

The Effect of Smoked Marijuana on Chronic Neuropathic and Experimentally-Induced Pain in HIV Neuropathy: Results of an Open-Label Pilot Study

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ABSTRACT

Background: Painful peripheral neuropathy continues to be a significant clinical problem in patients (pts) with HIV infection. Preclinical studies suggest that cannabinoids may be effective in neuropathic pain syndromes.

Methods: Open-label pilot inpatient study conducted over nine days in the General Clinical Research Center. Eligible subjects with confirmed HIV neuropathy and persistent pain greater than or equal to 30/100 as assessed by a 7-day pain diary were enrolled. All subjects had prior experience smoking marijuana but had ceased for 30 days prior to admission. After a 2-day lead-in period, pts smoked one 3.56% THC-containing marijuana cigarette three times daily for 7 days. A heat-capsaicin model induced experimental pain that was also evaluated. Pts experiencing a $\geq 30\%$ reduction in their neuropathy pain were assessed as responders. The pilot study was designed to assess the effect size and calculate the sample size for a follow-on randomized, placebo-controlled trial if warranted.

Results: 16 pts (14 men), median age 43 with an average of 6 yrs duration of neuropathy were enrolled. Neuropathy was related to HIV alone (3), nucleoside therapy (8) or both (5). The mean baseline average daily pain value of 47/100 dropped to 40/100 following the 2-day lead-in. Marijuana smoking caused a drop in pain score to 20/100 with 10/16 pts experiencing a $\geq 30\%$ reduction in average daily pain. Excellent correlation was seen in the response to the heat-capsaicin model where 14/16 pts experienced a $\geq 30\%$ reduction in the area of secondary hyperalgesia after smoking.

Conclusions: Results from this open-label pilot suggest an analgesic effect of smoked marijuana in HIV neuropathy as well as the experimental pain model. A 50 subject 7-day randomized placebo-controlled trial has been initiated in an attempt to confirm these preliminary findings.

BACKGROUND

While the incidence and natural history of many cerebral complications of HIV/AIDS have been favorably affected by HAART, decreased incidence of neuropathy resulting from HIV appears to have been offset by rising rates of neuropathy due to the "d-drug" nucleoside antiretrovirals (ddI, ddC and d4T). Hence painful neuropathy remains an important clinical problem in the era of HAART.

Treatment options are limited, with negative trials for capsaicin, peptide T, mexilitene, amitriptyline, and acupuncture². The antiepileptic drug (AED) gabapentin is effective in many, but not all, patients. Lamotrigine appears to be beneficial in neuropathy due to nucleosides, but not HIV. Carbamazepine and other enzyme-inducing AEDs have drug-drug interactions that can undermine efficacy of HAART³. Chronic narcotics are not always effective for neuropathic pain and have significant side effects.

There is need for new treatments, compatible with HAART, for painful neuropathy. Preclinical models indicate cannabinoids are beneficial in neuropathic pain⁴. Anecdotal reports suggest chronic pain improves with marijuana, which does not have upward interactions with antiretrovirals⁵. This open-label pilot study assessed the effect of smoked marijuana on neuropathic and experimentally-induced pain in individuals with painful neuropathy due to HIV or nucleoside antiretrovirals.

METHODS

9 day inpatient study (2 days lead-in + 7 days treatment, 3.56% THC cigarettes tid) with baseline and post-treatment visual analog scale (VAS) diaries for 7 days:



Inclusion criteria:

- Adults with painful neuropathy due to HIV, nucleosides, or both
- stable ARV (8 wks) & pain (2 wks) regimen
- average pain $\geq 30/100$ on VAS
- Experienced marijuana smokers, abstinent for ≥ 30 days

Outcome measures:

- Neuropathy pain, as assessed by VAS
- average daily pain
- post-smoking pain
- Experimental pain: area of induced secondary hyperalgesia (heat-capsaicin pain model)
- $>$ number of subjects with $\geq 30\%$ pain reduction

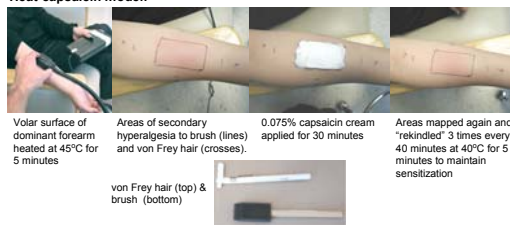
Exclusion criteria:

- Significant systemic illness, including confounding neurologic disease
- Active substance abuse
- Other causes of neuropathy, including ethanol, other neurotoxic exposures, diabetes mellitus

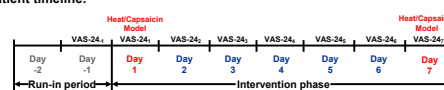
Experimentally-induced pain: heat-capsaicin model

- Standardized, non-injurious method to quantify areas of secondary hyperalgesia
- Complements VAS, a subjective measure
- Successfully used to test other analgesics, including opiates⁶

Heat-capsaicin model:



Inpatient timeline:

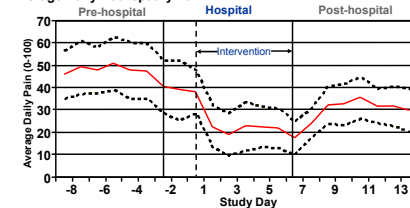


RESULTS

Demographics: 16 subjects

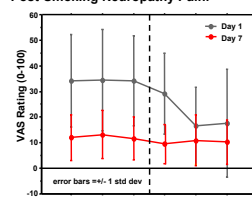
- 14 men, 2 women
- Median age: 43 (36-54)
- Current marijuana users: 8
- Median CD4: 412/mm³ (49-1120)
- Mean duration (years): HIV disease 13 (3-20), Neuropathy 6 (1-13)
- Neuropathy due to: HIV 3, Nucleosides 8, Both 5
- Undetectable viral load: 9

Average Daily Neuropathy Pain:



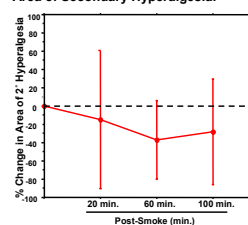
→ 10 of 16 subjects experienced $\geq 30\%$ reduction in average daily pain.

Post-Smoking Neuropathy Pain:



→ 13 of 16 subjects experienced $\geq 30\%$ reduction in pain after smoking their first cigarette on day 1.

Area of Secondary Hyperalgesia:



→ 14 of 16 subjects experienced $\geq 30\%$ reduction in area of secondary hyperalgesia after smoking on day 1.

RESULTS (continued)

Post-Smoking Neuropathy Pain vs. Area of Secondary Hyperalgesia

Neuropathy Pain \ Area of 2' Hyperalgesia	$\geq 30\%$ reduction	$< 30\%$ reduction
$\geq 30\%$ reduction	12	2
$< 30\%$ reduction	1	1

CONCLUSIONS

- In this pilot study, smoked marijuana was associated with $\geq 30\%$ reduction of average daily neuropathic pain in 10 of 16 experienced marijuana users with neuropathy due to HIV, nucleosides, or both.
- Pain relief correlated well with reduction in area of secondary hyperalgesia in the heat-capsaicin experimental pain model.
- A limitation of the study was its open-label design; a randomized, double-blind, placebo-controlled study to confirm these preliminary findings is in progress.

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