

**COMBINATION OF  
TOPICAL AND ORAL  
CANNABINOIDS FOR  
DIABETIC NEUROPATHY:  
A CASE REPORT**

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**Abstract:** Polyneuropathy caused by *Diabetes Mellitus* is a frequent and prevalent complication in the population. It usually presents changes in sensitivity and, in a part of the cases, it evolved to chronic painful conditions. A growing number of publications have demonstrated the analgesic effect produced by compounds based on Cannabis Sativa derivatives. In addition to the already known central effects, we have an increase in studies related to their peripheral effects, in topical applications, both for skin lesions and for chronic painful conditions, alone or in association with oral presentations. This case report aims to demonstrate the effect of topical application of cannabinoid derivatives, as an adjunct therapy to oral oil treatment and conventional allopathic treatment.

**Keywords:** Cannabidiol, Peripheral neuropathic pain, diabetes.

## INTRODUCTION

Diabetic neuropathy (DN) is the most frequent form of acquired peripheral nerve injury. It is estimated that about 50% of people with diabetes can develop DN.

In Brazil, Diabetes affects about 6.5% of the population, occupying fourth place in the world prevalence position (1)

It is the most common microvascular complication, leading to high rates of hospital admissions, non-traumatic amputation and disability.

It can present as a heterogeneous group of clinical and subclinical manifestations, with different pathophysiological mechanisms, installation and evolution. The most common presentation is presentation as a distal symmetric polyneuropathy.

This neuropathy is characterized by a progressive loss of nerve fibers, affecting both autonomic and somatic fibers of the peripheral nervous system.

DN begins insidiously, often in the toes, later evolving into the classic “boot” and “gloves” presentation.

The most common neuropathic symptoms are loss of sensation, paraesthesia, pain (burning, shock), allodynia and hyperesthesia, sensation of swelling and, eventually, loss of strength.

It can be associated with autonomic symptoms, such as trophic changes in the extremities, changes in color and distal temperature, hair loss, intolerance to heat/cold, dry skin, reduced sweating, edema and plantar perforating disease.

It is estimated that 10-26% of cases are associated with the presence of chronic pain. Studies show that about 12% of patients have never reported the presence of pain to their physicians and 39% have never received specific treatment for their pain (2).

To date, there is no specific treatment for DN remission, only alternatives for the treatment of symptoms and complications that may be caused (3).

For pain, first-line treatments involve the use of medications that are already known and used in other chronic pain conditions, such as anticonvulsants and antidepressants.

## GOAL

The objective of this text is to report the case of a patient with DN, refractory to conventional treatments and its benefit from the association of oral and topical cannabinoid-based compound formulations, with significant improvement in pain, autonomic symptoms and thus improvement of his quality of life.

## CASE REPORT

This is a 71-year-old man with Systemic Arterial Hypertension and Diabetes Mellitus.

His first appointment was in March/2016, referred by the endocrinologist complaining

of dizziness, balance change and pain in the lower limbs, worse at night.

Neurological examination revealed absent Achilles and hypoactive patellar reflexes, associated with hypopallesthesia in the distal part of the feet.

At the time, the clinical diagnosis was made, later confirmed by electroneuromyography, of diabetic neuropathy.

I was already using Pregabalin 75mg, which was scaled up to 75-0-150 mg, with initial improvement, maintaining this treatment, associated with the use of vitamin complexes and specialized physiotherapy until July/2017. At that time, she began to complain of allodynia, evolving to significant difficulty in wearing clothes, covered when lying down, considering her pain 09/10 on the Visual Analog Scale (VAS)

The dose of pregabalin was increased and the use of duloxetine was associated, progressively, up to a dose of 60-60-0 mg, classified as 05/10 by the VAS.

At that time, he presented dyspnea, without elucidation, evolving to the need for hospitalization, cardiac catheterization and placement of drug-eluting stents, with significant decompensation of the diabetes picture in that period.

He spent approximately 01 year without neurological follow-up, returning in 04/2019, with worsening pain. She reported changes in temperature and skin color in the distal region of her legs and feet, and could no longer wear closed shoes due to discomfort.

I had maintained the use and dose of Pregabalin and Duloxetine.

Carbamazepine was started, with no improvement, later amitriptyline and gabapentin, both with severe adverse effects, which was discontinued. It kept EAV on 7/10.

In July/2020, he opted to start treatment with cannabinoid-based oil, due to the refractoriness of pain and significant

impairment of quality of life.

Opted for full spectrum Hempflex 3000 oil (50mg/ml). Treatment started in August/2020, with gradual titration, until reaching 10 drops in the morning and 20 drops at night, with significant improvement in pain after about 15 days of use, with EAV 4/10.

However, he still complained of hyperemia and hypothermia, edema in the lower limbs, in addition to allodynia, and difficulty in wearing closed shoes.

Then, the possibility of associating the use of the topical compound was offered, with Cannabidiol (CBD): 8.3 mg/g and Tetrahydrocannabinol (THC): < 0.3 mg/ml. The patient started using it in September/2020, 3 times a day.

He returned for a medical appointment in October/2020, reporting important relief from allodynia, reduction of edema, improvement in intolerance to temperature variations and skin hyperemia, as well as significant relief of discomfort and pain when using shoes such as tennis.

During this period, he maintained the use of Pregabalin and Duloxetine, in addition to Hempflex 3000.

## DISCUSSION

Due to the high prevalence of Diabetes and DN, this is a case that we can easily come across in our clinical practice and illustrates some of the difficulties we may have, not only in controlling pain symptoms, but also in autonomic symptoms.

The pathogenesis of diabetic neuropathy includes several factors such as metabolic, vascular, autoimmune, neurohormonal, growth factor deficiency and oxidative stress

The main form of prevention is proper glycemic control.

DN has no specific curative treatment, and the use of  $\alpha$ -lipoic acid (Thioctacid R) is currently approved, based on the oxidative

stress control mechanism, however, when the disease is already installed.

For the treatment of chronic pain, medications with evidence level A are tricyclic antidepressants, anticonvulsants such as gabapentin and pregabalin and duloxetine, a dual antidepressant.

As a second line, opioid analgesics can be used, such as tramadol and oxycodone, with potential for abuse and a wide range of adverse effects (3).

The patient described was already using the most commonly used medications for pain treatment, but was refractory to the proposed treatment.

The use of oils derived from cannabinoids is already well known as a treatment for chronic pain, in a growing number of publications. This patient had a good response to the painful condition, but persisted with local sensory and autonomic symptoms in the lower limbs, being then opted for the combined use of the topical presentation, with an excellent response.

The stimulation of cannabinoid receptors has been suggested as a possible target in inflammation and therapies for the treatment of neuropathic pain(4,5)

It is known that in the skin, CB1 and CB2 receptors are expressed in the endings of the sensory nerve, keratinocytes and mast cells. These receptors play an important role in the modulation of peripheral nociception, mainly related to the generation of inflammation, thermal changes and neuropathic pain, which could justify the improvement in autonomic symptoms, so consistently observed in this patient.

A study carried out in patients with peripheral neuropathy (6,7), with topical application of CBD, shows the favorable response of pain control, without mentioning, however, the control of autonomic symptoms, as observed in the patient in question.

Thus, we conclude that in the presence of local symptoms, unresponsive to systemic treatment with oil, the topical presentation must be remembered as a viable alternative, without adverse effects and with great potential for benefit to improve the quality of life of patients with neuropathies.

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