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Clin Ther. 2007 Sep;29(9):2068-79.

Oromucosal delta9-tetrahydrocannabinol/cannabidiol for neuropathic pain associated with multiple sclerosis: an uncontrolled, open-label, 2-year extension trial.

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Abstract

BACKGROUND: Central neuropathic pain (CNP), pain initiated or caused by a primary lesion or dysfunction of the central nervous system, occurs in ~28% of patients with multiple sclerosis (MS). Delta(9)-Tetrahydrocannabinol/**cannabidiol** (THC/CBD), an endocannabinoid system modulator, has demonstrated efficacy for up to 4 weeks in randomized controlled trials in the treatment of CNP in patients with MS.

OBJECTIVE: The purpose of this extension was to establish long-term tolerability and effectiveness profiles for THC/CBD (Sativex (R), GW Pharmaceuticals plc, Salisbury, United Kingdom) oromucosal spray in CNP associated with MS.

METHODS: This uncontrolled, open-label trial was an indefinite-duration extension of a previously reported 5-week randomized study in patients with MS and CNP. In the initial trial, patients were randomized to placebo or THC/CBD. Patients were only required to maintain their existing analgesia in the randomized study. In the open-label trial they could vary their other analgesia as required. All patients (placebo and THC/CBD) who completed the randomized trial commenced the open-label follow-up on THC/CBD (27 mg/mL: 25 mg/mL). Patients titrated their dosage, maintaining their existing analgesia. The primary end point of the trial was the number, frequency, and type of adverse events (AEs) reported by patients. Secondary end points included changes from baseline in 11-point numerical rating scale (NRS-11) neuropathic pain score, hematology and clinical chemistry test results, vital signs, trial drug usage, and intoxication visual analogue scale scores.

RESULTS: Sixty-six patients were enrolled in the randomized trial; 64 (97%) completed the randomized trial and 63 (95%) entered the open-label extension (race, white, 100%; sex, male, 14 [22%]; mean [SD] age, 49 [8.4] years [range, 27-71 years[). The mean (SD) duration of open-label treatment was 463 (378) days (median, 638 days; range, 3-917 days), with 34 (54%) patients completing >1 year of treatment with THC/CBD and 28 (44%) patients completing the open-label trial with a mean (SD) duration of treatment of 839 (42) days (median, 845 days; range, 701-917 days). Mean NRS-11 pain scores in the final week of the randomized trial were 3.8 in the treatment group and 5.0 in the placebo group. In the 28 (44%) patients who completed the 2-year follow up, the mean (SD) NRS-11 pain score in the final week of treatment was 2.9 (2.0) (range, 0-8.0). Fifty-eight (92%)

patients experienced > or =1 treatment-related AE. These AEs were rated by the investigator as mild in 47 (75%) patients, moderate in 49 (78%), and severe in 32 (51%). The most commonly reported AEs were dizziness (27%), nausea (18 %), and feeling intoxicated (11%). Two treatment-related serious AEs (ventricular bigeminy and circulatory collapse) were judged to be treatment-related. Both serious AEs occurred in the same patient and resolved completely following a period of discontinuation. Eleven (17%) patients experienced oral discomfort, 4 persistently. Regular oral examinations revealed that 7 (11%) patients developed white buccal mucosal patches and 2 (3%) developed red buccal mucosal patches; all cases were deemed mild and resolved. Seventeen (25%) patients withdrew due to AEs. The mean number of sprays and patients experiencing intoxication remained stable throughout the follow-up trial.

CONCLUSIONS: THC/CBD was effective, with no evidence of tolerance, in these select patients with CNP and MS who completed approximately 2 years of treatment (n = 28). Ninety-two percent of patients experienced an AE, the most common of which were dizziness and nausea. The majority of AEs were deemed to be of mild to moderate severity by the investigators.

PMID: 18035205 DOI: 10.1016/j.clinthera.2007.09.013

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