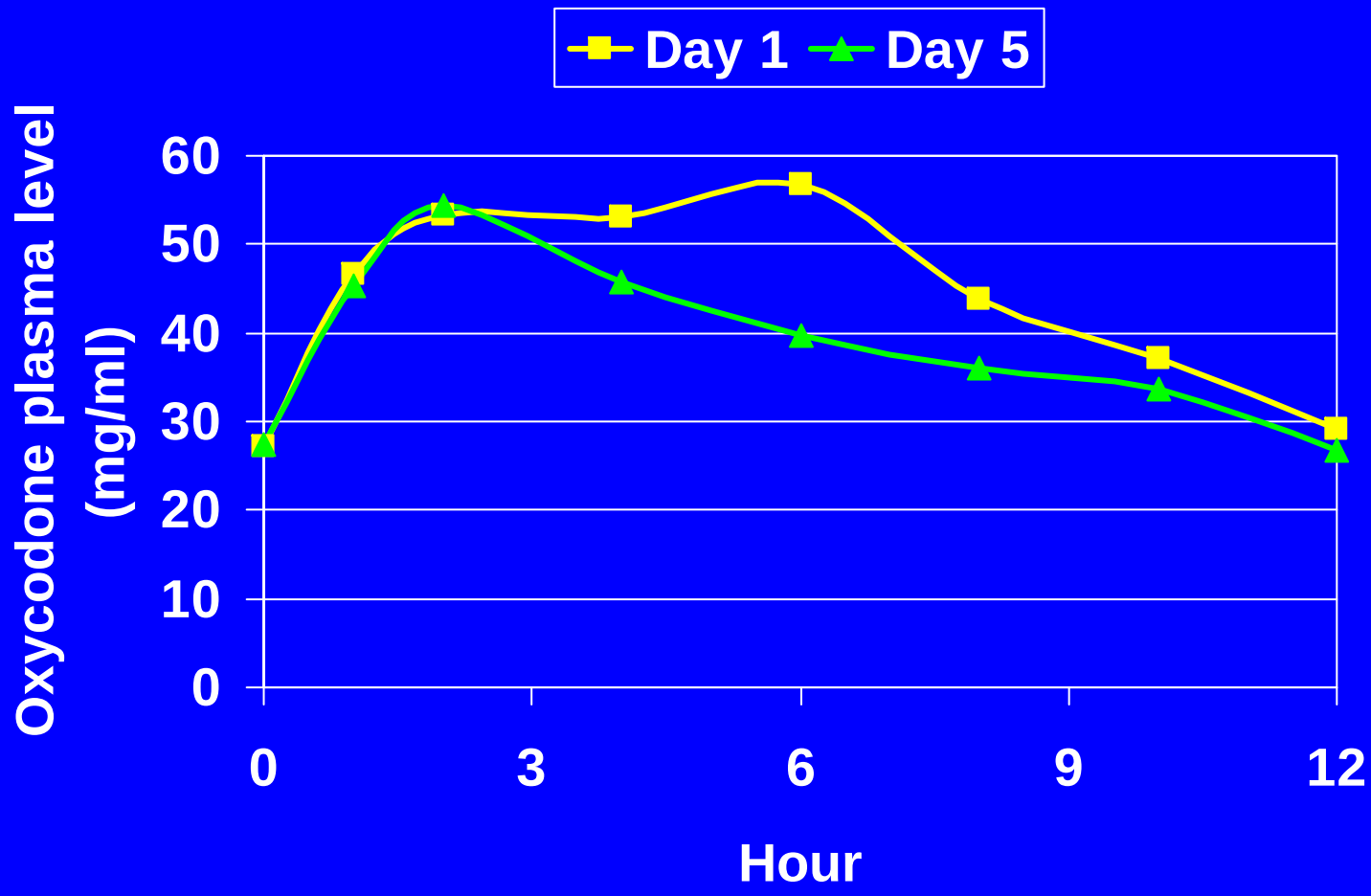
Pain Characteristics

- 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

Mean Morphine Level by Study Day



Mean Oxycodone Level by Study Day



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	11	34.8 (29.4, 40.1)	24.1 (18.8, 29.4)	**-11.2 (-16.5, -6.0)**
Oxycodone	10	43.8 (38.6, 49.1)	33.6 (28.5, 38.6)	**-10.3 (-14.8, -5.8)**

*** Bold indicates p<0.001**

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*rends 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
8721 96A
SHARP & DOHME
BALTIMORE

Case 3

- 62 yo woman with pancreatic neuroendocrine tumor initially dx 1997
  - Liver mets first noted 2003
  - Multiple complications of her disease and it's Rx
    - Diarrhea
    - Diabetes
    - Hypercalcemia
    - Weight loss (138→96 → 120 pounds) on HAL
    - GERD
    - Hx reactive airways disease
    - Depression

Case 3

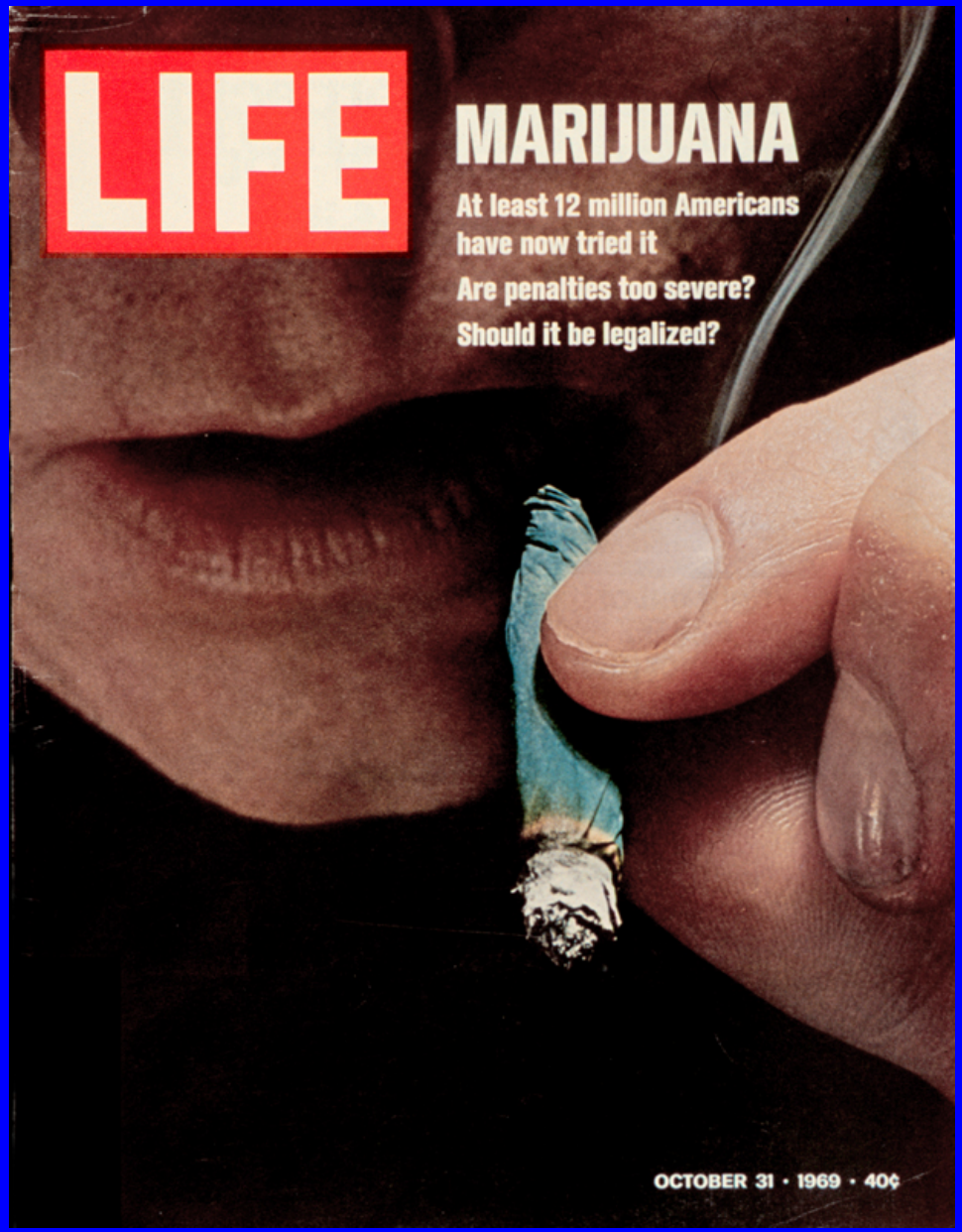
- Current Rx: Octreotide tid, metformin, bupropion, modafinil, pancrelipase, loperamide, DTO, zoledronic acid, iron-free MVI
- EtOH, tobacco: 0 Marijuana: brownies
- O/E Walks with cane, tearful episode
- BMI-20.6, P-124, harsh 2/6 syst m, abd with multiple well-healed surgical scars

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 combustion
- 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


LIFE
MARIJUANA
At least 12 million Americans
have now tried it
Are penalties too severe?
Should it be legalized?
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