



Medical Marijuana and the Diabetic Foot



Cannabis prescriptions may be on the horizon.

BY WENJAY SUNG, DPM

Diabetic peripheral neuropathy is increasing in prevalence, affecting approximately half of patients with diabetes, with roughly 15% being painful.^{1,2} Control of pain is insufficient in many patients using either of the two medications currently approved by the U.S. Food and Drug Administration.³ Although these medicines can help with the pain, they do not change the nerve damage. Therefore, if there is no improvement with a medicine to treat pain, there is no benefit to continuing to take it, and another medication may be tried.

Medical marijuana (medical cannabis) has been documented as an alternative to opioids for neuropathic, chronic, and neurogenic pain.⁴ Cannabis contains over 483 known compounds in the plant and more than 65 active cannabinoids with the primary cannabinoids being Δ 9-tetrahydrocannabinol (THC) and cannabidiol.⁵ Cannabinoids are a class of diverse chemical compounds that act on the cannabinoid receptors in cells. Some receptors are found in the brain and spinal cord (CB1 receptors), or more specifically, the basal ganglia and limbic system.

Other receptors are found throughout the entire body, particularly within the immune system or immune-derived cells (CB2 receptors).⁶ CB2 receptors appear to be responsible for the anti-inflammatory and possibly other therapeutic

effects of cannabis seen in animal models.⁷ Cannabinoid receptor activation also produces physiological effects including euphoria, psychosis, impaired memory and cognition, reduced locomotor function, and increased appetite as well as anti-emetic, pain-relieving, anti-spasticity and sleep-promoting effects.⁸

New Emerging Evidence

New emerging evidence has correlated a benefit of medical cannabis for patients suffering with diabe-

assist in the “use and prescription of THC in its synthetic or herbal form.” The authors concluded that for thousands of subjects, past and current cannabis use was associated with lower levels of fasting insulin, blood glucose, insulin resistance, BMI, and waist circumference.

In 2010, the efficacy of a cannabis-based medicinal extract (Sativex-tetrahydrocannabinol [27 mg/ml] and cannabidiol [25 mg/ml]) applied as a pump-action spray administered sublingually was assessed

Medical marijuana (medical cannabis) has been documented as an alternative to opioids for neuropathic, chronic, and neurogenic pain.

tes. A milestone study published in the *American Journal of Medicine*⁹ in 2013 concluded that cannabis compounds may help control blood sugar, marijuana users are less likely to be obese, and have lower body mass index (BMI) measurements—despite the fact that they seemed to take in more calories, and pot smokers also had higher levels of “good cholesterol” and smaller waistlines.

In 2014, an editorial¹⁰ called upon the National Institutes of Health and Drug Enforcement Administration collaboration to facilitate the development of scientific investigations to provide physicians with data to

in a randomized controlled trial of 30 subjects with painful diabetic peripheral neuropathy.¹¹ The authors concluded that the efficacy of Sativex was no more efficacious than placebo. Moreover, depression was a major confounder and may have important implications for future trials on painful diabetic peripheral neuropathy.

In 2015, a short-term, placebo-controlled trial¹² of inhaled cannabis demonstrated a dose-dependent reduction in diabetic peripheral neuropathy pain in patients with treatment-refractory pain. This evi-

Continued on page 88



Medical Marijuana (from page 87)

dence supports further research on the efficacy of the cannabinoids in neuropathic pain. Vaporization was used as a method for research since it permitted the inhalation of volatilized gases without exposure to hazardous pyrroles and the high concentrations of carbon monoxide that occurs with combustion.

Also, because the CBD concentration in the cannabis used in the study was so low, the effects observed were most likely due to THC. Using the Michigan Neuropathy Screening Instrument, a validated screening tool, the primary analysis compared differences in spontaneous pain over time between doses using linear mixed effects models. There was a significant difference in spontaneous pain scores between doses ($P < .001$). Specific significant comparisons were placebo versus low, medium, and high doses ($P = .031, .04,$ and $< .001$, respectively) and high versus low and medium doses (both $P < .001$). Despite limitations, these findings suggested that THC in cannabis might have analgesic effects in neuropathic pain syndromes, including in patients with treatment-refractory diabetic peripheral neuropathy.

FDA Approval

Surprising to most people, the FDA has approved two medications with synthetic THC analogues since the 1990s: dronabinol (Marinol, AbbVie) and nabilone (Cesamet, Meda Pharmaceuticals). These THC drugs are classified as schedule III drugs by the Drug Enforcement Agency, while Cannabis (the plant) is classified as schedule I.¹³

On June 25, 2018, the FDA approved Epidiolex¹⁴ (Greenwich Biosciences), a CBD-heavy formula indicated for pediatric epilepsy. With over 30 states including the District of Columbia having a medical exemption or allowing recreational use of cannabis (consumption of the totality of the plant), physicians are increasingly likely to be asked to prescribe some type of marijuana-based medication. Dr. Patrick DeHeer has called for podiatrists to also achieve parity through the treatment of diabetic pe-

ripheral neuropathy using available cannabis-based drugs.¹⁵ “Not only will the patients suffering from lower extremity maladies benefit from podiatric physicians being able to provide an evidence-based treatment with medical marijuana but the profession will continue to close the parity gap as well.”

However, caution is advised to any physician when it comes to cannabis-based prescriptions as studies are still preliminary, although positive, and done with small sample

Systematic review: Efficacy and safety of medical marijuana in selected neurologic disorders report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology*. 2014; 82(17):1556–1563.

⁹ The Impact of Marijuana Use on Glucose, Insulin, and Insulin Resistance among US Adults Penner, Elizabeth A. et al. *The American Journal of Medicine*, Volume 126, Issue 7, 583–589.

¹⁰ Donald I. Abrams, MD, and Clint Werner. Marijuana in the Management of Diabetes: A summary of the promising epidemiological evidence. *Natural Medicine*

New emerging evidence has correlated a benefit of medical cannabis for patients suffering with diabetes.

sizes. These studies and the pursuit of parity should be a call to action by podiatrists to further research into the effects of DPN and lay the needed groundwork for widespread acceptance. **PM**

References

- ¹ Pop-Busui R, Boulton AJ, Feldman EL, et al. Diabetic neuropathy: a position statement by the American Diabetes Association. *Diabetes Care*. 2017;40(1):136–154.
- ² Izenberg A, Perkins BA, Bril V. Diabetic neuropathies. *Seminars in Neurology*. 2015;35(4):424–430.
- ³ Dworkin RH, et al. Recommendations for the pharmacological management of neuropathic pain: an overview and literature update. *Mayo Clin Proc*. 2010;85(3 Suppl):S3–14.
- ⁴ Hill KP. Medical marijuana for treatment of chronic pain and other medical and psychiatric problems: a clinical review. *J Am Med Assoc*. 2015; 313(24):2474–2483.
- ⁵ Pertwee RG. Cannabinoid pharmacology: the first 66 years. *Br J Pharmacol*. 2006; 147(S1):S163–S171.
- ⁶ Joy JE, Watson SJ Jr., Benson JA Jr., eds. *Marijuana and Medicine: Assessing the Science Base*. National Academies Press, 1999.
- ⁷ Pacher P, Mechoulam R (April 2011). “Is lipid signaling through cannabinoid 2 receptors part of a protective system?”. *Progress in Lipid Research*. 50 (2): 193–211. doi:10.1016/j.plipres.2011.01.001. PMC 3062638?. PMID 21295074.
- ⁸ Koppel BS, Brust JC, Fife T, et al.

Journal. May 2014 Vol. 6 Issue 5.

¹¹ Selvarajah D, Gandhi R, Emery CJ, Tesfaye S. Randomized Placebo-Controlled Double-Blind Clinical Trial of Cannabis-Based Medicinal Product (Sativex) in Painful Diabetic Neuropathy: Depression is a major confounding factor. *Diabetes Care*. 2010;33(1):128–130. doi:10.2337/dc09-1029.

¹² Wallace MS, Marcotte TD, Umlauf A, Gouaux B, Atkinson JH. Efficacy of Inhaled Cannabis on Painful Diabetic Neuropathy. *The journal of pain?: official journal of the American Pain Society*. 2015;16(7):616–627. doi:10.1016/j.jpain.2015.03.008.

¹³ https://www.accessdata.fda.gov/drugsatfda_docs/label/2005/018651s0211-bl.pdf

¹⁴ https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/2103651bl.pdf.

¹⁵ Patrick DeHeer, Clarifying the Role of podiatric physicians prescribing medical marijuana, *Podiatry Today*, July 20, 2016.



Dr. Wenjay Sung, DPM, FACFAS practices in Arcadia and Orange, California. He completed his advanced surgical fellowship at the ACFAS recognized Weil Foot-Ankle & Orthopedic Institute (2011, Chicago, IL)

after graduating as chief resident from the University of Pittsburgh Medical Center (2010). Dr. Sung is board certified by the American Board of Foot and Ankle Surgery and is a fellow of the American College of Foot and Ankle Surgeons.