

Marijuana Relieves HIV-Related Neuropathic Pain

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SAN DIEGO, Aug. 6 -- Medical marijuana may ease intractable neuropathic pain associated with HIV infection as well as other standard treatments, researchers said.

Cannabis reduced neuropathic pain intensity from "strong" to "mild to moderate" on average, reported Ron Ellis, M.D., Ph.D., of the University of California San Diego, and colleagues online in *Neuropsychopharmacology*.

The number needed to treat to achieve a clinically meaningful 30% reduction in pain was comparable to other treatments for painful distal, sensory predominant polyneuropathy (3.5 versus 5.4 for lamotrigine [Lamictal] and 3.8 for gabapentin [Gabarone, Neurontin]). .

Neuropathic pain affects 30% or more of people infected with HIV and antiretroviral therapy doesn't substantially improve it, the researchers said. Nucleoside-analogue HIV reverse transcriptase inhibitors like didanosine (Videx) and stavudine (Zerit) can actually make it worse, possibly through mitochondrial toxicity.

These new findings support a role for cannabinoids in HIV-neuropathy, particularly because none of the current treatment options are highly effective, said Igor Grant, M.D., director of the University of California's Center for Medicinal Cannabis Research, where the study was done.

"Whether they should be first-line drugs or adjuncts is something that needs to be determined," he said. "I think what the study really suggests is a need to explore cannabinoid agonists that might be able to be delivered in another fashion."

California and a few other states allow prescription of marijuana for specific medical indications, but federal law prohibits its use, whether for medical purposes or not.

"There has been basically a collision of state and federal law leading to medical marijuana not really being available because of fear of federal prosecution," Dr. Grant said.

The researchers' phase II, double-blind study included 28 HIV-infected patients with distal, sensory predominant polyneuropathy refractory to a least two prior analgesics.

Participants were randomized to placebo or cannabis four times a day with 90- to 120-minute intervals between onsite smoking sessions under the

supervision of a study nurse.

Cannabis cigarettes ranged in strength from 1% to 8% delta-9-tetrahydrocannabinol (THC). Placebo cigarettes were from whole plant material with cannabinoids removed.

Over the course of seven weeks, the researchers tested participants' pain and neuropsychological functioning in a one-week wash-in period, during five days of smoking cannabis or placebo cigarettes, the same duration of treatment cross-over, and two-week washout after each smoking phase.

Participants were men, typically on combination antiretroviral therapy (93%) for advanced HIV disease with most exposed to potentially neurotoxic dideoxynucleoside reverse transcriptase inhibitors (72%).

Mean neuropathy scores showed mild-to-moderately severe neuropathy for which most continued on opioid pain medication and anticonvulsants throughout the trial (both 64%).

Pain reduction with cannabis averaged 3.3 points greater on the Descriptor Differential Scale than with placebo for what Dr. Grant called a medium effect size of 0.60 ($P=0.016$).

Medical marijuana also provided 46% of patients with clinically meaningful pain reduction of at least 30% compared with baseline, whereas only 18% of patients on placebo had the same degree of pain relief ($P=0.043$).

The number needed to treat to have one patient with at least a 30% reduction in neuropathic pain was 3.5 (95% CI 1.9 to 20.8).

Pain also improved significantly during treatment with cannabis as reported by patients on the Visual Analog Scale (median change -17 versus -4, $P<0.001$).

However, cannabis did not significantly impact mood disturbance, physical disability, or quality of life compared with placebo cigarettes.

Cannabis appeared to be well-tolerated overall with most side effects being mild and self-limited. Two patients, though, had treatment-limiting toxicities and were withdrawn for safety reasons.

One patient who had never used cannabis before had an acute episode of psychosis brought on with the drug. A second developed an intractable, smoking-related cough during cannabis treatment, which resolved after cessation.

There was no interaction of cannabis with opioid painkillers.

The researchers noted that the short-term study could not assess durability of analgesia, "which is of paramount concern in chronic pain syndromes."

The study was limited by a high drop-out rate of 18%.

Another concern is that smoking can lead to obstructive lung disease long term and may not be tolerated short term, they said.

Other routes of administration for cannabinoids, such as vaporization and mucosal sprays, are under evaluation in the United States, the investigators said.

Source reference:

Ellis RJ, et al "Smoked Medicinal Cannabis for Neuropathic Pain in HIV: A randomized, cross-over clinical trial" *Neuropsychopharmacology* 2008.

"This study helps to build a case that cannabis does have therapeutic value at a medium-dose level," said Grant. "It also suggests that higher doses aren't necessarily better in certain situations -- something also observed with other medications, such as antidepressants."

The researchers stated that more and larger studies need to be conducted to measure the efficacy of cannabis, noting that medical marijuana could play an important role in treating patients who don't respond well to the usual pain relievers or can't tolerate drugs such as ibuprofen or opioids used for severe pain.

"The results of this study might help guide others doing clinical research into pain management," said Wallace.

The paper, to be published in the November issue of the journal *Anesthesiology*, is the second published study out of the CMCR.