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Management of Central Neuropathic Pain, Fibromyalgia and Chronic Allodynia: Examining Modulation of the Endocannabinoid System

Victoria - The discovery of the physiological functions of the endocannabinoid system in the central and peripheral nervous systems and peripheral organs has created opportunities to develop and study new treatment alternatives in a variety of pain states. At this year's Canadian Pain Society conference, experts from the field of pain medicine presented new and updated findings on central neuropathic pain (CNP), fibromyalgia and chronic allodynia treated with an endocannabinoid system modulator. For CNP in multiple sclerosis, flexible dosing and long-term use of the buccal spray containing delta-9-tetrahydrocannabinol and cannabidiol provided efficient pain relief without signs of tolerance. Other findings suggest that it alleviated pain in fibromyalgia and chronic allodynia.

Central neuropathic pain (CNP) that is initiated or triggered by a primary lesion or dysfunction of the central nervous system occurs in approximately 28% of patients with multiple sclerosis (MS). According to Dr. David J. Rog, consultant neurologist, Greater Manchester Neurosciences Centre, UK, "MS is a disease of young people. It is the leading non-traumatic cause of chronic disability in young people."

In 2005, Dr. Rog and colleagues reported on a randomized, double-blind, placebo-controlled, parallel group trial involving 66 patients with MS. They concluded that a cannabis-based buccal spray containing delta-9-tetrahydrocannabinol (THC) 2.7 mg and cannabidiol (CBD) 2.5 mg in each 100- μ L spray is effective in reducing pain and sleep disturbance in patients with MS-related CNP and is mostly well tolerated (*Neurology* 2005;65:812-9).

Long-term Results

From this study, 63 patients entered an uncontrolled, open-label, two-year extension phase (*Clin Ther* 2007;29(9):2068-79). Results demonstrated continued efficacy of the THC:CBD-containing buccal spray and no evidence of tolerance to the medication was observed in the 28 patients who completed approximately two years of treatment. Adverse events, mostly dizziness and nausea, were mild to moderate.

Dr. Rog told delegates, "The benefits that patients achieved in terms of pain relief were in addition to those achieved with standard analgesia." The investigators stipulated that patients in the trial should remain on their concomitant medications and not change the doses. Use of concomitant analgesic medication remained relatively stable.

Dr. Rog presented an analysis of dosing patterns and changes in concomitant analgesia used in the study. Patients could self-titrate their dosage to a maximum of 48 sprays (THC 129.6 mg, CBD 120 mg) in 24 hours. The mean number of sprays

taken in the final six full days of treatment was 6.5 (range 0.5-24.8, SD 5.8). Thirteen patients (46%) took <5 sprays, 10 patients (36%) took between 5 and 10 sprays and five patients (18%) took >10 sprays (per 24 hours).

At the commencement of the open-label phase of the trial, patients who subsequently completed the study were taking 31 concomitant analgesics. At the end of the study, doses of 15 (48%) of these analgesics remained unchanged. New analgesics were started during the study by 14 (50%) patients; half of these patients continued these medications at the end of the study. Similar patterns were observed with "non-analgesic" medications that may affect pain. "Most medications in the pain sphere have a fairly strict dosing regime," explained Dr. Rog. "In this study, we've shown there is flexibility with a [buccal] cannabis-based medicine... It offers the opportunity of individualized dosing."

There remains a need for good quality evidence in the treatment of CNP in MS, he emphasized. "Prior to 2003, there was very little in terms of controlled evidence for the use of cannabinoids within MS for any symptom," noted Dr. Rog. "Following 2003, there have been a number of randomized controlled trials. These are starting to bring some scientific methodology to the assessment of the potential benefits of cannabinoids."

Findings in the Management of Fibromyalgia Pain

General practitioner Dr. David Saul, North York Men's Health Centre, Toronto, Ontario, has a special interest in fibromyalgia and myalgic encephalomyelitis. He reported on two observational trials investigating treatment of fibromyalgia with the buccal spray containing THC:CBD. The first of these trials was conducted in late autumn 2005/early winter 2006 and the second in spring/early summer 2007.

The eight-week trial conducted in late autumn/early winter found that the spray reduced fibromyalgia pain and substantially improved function in 32 of 67 FM patients with moderate to severe symptoms. Thirty-two patients (47.8%) in this cold weather cohort reported reduced pain from baseline to week 4, including reductions in Numerical Rating Scale (NRS) pain scores and Fibromyalgia Impact Questionnaire (FIQ) scores; 22 patients were followed to week 8, with 17 patients continuing good FIQ reductions during weeks 4 to 8. In the second trial undertaken in spring/early summer, 30 of 53 patients (56.6%) reported similar benefits. Seventeen patients were followed to week 8 with 15 showing continued FIQ improvement.

In both trials, patients continued all other prescribed medications, without dose alterations. Improvements were observed in both cohorts, in both NRS pain scores and FIQ scores (pain and comorbid symptoms). Patients reporting benefits had improved function and mobility. About half the patients in each trial discontinued therapy, either because they could not tolerate the medication or because there was insufficient benefit.

Time of year appears to have an influence when treating patients with fibromyalgia with this medication, with more patients benefiting from the therapy when exposed to the agent during the spring, suggested Dr. Saul.

Chronic Allodynia Case Report

A University of British Columbia research team presented a case study of a patient with a 14-year history of chronic allodynia who was treated with THC:CBD-containing buccal spray.

“There is a role for cannabinoids in the management of complex CNP,” stated principal investigator Dr. May Ong-Lam, Clinical Associate Professor of Medicine, University of British Columbia, and founder, Chronic Pain Program, St. Paul’s Hospital, Vancouver.

Dr. Ong-Lam described a case involving a 46-year-old Caucasian woman who presented with burning, aching, stabbing pain affecting the right neck and shoulder girdle. The pain radiated to the inferomedial border of the scapula and was associated with hypersensitivity to clothing in the same area.

Fourteen years earlier the patient had undergone a benign tumour resection from the right parotid gland. Post-surgically she developed Frey’s syndrome, with right facial nerve palsy and numbness in the distribution of the right V2, V3 trigeminal nerve with sympathetic nervous system involvement. The patient slowly recovered over a six-month period but afterward became aware of hyperesthesia to clothing, involving the right trapezius and parascapula region, with muscle spasm. There was gradual spreading of the allodynia so that the patient could not wear clothing above the T2 level. The allodynia was specific to clothing (not to cold, touch, temperature variations or water during showering). Neurological exams revealed a partial sensory paresthesia affecting the right V2 dermatome.

Five weeks after the patient began taking 1 to 2 sprays of THC:CBD t.i.d. (8 am, noon, 6 pm), she presented fully clothed with all symptoms alleviated, stated Dr. Ong-Lam. After 14 months, all the patient’s symptoms had essentially resolved. The patient noted decreased alertness for about 30 minutes, one hour after each spray but was otherwise fully functional and working.

Two years following the inception of treatment, the patient continues to use one spray of THC:CBD t.i.d. “There is no change in her requirement,” noted Dr. Ong-Lam. “There is no abuse, overuse or secondary gain. She is totally functional and works full-time.” She concluded that cannabis-based therapy is effective in the management of chronic allodynia associated with CNP. Results from a five-week trial of patients with NP also indicated successful resolution of allodynia (Nurmikko et al. *Pain* 2007;133:210-20).

Summary

The approval of THC:CBD in Canada as an adjunctive treatment for symptomatic relief of CNP in patients with MS brought new hope in the field of pain management. This buccal spray formulation allows for flexible dosing as patients can individualize their dose. The long-term effects and tolerability profile in the treatment of CNP in MS are promising but there still remains a need for further assessment. In demonstrating effective pain relief in other conditions such as fibromyalgia and chronic allodynia, treatment with endocannabinoid system modulators may become a welcome addition to pain management therapy. □

Note: In Canada, the THC:CBD buccal spray is also indicated as adjunctive analgesic treatment in adult patients with advanced cancer who experience moderate to severe pain during the highest tolerated dose of strong opioid therapy for persistent background pain.

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