Analgesic Effect of Delta-9-Tetrahydrocannabinol (THC) on Patients With Chronic Neuropathic Pain During a Four-Week Period: Pilot Study

Frederick J Goldstein[1] PhD, Katherine Galluzzi[2] DO, Madeleine Brown[1,4] MS, Jenayle Smith[2] LPN, Joseph Lubeck[3] DO

Philadelphia College of Osteopathic Medicine, Philadelphia, PA, USA

1: Department of Biomedical Sciences, 2: Department of Geriatrics and Palliative Care, 3: Department of Neurology, 4: OMS 2

INTRODUCTION

Background: Neuropathic Pain

- Neuropathic pain (NP) results from damage to both central and peripheral nervous system. Unlike nociceptive pain, which results from traumatic or noxious insults, *e.g.*, burn or fracture, NP results from derangement in pain processing system caused by disease, toxins, drugs or other non-acute injury, *e.g.,*
  - ♦ postherpetic neuralgia
  - ♦ diabetic peripheral neuropathy
  - ♦ chemotherapy-induced
  - ♦ post-mastectomy pain
  - ♦ chronic regional pain syndromes
- Current Treatment of NP:
  - ♦ Calcium channel alpha-2-delta ligands (*e.g.,* gabapentin, pregabalin)
  - ♦ Opioid analgesics (*e.g.,* oxycodone)
  - ♦ Tricyclic antidepressants (*e.g.,* amitriptyline)
  - ♦ Antiepileptic agents (*e.g.,* carbamazepine)
  - ♦ Selective serotonin-norepinephrine re-uptake inhibitor (*e.g.,* duloxetine)
- Disadvantages of current NP treatment include:
  - ♦ Limited effectiveness
  - ♦ Intolerable adverse reactions
  - ♦ Discontinuation
  - ♦ Decreased patient compliance
  - ♦ Opioids have added risks (*e.g.* addiction, hyperalgesia, endocrinopathy)

Background: THC

Cannabis (marijuana) is used for pain relief for millennia. ∆-9-THC is one of two main cannabinoids in marijuana. Humans have an endogenous cannabinoid system. Limited evidence supports analgesic effects of cannabinoids across various NP conditions. Dronabinol-C-III is the synthetic version of THC. It is FDA-approved as appetite stimulant and antiemetic but currently not for treatment chronic NP

Additional research studies of dronabinol in a broad range of clinical conditions that cause NP may prove beneficial.

HYPOTHESIS

Dronabinol will improve analgesia in patients with chronic NP and decrease use of pain medications. As a result, patients should experience decreased pain and use less co-analgesics.

METHODS

Inclusion Criteria

- 25 to 75 years of age
- Diagnosis of NP occurring for 2 or more months
- Able to understand and sign Informed Consent

Exclusion Criteria

- Cardiovascular conditions, epilepsy/seizure disorder, hepatic impairment (↓ LFT), depression or other psychological problems as determined by PHQ-9 score ≥ 10
- Substance Use Disorder as determined by SOAPP-R ≥ 18
- Use of Antidepressants (≤ 8 wks), antipsychotics, Alzheimer Disease medications or CNS stimulants
- Non-English speaking
- Pregnant or planning to become pregnant during the 6-week study period

METHODS (continued)

Procedure

- Study duration = six weeks
  - ♦ Patients were seen weekly with vital signs taken at each visit. Total of seven visits (Figure 1)
- Each day, study patient:
  - ♦ completed a 0 –10 pain diary three times daily.
    0 = no pain → **10** = worst pain I've ever had
  - ♦ recorded doses of their pain medications

THC Dosage Schedule

		THC - Oral
PART 1 *Baseline*	Start of WEEK 1	NONE
	Start of WEEK 2	NONE
PART 2 *Drug*	Start of WEEK 3	5 mg at Bedtime
	Start of WEEK 4	10 mg at Bedtime
	Start of WEEK 5	15 mg at Bedtime
	Start of WEEK 6	20 mg at Bedtime
	Start of WEEK 7	**End of Study Visit**

Figure 1) *Weeks 1 and 2: establish each patient's baseline pain scores and analgesic usage. Weeks 3 to 6: up-titration process initiated; 5 mg THC orally at bedtime. dose increased 5 mg/ week.*

RESULTS

Alterations in Body Weigh During Weeks 3 to 6

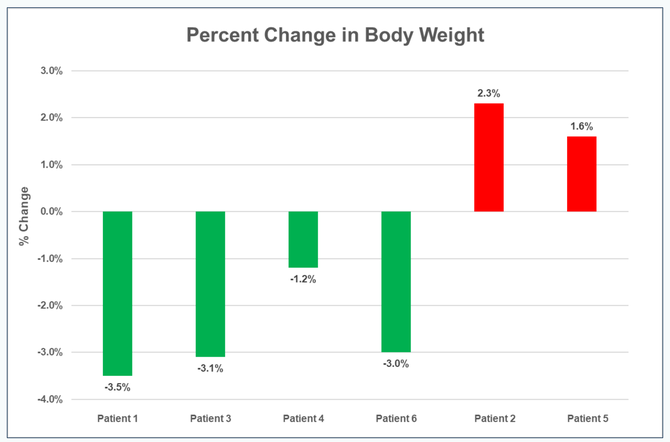

Figure 2) *Four of the six patients experienced a reduction in weight during the THC-dosing phase. The other two patients experienced a weight increase*

RESULTS

Analgesic Medication Usage

	Wk. 1 & 2 Avg. Daily Dose	Wk. 6 Avg. Daily Dose
PATIENT 1		
Morphine	120.0 mg	120.0 mg
Gabapentin	600.0 mg	385.7 mg
PATIENT 3		
Gabapentin	1414.3 mg	0.0 mg
Tramadol ER	200.0 mg	200.0 mg
PATIENT 4		
Gabapentin	2000.0 mg	571.4 mg
Tylenol ES	464.3 mg	1785.7 mg
PATIENT 5		
Gabapentin	1714.3 mg	1800.0 mg
Ibuprofen	1085.7 mg	942.9 mg
PATIENT 6		
Carbamazepine	314.3 mg	0.0 mg
Diclofenac	75.0 mg	100.0 mg

Figure 3) *Patient 2 was not on any pain medication during the study.*

Pain Scores

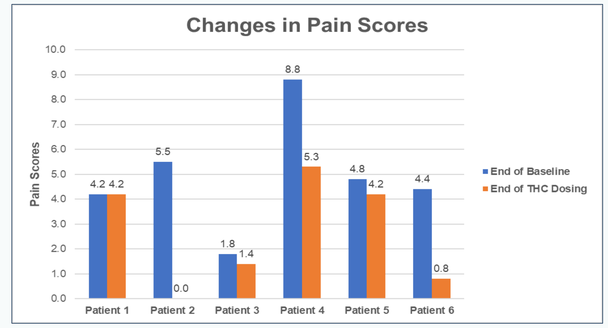

Figure 4) *Average Decrease in Pain Scores:* ***4.9 → 2.7.***
Average % Reduction in Pain Scores: ***44.9%***

CONCLUSION

In this ongoing pilot investigation, 5 mg of THC orally at bedtime in Week 3, and up-titrating 5 mg per week to 20 mg in Week 6, produced an average 44.9% reduction in pain scores, and a decrease in use of co-analgesic medications. Of the six patients, two did gain but four lost weight.

REFERENCES

1. Banner Pharmacaps,Inc. . Marinol.[package insert]. 2006. High Point, NC. Banner Pharmacaps,Inc.
2. Boychuk D, Goddard G, Mauro G, Orellana MF. The Effectiveness of cannabinoids in the management of chronic nonmalignant neuropathic pain: A Systematic review. J Oral Facial Pain Headache. 2015;29: 7-14. doi: 10.11607/ofph.1274.
3. deVries M, Rijckevorsel DC, Wilder-Smith OH, Goor H. Dronabinol and chronic pain: importance of mechanistic considerations. Expert Opin Pharmacother. 2014;15:1525-34.
4. Hillard CJ, Weinlander KM, Stuhr KL. Contributions of endocannabinoid signaling to psychiatric disorders in humans: genetic and biochemical evidence. Neuroscience 2012;204:207-29.
5. Jensen B, Chen J, Furnish T, Wallace M. Medical marijuana and chronic pain: a review of basic science and clinical evidence. Curr Pain Headache Rep. 2015;19:524.
6. Kowal MA, Hazekamp A, Grotenhermen F. Review on clinical studies with cannabis and cannabinoids 2010-2014. Int Assoc Cannabinoid Med. 2016;11:1-18.
7. Lawson K. Potential drug therapies for the treatment of fibromyalgia. Expert Opin Invest Drugs. 2016;25(9):1071-1081
8. Rintala D, Fiess RN, Tan G, Holmes SA, Bruel BM. Effect of dronabinol on central neuropathic pain after spinal cord injury. Am J Phys Med Rehab. 2010;89: 840-848. doi: 10.1097/PHM.0b013e3181f1c4ec.
9. Schimrigk S, Marziniak M, Neubauer C, Kugler EM, Werner G, Abramov-Sommariva D. Dronabinol is a safe long-term treatment option for neuropathic pain patients. Eur Neurol. 2017;78: 320-329. doi: 10.1159/000481089.
10. Solvay Pharmaceuticals. (2004). Marinol. [package insert]. US Food and Drug Administration. https://www.accessdata.fda.gov/drugsatfda_docs/label/2005/018651s021lbl.pdf
11. Tanda G, Pontieri FE, Di Chiara G. Cannabinoid and heroin activation of mesolimbic dopamine transmission by a common μ1 opioid receptor mechanism. Science. 1997;276: 2048 -2050.
12. Zhang J, Echeverry S, Lim TK, Lee SH, Shi XQ, Huang H. Can modulating inflammatory response be a good strategy to treat neuropathic pain?. Current Pharmaceutical Design 2015;21:831-9.