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Oral tetra-hydro-cannabinol, cannabidiol and their combination for peripheral neuropathic pain

***Aim*:** The efficacy of tetra-hydro-cannabinol (THC) monotherapy, cannabidiol (CBD) monotherapy, and combination THC/CBD were evaluated for the treatment of peripheral neuropathic pain (PPN).
***Methods*:** In this multicenter, randomized, double-blinded, placebo-controlled trial, N=115 participants PPN inadequately responsive to previous evidence-based pharmacologic therapy were enrolled, randomized in a 1:1:1:1 ratio (THC n=28, CBD n=27, THC/CBD n=30, placebo n=30), and included in the intent-to-treat analysis. The presence of peripheral neuropathy at baseline was confirmed with clinical exam plus either nerve conduction or nerve fiber density evaluations. Within the cannabinoid arms, "flexible" dosing of THC (2.5-25 mg), CBD (5-50 mg) and THC/CBD (2.5-25 + 5-50 mg) twice daily was permitted throughout the 8-week treatment period. The primary outcome was a change in average weekly pain intensity on a numeric rating scale over the 8-week treatment period. Secondary outcomes included changes in pain intensity of different pain domains; impact on daily activities, mood, and sleep; and global impression of change in addition to use of paracetamol as a pain "escape" medication. Exploratory outcomes included effects on mental function (psychomotor speed, attention, and cognitive sequencing), anxiety, depression, euphoria, and quality of life at 8 weeks.
***Results*:** In N=115 participants with PPN (of which 26 had confirmed diabetic polyneuropathy and ~50% were on concomitant stable evidence-based pain treatment), pain intensity decreased in all treatment/placebo arms at 8 weeks without differences in any treatment arms in either the intent-to-treat or per-protocol analyses; CBD demonstrated less pain reduction than placebo in the per-protocol analysis. None of the cannabinoid treatment arms were superior to placebo in any of the specific pain domains or pain impact on daily activities, mood, or sleep, or mental functioning, depression, anxiety, or quality of life scores. Euphoria was seen more commonly in the THC and THC/CBD arms.
***Conclusions*:** Cannabinoids (THC, CBD, combination THC/CBD) are not superior to placebo in reducing neuropathic pain in peripheral neuropathy in patients failing at least one evidence-based treatment.

Comments. There is increasing use of cannabis and cannabinoids, particularly in the United States (CBHSQ National Survey on Drug Use and Health 2019) and European countries (Manthey J et al *Lancet Reg Health Eur 2021;10:100227*), for both recreational and medicinal use. Prior studies of combination THC/CBD products for neuropathic pain have shown mixed results (Nurmikko TJ et al *Pain 2007;133210-220*; Selvarajah D et al *Diabetes Care 2010;33:128-130*) but there is limited data on either THC or CBD monotherapies. In light of concerns regarding the psychoactive effects and the recently noted higher potency of THC products (Manthey J et al *Lancet Reg Health Eur 2021;10:1000227*), understanding the pain-reducing benefits of cannabinoid mono- or combination-therapies (especially CBD) while balancing their side effects is of great interest. This is important in painful diabetic polyneuropathy, where <50% of patients achieve adequate pain relief with conventional pharmacotherapies. This trial found that THC and CBD monotherapy or combination therapies were not efficacious in reducing pain symptoms in patients with PPN. CBD performed worse than placebo at pain reduction in the per-protocol analysis. Although only a subset had painful diabetic polyneuropathy, there did not seem to be a difference in response based on etiology of peripheral neuropathy. The strengths of this trial include the evaluation of both cannabinoid mono- and combination therapy. The main limitation is that the study may have been underpowered as the investigators aimed for an n=35 participants in each of the 4 arms and this was not achieved. Larger scale studies can hopefully provide further clarification on the efficacy of cannabinoids for painful diabetic neuropathy in the future.

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Reference. Zubcevic K, Petersen M, Bach FW, Heinesen A, Enggaard TP, Almdal TP, Holbech JV, Vase L, Jensen TS, Hansen CS, Finnerup NB, Sindrup SH. Oral capsules of tetra-hydro-cannabinol (THC), cannabidiol (CBD) and their combination in peripheral neuropathic pain treatment. Eur J Pain. 2023 Apr;27(4):492-506. doi: 10.1002/ejp.2072. Epub 2023 Jan 12. PMID: 36571471. https://onlinelibrary.wiley.com/doi/10.1002/ejp.2072