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Experience with the Synthetic Cannabinoid Nabilone in Chronic Noncancer Pain

David M. Berlach,* Yoram Shir, MD,† and Mark A. Ware, MRCP, MSc†

*McGill University Medical School, †Pain Center, McGill University Health Center, Montreal, Quebec, Canada

ABSTRACT

Chronic noncancer pain includes a heterogenous group of disorders and is often refractory to treatment. Cannabis products have historically been used for chronic pain and are attracting renewed pharmaceutical interest. Nabilone is a synthetic cannabinoid licensed in Canada for the treatment of severe nausea and vomiting associated with cancer chemotherapy. We have used nabilone off-label for the treatment of chronic noncancer pain since 1999. In this article, we review our clinical experience of 20 adult patients with chronic noncancer pain who had been treated with nabilone and followed up for an average of 1.5 years. Prior to nabilone therapy, patients had used a wide range of therapies, including 11 who had used cannabis. Fifteen patients reported subjective overall improvement with nabilone, and nine reported reduced pain intensity. Beneficial effects on sleep and nausea were the main reasons for continuing use. Intolerable side effects were experienced in three patients (palpitations, urinary retention, dry mouth). Nabilone may be a useful addition to pain management and should be further evaluated in randomized controlled trials.

Key Words. Chronic Pain; Nabilone; Cannabinoids; Marijuana; Case Series; Therapy

Introduction

Chronic pain, caused by neurological disorders, trauma, malignancy, and other illnesses, can be highly debilitating and is difficult to manage. The prevalence of chronic noncancer pain has been estimated to be between 2% and 40% (median 15%) [1], with an estimated annual cost in the United States of more than US$40 billion [2]. New therapeutic options are needed for patients who are untreatable by conventional methods. Cannabinoids are psychoactive constituents of the plant *Cannabis sativa* (marijuana), principally delta-9-tetrahydrocannabinol (THC), which have been shown to be antinociceptive in animal models of acute and chronic pain [3–5].

Nabilone (Cesamet®), an orally administered synthetic cannabinoid derived from cannabinol, is licensed in Canada as an antiemetic for management of patients suffering from severe nausea and vomiting associated with cancer chemotherapy. Its clinical pharmacology is well described [6]. Specifically, this agent has been found to have antianxiety effects in one randomized controlled trial [7,8]; has been shown to have anti-inflammatory and antihyperalgesic actions in the carageenan model of acute inflammation in rats [9]; and has been found to have analgesic and sedative properties in patients suffering from chronic noncancer pain [10,11]. To our knowledge, nabilone has never been systematically evaluated in chronic noncan-

Reprint requests to: Dr. Mark A. Ware, Bureau E19.145, Montreal General Hospital, 1650 Cedar Avenue, Montreal, Quebec, Canada H3G 1A4. Tel: 514-934-8222; Fax: 514-934-8096; E-mail: mark.ware@muhc.mcgill.ca.

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cer pain. We present a retrospective chart review of our clinical experience of the use of nabilone in a small series of 20 adult patients with chronic noncancer pain, with the primary objective of describing pain responses and adverse event experiences.

Methodology

The Pain Center of the McGill University Health Center provides multidisciplinary pain management to more than 1,200 patients a year from the Montreal region. We performed a retrospective chart review of patients who had been prescribed nabilone as part of the treatment of their chronic pain between November 1999 and August 2003. Patients were identified because they were known to one of the authors (M.A.W.) to have been prescribed nabilone. Nabilone was prescribed because anecdotal reports have suggested a possible role for cannabinoids in pain management, and nabilone offers one prescribable therapeutic option although it is unlicensed for this indication. Nabilone was introduced as an adjunctive therapy for all patients. No formal treatment protocol had been established prior to treatment; the use of nabilone was therefore off-label. The chart review was approved by the Director of Professional Services of the Montreal General Hospital.

Data were collected from clinic and hospital charts. Baseline demographic data included age, gender, diagnosis, number of medical specialists seen prior to clinic referral, medications used, and previously attempted therapies including over-the-counter medications. Information was collected on pain diagnosis, pain intensity, and associated symptoms. Pain intensity was reported using numerical rating scales (NRS) (0 = no pain at all, 10 = worst pain imaginable) as current level, average level in the past week, highest level in the past week, and lowest level in the past week. This is standard practice at the Pain Center, and was reported at baseline (prior to nabilone) and at subsequent visits. Other changes in pain (e.g., nighttime pain, pain exacerbations) were described if reported by patient and documented. Information on nabilone included doses used, duration of treatment, effect on other symptoms, and side-effect experiences. Side effects of the drug as expressed by the patient were recorded. Specific comments recorded in the chart related to nabilone were recorded.

Data were extracted from charts and entered into an anonymized database. Missing pain intensity data were imputed by using most recent NRS scores prior to nabilone use, and final scores were calculated based on last measured NRS scores during nabilone therapy. Average baseline and final NRS scores were compared using paired *t*-tests.

Results

Demographics

Twenty-one patients were identified who had been treated with nabilone over the 4-year period; one chart could not be found. Of the 20 patients in whom data were available, 11 were male and nine were female, with a mean age of 48 years. The patients had a wide range of chronic pain disorders including postoperative or traumatic pain (7), reflex sympathetic dystrophy (3), arthritis (2), Crohn's disease (2), neuropathic pain, interstitial cystitis, HIV-associated myopathy, post-polio syndrome, idiopathic inguinal pain, and chronic headaches.

Patients had all attempted several treatments prior to nabilone. Only one patient had tried five or fewer treatments, 10 patients had previously attempted between six and 10 treatments, seven had attempted between 11 and 15, and two had tried more than 15 treatments prior to nabilone. Prior treatments included medications such as nonsteroidal anti-inflammatory drugs, acetaminophen, opioids, anticonvulsants, and topical steroids. Other less conventional medications included capsaicin cream and smoked cannabis. Nondrug prior therapies included physiotherapy, transcutaneous electrical nerve stimulation (TENS), aquatherapy, chiropractic, hypnotherapy, and surgery. Demographic data and previously attempted medications are shown in more detail in Table 1 and Table 2.

Changes in Pain Measures

The baseline and final pain NRS scores are shown in Figure 1. Pain scores were complete (after imputation) for current pain intensity in nine patients, for average and lowest pain in 12 patients, and for highest pain in 14 patients. No significant differences between baseline and final scores were detected for any category. Nine out of 20 patients (45%) subjectively reported pain relief that was described by these patients as temporary (1), partial (3), or extensive (5). Several patients also described reductions in acute pain exacerbations and nighttime pain. One patient reported

Table 1 Demographic information of 20 patients using nabilone for chronic noncancer pain

Characteristic	N
Age (years)	
≤40	6
41–50	6
>50	8
Gender	
Male	11
Female	9
Diagnosis	
Postoperative or traumatic pain	7
Reflex sympathetic dystrophy	3
Arthritis	2
Crohn's disease	2
Other	6
Average number of medical specialists seen prior to pain clinic	4.9
Types of previously attempted treatments	
Opioids	18
Antiepileptics	15
TENS, physiotherapy, acupuncture, etc.	12
Antidepressants	11
Cannabis	11
Nonsteroidal anti-inflammatory drugs	4
Surgery	4
Other medications	13

Table 2 Medications and procedures used concurrently with nabilone

Drug Class/Name	Number of Subjects
Short-acting opioids	
Acetaminphen/oxycodone	4
Oxycodone short-acting	4
Methadone	3
Hydromorphone	3
Ketamine	1
Long-acting opioids	
Oxcontin	7
Fentanyl patch	3
Hydromorphone contin	3
Morphine sulfate contin	3
Antidepressants	
Tricyclic antidepression	
Amitriptyline	2
Selective serotonin re-uptake inhibitor	
Citalopram	2
Sertraline	1
Paroxetine	1
Others	
Venlafaxine	2
Bupropion	1
Doxepin	1
Methotrimeprazine	1
Trazodone	1
Procedures	
IV lidocaine	2
Trigger point injections	1

pain relief within the first week on nabilone. One patient who took nabilone at night stated that the pain became more localized and that relief lasted until the following afternoon. Another patient stated that nabilone made the pain "livable" and another stated that it "takes the edge off." One patient commented that nabilone was "better than good."

Nine patients (45%) remained on nabilone at the time of data collection of whom the average duration of use was 1.5 years with the longest usage lasting over 4 years. Of the nine patients who continued to use nabilone, four did not report any decreases in pain but continued to use it for other reasons (see below).

Changes in Other Symptoms

Half (10) of the patients reported improvements in quality or duration of sleep. Five patients reported decreased nausea or vomiting. One patient continued to use nabilone due to sleep improvements and one because of decreased nausea and increased appetite. Another patient reported both decreases in nausea and vomiting and increased sleep, and continued to use nabilone because it helped reduce cannabis intake.

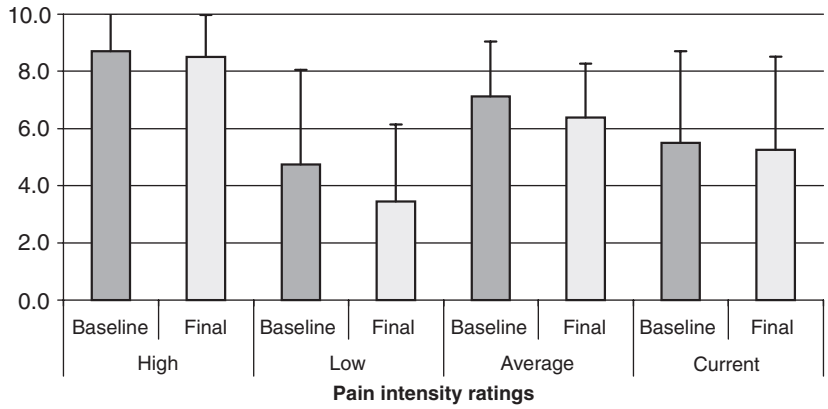

Figure 1 Pain reports during therapy with nabilone.

Dose Requirements

Patients were usually started on 1 mg nabilone at night, and the dose was increased to 1 mg bid if tolerated. Some patients had pain relief starting at 1 mg, but other patients required doses up to 2 mg bid to receive benefit. Patients using higher doses (1 mg tid, 2 mg bid) reported more sleep improvement but also reported more side effects, primarily headaches.

Other Medications

Over the course of follow-up, opioid and antidepressant medication profiles changed in seven patients. One decreased the amitriptyline dose, one decreased morphine sulfate contin dose; neither had reduced pain intensity. Two subjects increased opioid dose (both had reduced pain), two rotated opioids (pain unchanged), and one added an antidepressant (reduced pain).

Side Effects

No serious adverse events were experienced by any of the patients. Three patients could not tolerate nabilone and discontinued the drug within the first week. One patient cited palpitations, one cited dry mouth, and one cited increased urinary retention as the reasons for discontinuing nabilone. Other side effects reported by patients included dry mouth, headaches, nausea and vomiting in the first week of use, apathy, puffy lips, red cheeks, fatigue, palpitations, decreased clarity, decreased concentration, decreased focus, dizziness, drowsiness, transient deformity of left side of face in the first week, depression, and forgetfulness. One patient reported increased pain on stopping using nabilone. A summary of the adverse events reported is shown in Table 3.

Table 3 Reported negative side effects of nabilone among 20 chronic noncancer pain patients

Symptom	N
Decreased clarity/concentration/focus	3
Dry mouth	2
Headaches	2
Nausea/vomiting	2
Apathy	1
Puffy lips	1
Red cheeks	1
Fatigue	1
Loss of effect	1
Palpitations	1
Dizziness	1
Drowsiness	1
Transient facial deformation	1
Depression	1
Forgetfulness	1
Increased urinary retention	1

Discussion

Chronic noncancer pain is a complex syndrome that involves physical, psychological, and psychosocial factors that contribute to a reduced quality of life. In addition to pain relief, the goal of treatment of these patients is to improve their ability to function in society. There is an unmet therapeutic need for new approaches to pain management, and cannabinoids offer one potential target for new therapeutic approaches.

Cannabinoid compounds are believed to mediate their pharmacological actions by binding two principal receptors: CB1 receptors are located predominantly in the nervous system and CB2 receptors are located on immune cells [12]. Nabilone is a CB1 agonist with central activity when used systemically; selective CB2 agonists may reduce central effects but are not clinically available. The developing concept is that the cannabinoid neurophysiological system is distinct from, but functionally similar to, the opioid pain modulation system [13]. Epidemiologic studies have shown that 10–15% of chronic pain patients use cannabis to improve pain, sleep, and mood [14]. Recent clinical trials of new formulations of synthetic and naturally derived cannabinoids have found analgesic effects in intractable neurogenic pain, brachial plexus injuries, and chronic neuropathic pain [15–17].

This descriptive study reveals several interesting points about the use of nabilone in the treatment on chronic noncancer pain. Of the 20 patients using nabilone in this series, 15 (75%) reported obtaining some benefit, including effects on pain, sleep, and nausea. Patients were all adults suffering from pain disorders that had been poorly managed by other available therapies. Overall, nabilone was well tolerated and was not associated with any serious side effects. Due to the small number of patients in this study and the lack of a control group, it is not possible to assess the true effect or to identify which patient population would likely respond to nabilone. It is apparent, however, that some patients did receive benefit from this therapy including decreased pain, improved sleep, or reduced nausea. While some patients who had used cannabis felt that smoking cannabis was more beneficial, nabilone deserves

consideration as an adjunctive therapy in cannabis-naïve subjects with chronic pain. The effects on anxiety, confirmed in clinical trials [7,8,18], may provide additional benefit in the chronic pain sufferer. The effects of THC on sleep have already been examined [19–21], but we suggest that in the context of chronic pain, the effects of cannabinoid agonists on sleep architecture should be revisited. The side-effect profile of nabilone may limit its use at higher doses. The abuse potential of nabilone has not been formally evaluated, although early reports suggest that abuse of nabilone is unlikely to be a clinical problem [22].

In conclusion, we have found that nabilone is reasonably well tolerated by patients with chronic noncancer pain and may have important effects on symptoms such as pain, nausea, and poor sleep, which contribute to a reduced quality of life. More research, including randomized controlled trials, is required to assess the safety and efficacy of nabilone for chronic noncancer pain. Placebo-controlled trials may be difficult because the psychoactive effects associated with nabilone, but the side-effect profile of dry mouth and drowsiness is similar to other medications used for pain management. Amitriptyline, with a similar duration of action and adverse event profile to nabilone, may be a useful comparative agent. Doses of nabilone used in clinical trials should be kept low to minimize side effects, and sleep should be considered an important outcome in addition to pain measures.

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