

Community Consortium Research in CAM Therapies in HIV: Recent Results

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NCCAM Five CAM Domains

- Alternative medical systems
- Mind-body interventions
- Biologic-based therapies (herbs)
- Manipulative and body-based systems (massage)
- Energy therapies

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Distant Healing in AIDS

- Randomized double-blind trial
- 40 patients with advanced AIDS, pair-matched for age, CD4+, and number of AIDS-defining illnesses
- Patients seen at baseline for CD4+ count, QOL, and psychological distress measurements
- Measurements repeated at wk 10, 22-24 with chart abstraction at end of 6 mo

Distant Healing in AIDS

- DH intervention performed by 40 experienced self-identified healers of many different backgrounds on 20 patients
- Healers received photo, first name, CD4 count and current symptoms of patient
- Instructed to “direct an intention for health and wellbeing” 1 hour daily x 6 days
- In the end, 5 patients/healer, 10 healers/patient

Distant Healing in AIDS

- 37 men, 3 women enrolled, mean age 43
- CD4+ ~87, 92% on PI, all PCP prophylaxis
- 85% with *a priori* belief in benefit of DH
- Average 3.5 CAMs utilized
- DH and controls well-matched in most key variables, except all 5 baseline smokers and 4 minority patients were in control group

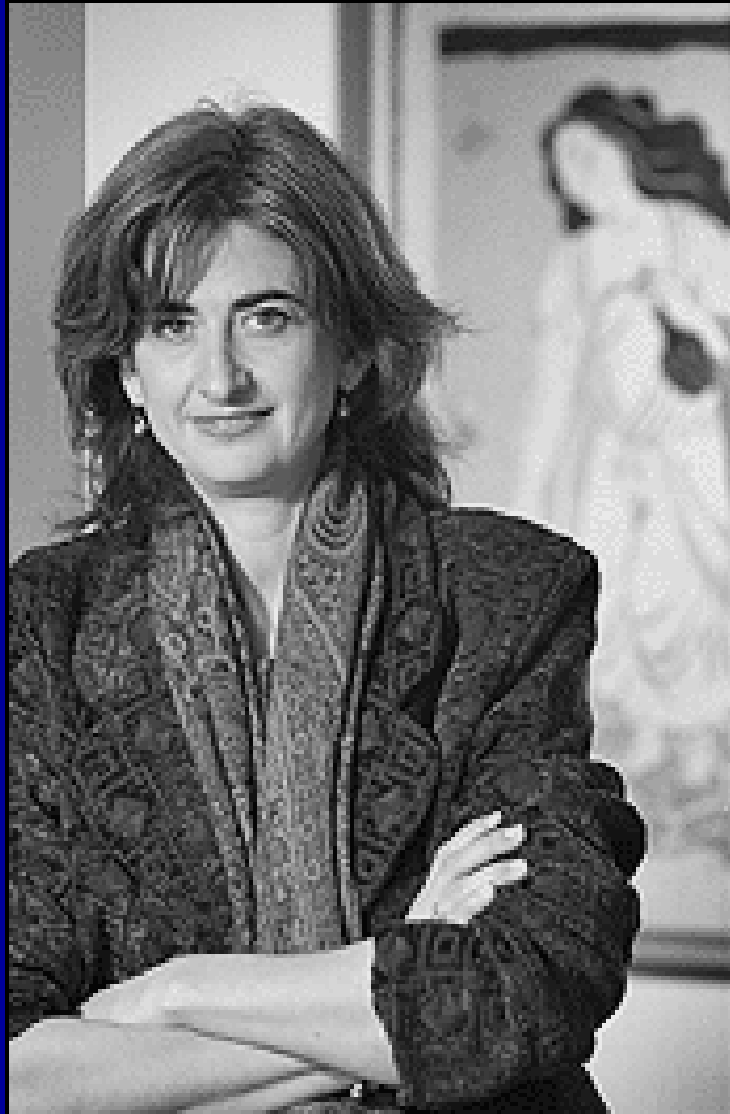
Distant Healing in AIDS: Results

	DH	Control	<i>P</i> value
New ADD	0.1	0.6	.04
Illness severity	0.8	2.65	.03
MD visits	9.2	13.0	.01
Hospitalizations	0.15	0.6	.04
Days in hospital	0.5	3.4	.04
Improved mood	-26	14	.02

3-Arm Distant Healing Trial

- Consortium assisted in accrual of participants for a larger confirmatory study
- 157 participants randomized to one of three arms
 - Distant healing by healers
 - Distant healing by trained nurses
 - No distant healing
- Data analysis currently ongoing

www.etarg.org



Elisabeth Targ, M.D.

Mindfulness Based Stress Reduction

- UCSF Osher Center recently awarded NCCAM Program Project Grant
- Objective to evaluate MBSR in maintaining CD4+ cell count $> 350/\text{mm}^3$ in naïve pts
- Immediate vs deferred MBSR format
- Substudies to evaluate cortisol levels and other physiologic markers of stress as well as HIV virus analyses

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Marijuana



The effects of smoked marijuana on chronic neuropathic and experimentally-induced pain in patients with HIV peripheral neuropathy – A feasibility study

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The University of California, San Francisco

Marijuana in HIV Neuropathy

- No *effective* therapy for HIV neuropathy pain
- Cannabinoids effective in preclinical models of neuropathic pain
 - CB1 agonists: analgesic activity in CNS
 - CB1 and CB2 agonists: peripheral analgesic actions
 - CB2: anti-inflammatory effect

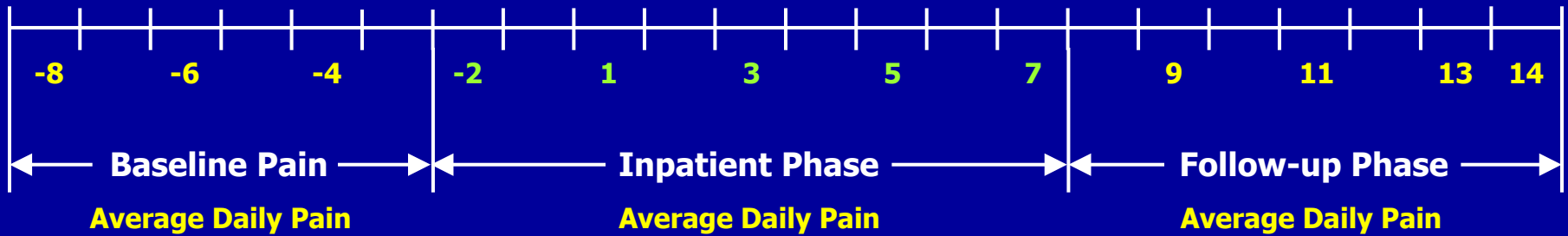
Objectives

- To assess the analgesic effects of smoked marijuana in patients with HIV neuropathy
- To compare analgesic effects of smoked marijuana on clinical and experimental pain

Heat/Capsaicin Sensitization Model

- Standardized anchor for subjective pain assessments
 - Quantitative measurements of sensory changes
- Non-invasive, non-injurious
- Reproducible in multi-session studies
- Opioid-responsive

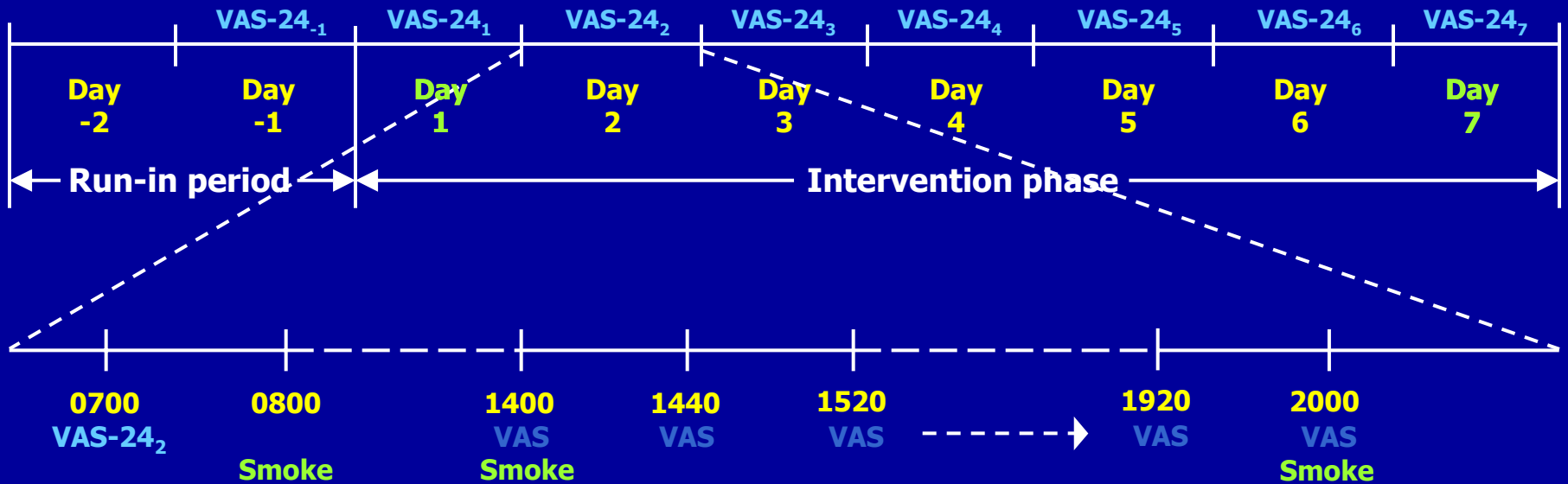
Study Timeline



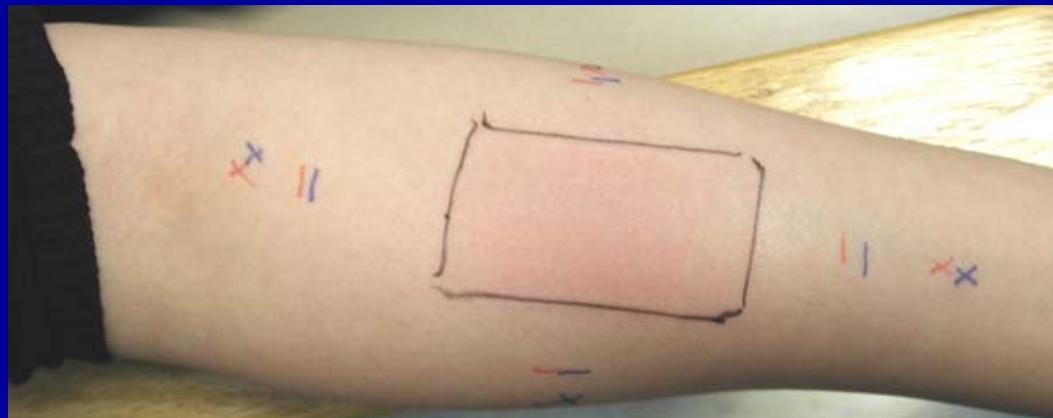
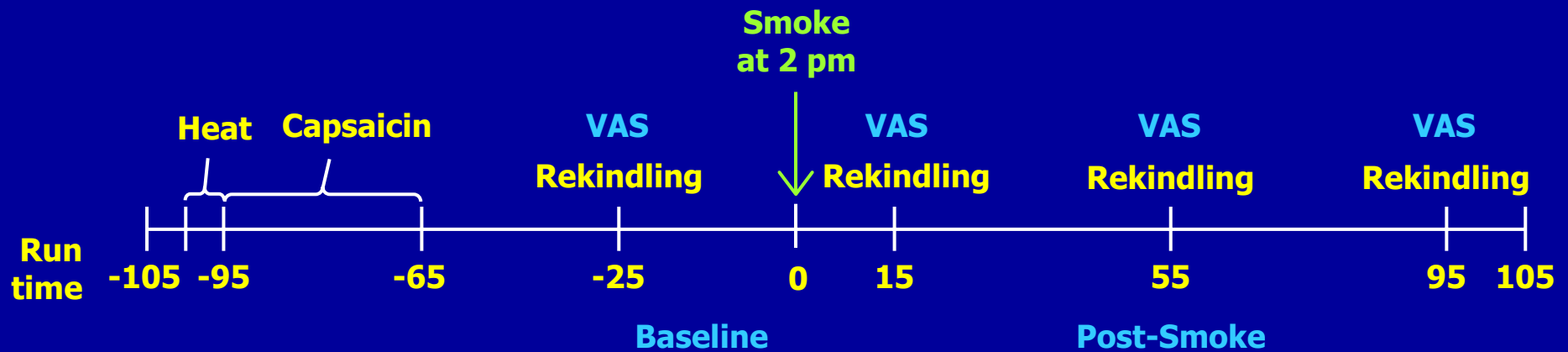
Inpatient Timeline

First cigarette
@ 2 pm

Last cigarette
@ 2 pm



Pain Model Timeline: Days 1 & 7



Primary Outcome Measures

- Average daily pain diary (0-100 VAS)
- Acute post-smoking pain (0-100 VAS)
- Experimental Pain
 - Painfulness of noxious thermal stimulation (0-100 VAS)
 - Areas of experimentally-induced secondary hyperalgesia

Inclusion Criteria

- HIV patients with peripheral neuropathy
 - Related to HIV, nucleosides, or both
- Average daily pain $\geq 30/100$
 - Pre-study diaries (Day -8 until Day -2)
- Experienced marijuana smokers
 - Abstain from smoking for 30 days prior to study

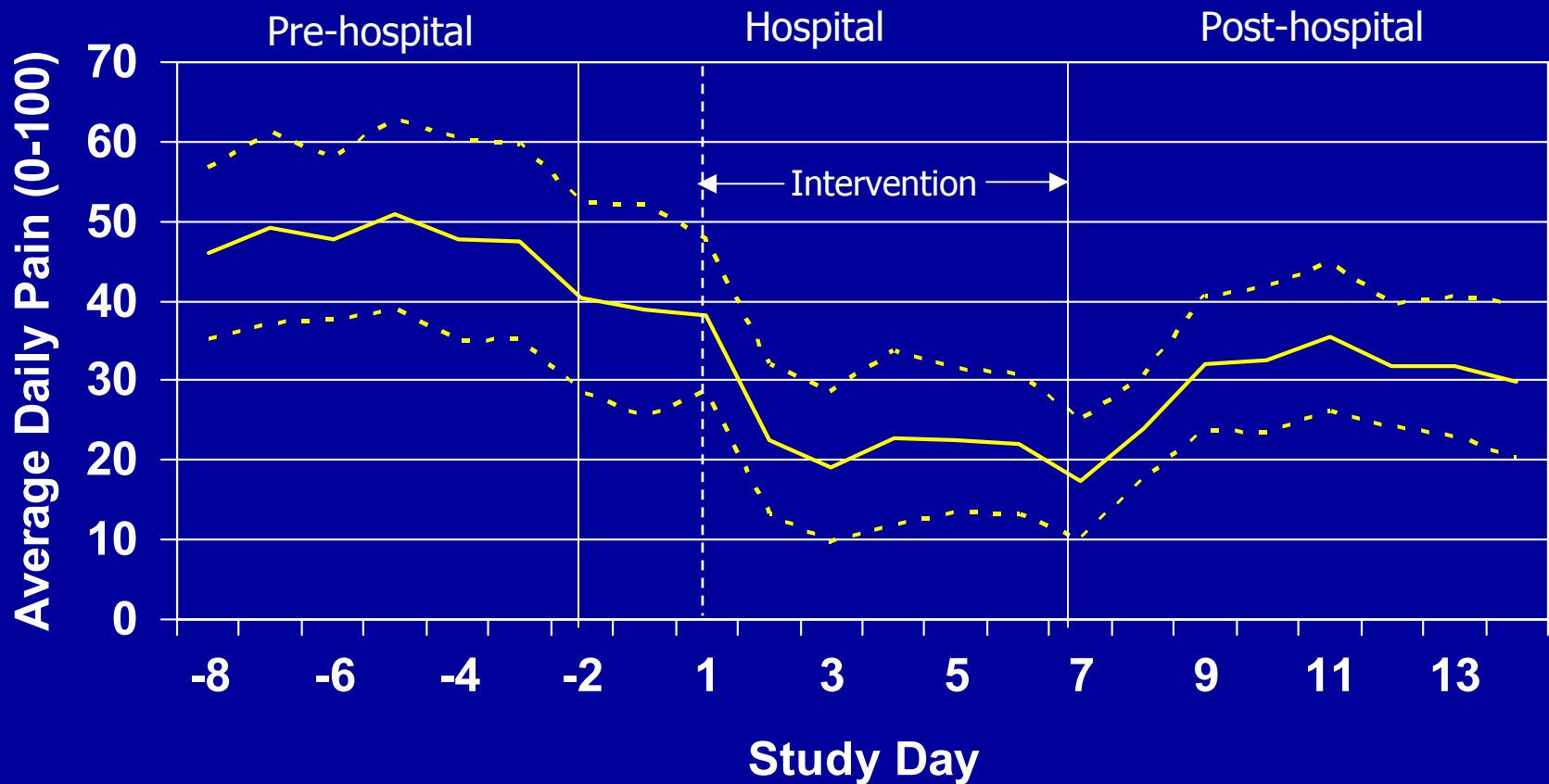
Methods

- 16 participants with HIV-related peripheral neuropathy
- Pre-study pain rating of at least 30 on 0-100 scale
- In-patient study
 - 2 baseline days, 7 intervention days
- Participants smoked 3.56% THC cigarette tid
 - 8am, 2pm, and 8pm
- Screening dates
 - March 14, 2002 – December 5, 2002
- Enrollment dates
 - March 27, 2002 – January 13, 2003

Demographic Characteristics

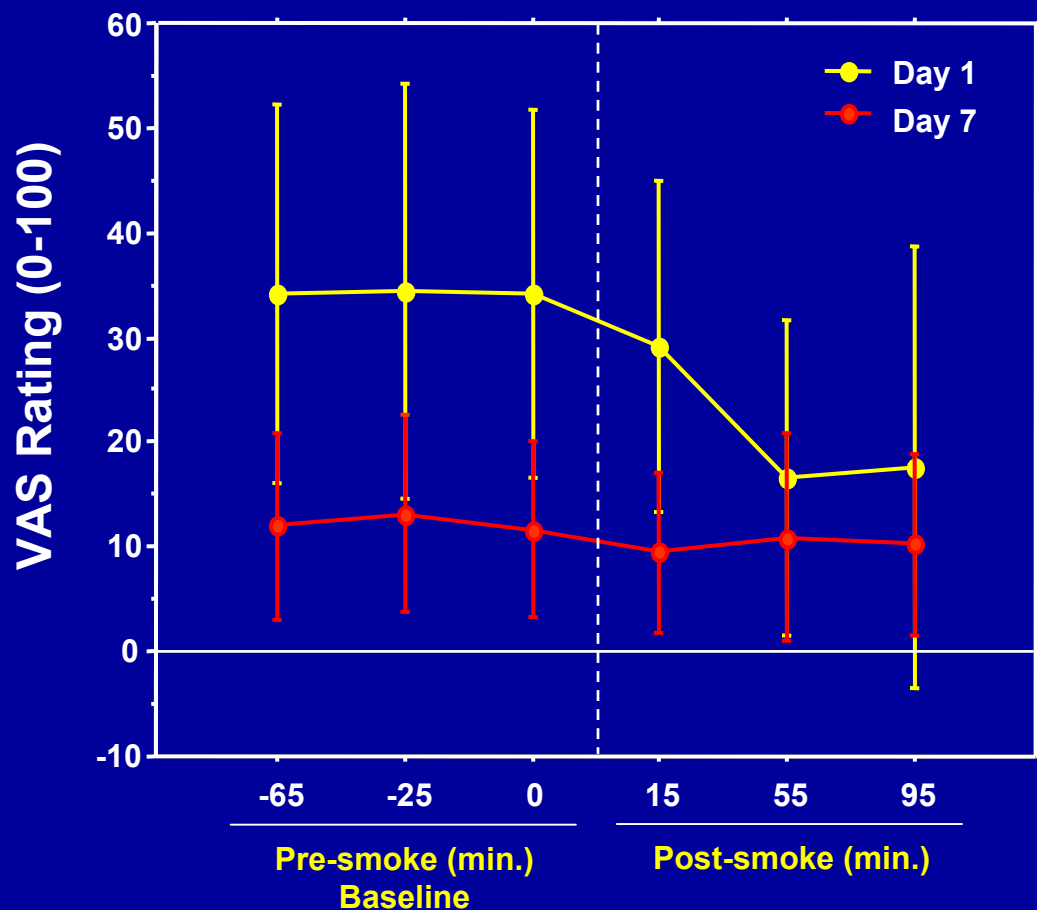
- Gender
 - 14 men, 2 women
- Ethnicity
 - 8 White, 5 Latino, 2 African American, 1 Other
- Age
 - Median=43, Range=36-54
- CD4+ T lymphocyte counts (/mm³)
 - < 200: 2, 200-349: 5, 350-499: 4, > 500: 5
- Viral load (copies/mL)
 - < 50:9, 50-9999: 4, >10,000:3

Chronic Effect of Marijuana on Neuropathy Pain



➔ 10 of 16 patients experienced $\geq 30\%$ reduction in average daily pain

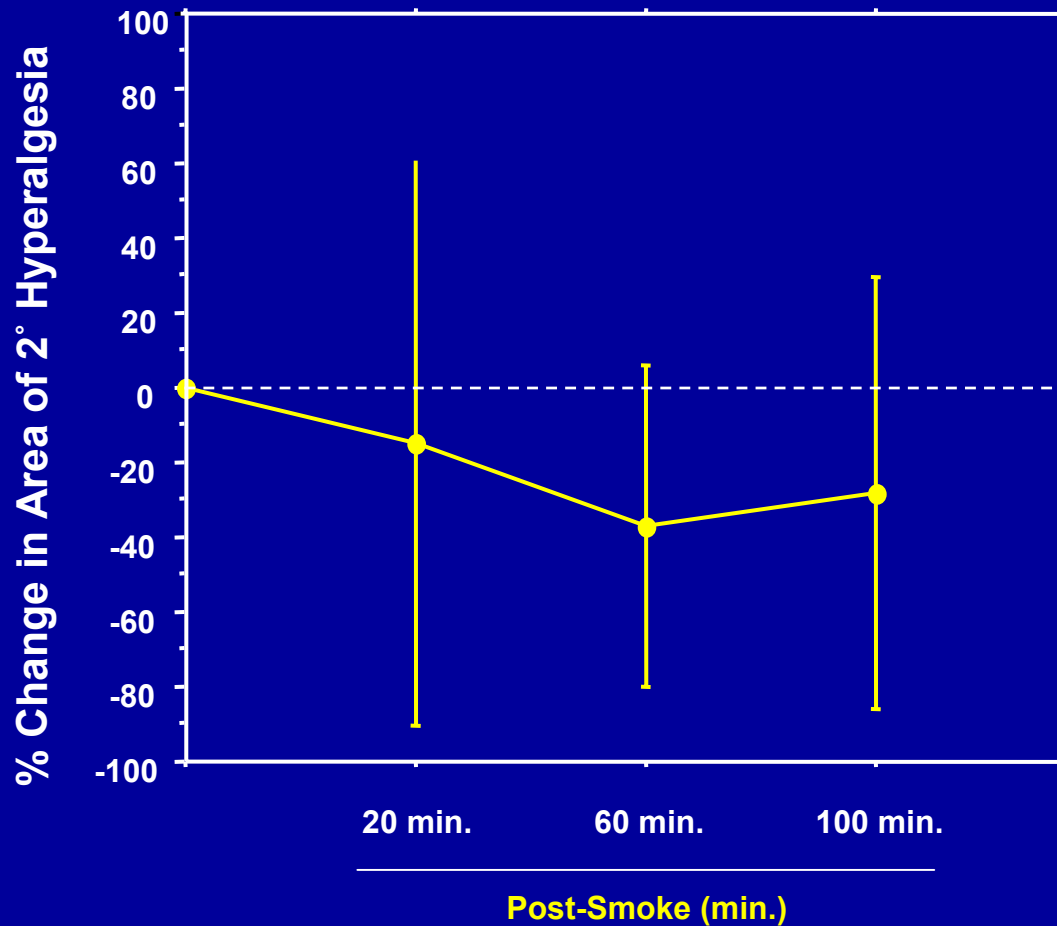
Acute Effect of Marijuana on Neuropathy Pain



➔ 13 of 16 patients experienced $\geq 30\%$ reduction in pain after smoking

Error bars = ± 1 Std Dev

Effect of Marijuana on Area of Secondary Hyperalgesia



➔ 14 of 16 patients experienced $\geq 30\%$ reduction in area of secondary hyperalgesia after smoking

Change in Average Daily Pain vs Change in Area of Secondary Hyperalgesia

Acute PN Pain Area of 2° hyperalgesia	$\geq 30\%$ reduction	$< 30\%$ reduction
$\geq 30\%$ reduction	12	2
$< 30\%$ reduction	1	1

Conclusions

- Results suggest analgesic effect of smoked marijuana on HIV neuropathy pain and experimental pain
 - Experienced users
 - Unblinded study
- Proceed to RCT
 - 10 of 16 participants \geq 30% reduction in average daily pain
 - 39/50 participants enrolled to date in RCT

Medical Marijuana Studies



Hector Vizoso, R.N.
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Statins and Cytochromes

- Very dependent on CYP3A
 - Lovastatin (Mevacor®)
 - Simvastatin (Zocor®)
- Less dependent on CYP3A
 - Atorvastatin (Lipitor®)
 - Cerivastatin (Baycol®)
- Not dependent on CYP3A
 - Fluvastatin (Lescol®)
 - Pravastatin (Pravachol®)

Reports of rhabdo and even death from statin/PI interactions

Pleurotus ostreatus



Antihyperlipidemic Effects of Oyster Mushrooms

- Animal models have demonstrated lipid-lowering effect of *Pleurotus* species
- Small human trial produced 30 mg/dl decrease in non-HDL cholesterol
- Mechanism of action believed to be via a natural lovastatin-like compound similar to red yeast on rice product

Antihyperlipidemic Effects of Oyster Mushrooms: Objectives

- To assess lipid-lowering effect of freeze-dried oyster mushrooms on Kaletra-related hyperlipidemia
- To determine if there is a significant interaction between oysters and the PI's
- To evaluate the short-term safety of oysters
- To determine whether there is an HMG Co-A reductase inhibitor activity of oysters

Antihyperlipidemic Effects of Oyster Mushrooms: Design

- Single arm, open label, 8 week proof of concept study
- 20 subjects on Kaletra with elevated non-HDL cholesterol (>160 mg/dl)
- Subjects will consume 15 gm freeze-dried *Pleurotus ostreatus* daily
- 2 overnight GCRC admissions for first 15 participants for PK studies



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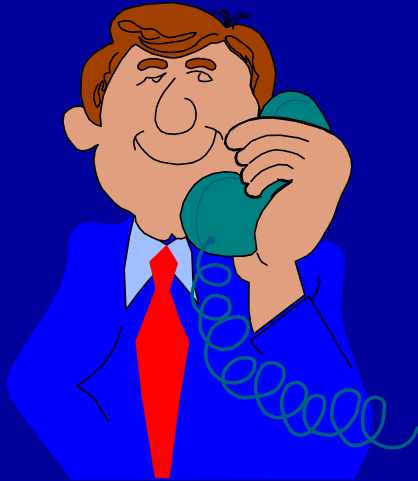
Freeze dried, organically wood-grown
Oyster mushrooms (*Pleurotus ostreatus*)

(Pelletized with 2% xanthum gum, and heat-treated to 160° F.)

Directions for use: Place contents of bag into cup, add boiling water. Stir vigorously. Recommend adding to Miso or soups!

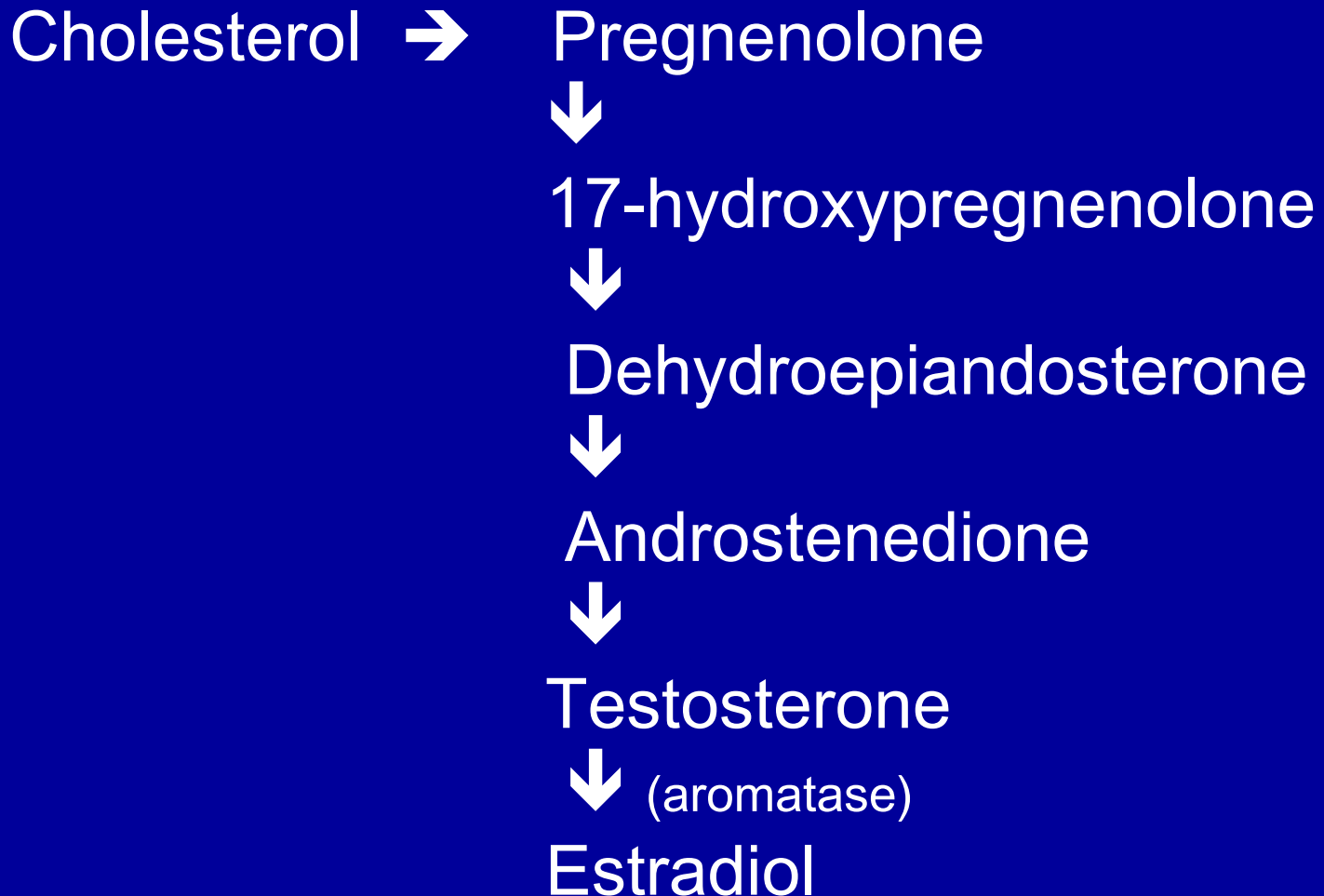
15 grams net weight **SAMPLE** 15 grams net weight

Oyster Mushroom Study



Paul Couey
476-9554, ext 315

Production of Androgens from Cholesterol



DHEA

- Dehydroepiandrosterone is a weak androgen produced by the adrenal gland
- Produced in men and women, levels decline with advancing age, chronic illness
- DHEA(S) \Rightarrow androstenedione \Rightarrow Testosterone (T) and Dihydroxytestosterone (DHT) in adrenals, gonads, liver and periphery
- DHEA(S) also serves as estrogen precursor thru aromatization of T and androstenedione

Normal Function of DHEA

- Exact function is unknown
- May have potential immunomodulatory role
 - Reverses immunosenescence in mice
 - Protects against anti-immune glucocorticoids
 - Rejuvenates immune system in elderly humans
 - Upregulates IL-2 production in mice and SLE
 - T-cells may have specific DHEA receptor

DHEA Levels in HIV Infection

- DHEA(S) levels lower in advanced HIV
- Cortisol levels remain normal or elevated
- Could reflect adrenocortical adaptation to illness
- Low levels predict progression of disease
- Cortisol: DHEA ratio correlates inversely with CD4 cell counts

DHEA and HIV Replication

- DHEA has modest effects vs HIV and EBV replication in laboratory studies
- May inhibit HIV after RT and integration
- DHEA may decrease activation of NF- κ B involved in mediation of T-cell activation
- DHEA and DHEA(S) may effect T-cell activation and HIV replication; especially in reservoir of latently infected cells

DHEA Trial Design

- Randomized, double-blind, placebo-controlled 24 week study
- 40 patients with HIV RNA <50 on HAART
- 1:1 randomization to DHEA 200 mg (men) or 100 mg (women) daily for 12 weeks
- All then receive 12 wk open-label DHEA

DHEA Trial Inclusion Criteria

- HIV+
- HIV RNA <50
- Stable ARV regimen for at least 8 wk
- Age >18 years
- No OI
- No DHEA, androgens, anabolics past 8 weeks
- NI mammograms or PSA

DHEA Study Measurements

- HIV RNA
- Proviral DNA assay
- Ultrasensitive viral culture
- Lymphocyte subset analyses for activation Ag, naive and memory T cells
- Functional analysis circulating CD4 cells

DHEA Study Measurements

- DHEA, DHEA(S), androstenedione, T, cortisol, LH, IGF-1 levels
- Anthropometric measures
- Body composition including bone density by DEXA
- Quality of life

DHEA Results Summary

- DHEA and placebo made by UCSF pharmacy
- 40 participants randomized
 - 95% male, 58% white, median age 44
 - All on HAART; 73% on PI regimen
 - Median baseline CD4+ - 463/mm³ (150-1124)
- Results being analyzed currently
 - Evidence of DHEA absorption
 - No clear beneficial effects noted

CAM and the Consortium

- Echinacea as an immune modulator
- TCM intervention for HIV/HCV coinfection
- Silymarin (milk thistle) effect on cirrhosis
- Mushroom extracts as immune enhancers
- MBSR on maintaining CD4+ counts
- Cannabinoid: Opioid interactions in cancer pain
- Marijuana/marinol in chemo-induced nausea (Jill Israel, R.N. 502-5240)
- Volcano vaporizer as smokeless marijuana

Criteria for Studying CAM Agents

- In wide use by the community
- Biologically plausible
- Anecdotal suggestions of effectiveness
- CAM agent safer or less costly than orthodox Rx
- Dismiss ineffective or unsafe agents
- Potential for drug-CAM interactions

Drug-CAM PK Interactions

- St. John's wort
 - Induces CYP 450
 - IDV AUC ↓ 57%; NVP ↓ 20%
- Garlic preparations
 - ↓ SQV levels ~ 50%
- Smoked marijuana
 - ↓ IND 15%; no effect on NLF

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.