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Nabilone for the Treatment of Pain in Fibromyalgia

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Abstract: A randomized, double-blind, placebo-controlled trial was conducted to determine the benefit of nabilone in pain management and quality of life improvement in 40 patients with fibromyalgia. After a baseline assessment, subjects were titrated up on nabilone, from 0.5 mg PO at bedtime to 1 mg BID over 4 weeks or received a corresponding placebo. At the 2- and 4-week visits, the primary outcome measure, visual analog scale (VAS) for pain, and the secondary outcome measures, number of tender points, the average tender point pain threshold, and the Fibromyalgia Impact Questionnaire (FIQ), were evaluated. After a 4-week washout period, subjects returned for reassessment of the outcome measures. There were no significant differences in population demographics between groups at baseline. There were significant decreases in the VAS (−2.04, $P < .02$), FIQ (−12.07, $P < .02$), and anxiety (−1.67, $P < .02$) in the nabilone treated group at 4 weeks. There were no significant improvements in the placebo group. The treatment group experienced more side effects per person at 2 and 4 weeks (1.58, $P < .02$ and 1.54, $P < .05$), respectively. Nabilone appears to be a beneficial, well-tolerated treatment option for fibromyalgia patients, with significant benefits in pain relief and functional improvement.

***Perspective:** To our knowledge, this is the first randomized, controlled trial to assess the benefit of nabilone, a synthetic cannabinoid, on pain reduction and quality of life improvement in patients with fibromyalgia. As nabilone improved symptoms and was well-tolerated, it may be a useful adjunct for pain management in fibromyalgia.*

***Key words:** Nabilone, cannabinoid, fibromyalgia, pain.*

Fibromyalgia is a syndrome of unknown etiology, characterized by diffuse musculoskeletal pain, fatigue, and sleep disturbance.[38] It affects 2% to 4% of the general population[35,36,37] and is 4 to 7 times more common in women, with symptoms usually arising between 20 and 55 years of age.[15]

The diagnostic criteria for fibromyalgia, established in 1990 by the American College of Rheumatology, includes widespread pain for at least 3 months and point tenderness with 4 kg of pressure at 11 or more of 18 characteristic tender points.[38] These criteria allow for the differentiation of fibromyalgia from other chronic musculoskeletal pain with a sensitivity and specificity of almost 85%.[16]

Patients with fibromyalgia have lower pain thresholds to both mechanical and thermal insults, give higher pain ratings, and experience an altered temporal summation to painful stimuli.[16] The sensitization of pain perception that is present in these patients can occur both peripherally and centrally after tissue damage but may also be present in patients with no obvious tissue damage.[20] Sensitization occurs in the dorsal horn of patients with fibromyalgia, as activity of both unmyelinated C fibers and A-δ fibers is increased[14,21]; however, it is unknown whether sensitization is due to increased pain fiber facilitation, or decreased inhibition.[20]

Given the lack of understanding in the pathophysiology of fibromyalgia, it is not surprising that until recently, with the approval of pregabalin, no medical treatment had been specifically approved by the United States Food and Drug Administration for its management.[13] There is also evidence that tricyclic antidepressants, cardiovascular exercise, cognitive behavioral therapy and patient

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education are effective in reducing the pain experienced by fibromyalgia patients.[16] A recent case series of 4 patients has suggested the possible benefit of nabilone, a synthetic cannabinoid, in the treatment of fibromyalgia, however more studies are required.[18]

Two types of cannabinoid receptors have been isolated: CB1 and CB2. The CB1 receptor is found predominantly in the central and peripheral nervous system,[25] whereas CB2 receptors are found principally in the immune system.[27] Endogenous cannabinoids have been isolated that interact with these receptors.[10] CB1 agonists have been shown to have an analgesic effect in acute and chronic pain models.[10] The CB1 agonists act at many sites along pain transmission pathways including activation of peripheral, spinal, and supraspinal CB1 receptors, each independently decreasing nociception.[10]

The endocannabinoid system shares several similarities with the opioid system.[9] CB1 and opioid receptors are both found in similar areas of the nervous system involved in pain control, including the periaqueductal gray matter, rostral ventromedial medulla, and the spinal cord.[29] Besides the similarities with the opioid system, cannabinoids have also been shown to inhibit prostaglandin E-2 synthesis,[8] reduce platelet aggregation,[31] and have an anti-inflammatory effect twice as great as hydrocortisone and 20 times that of aspirin.[12]

Nabilone is 1 of 2 orally administered cannabinoids available in Canada and is currently approved for the management of nausea and vomiting during chemotherapy. Research into oral cannabinoid use in the management of chronic and neuropathic pain has been encouraging.[18,32] As no treatment has been specifically approved for management of fibromyalgia, further research into treatment strategies is important. To date, no randomized, controlled trials have been conducted to assess the efficacy of a synthetic cannabinoid on pain and quality of life in patients with fibromyalgia.

Our hypothesis was that nabilone will significantly reduce the pain and improve quality of life in fibromyalgia patients compared with placebo, as evidenced by significant improvements in visual analog scale pain scores (VAS), number of tender points, average tender point pain threshold, and scores on the Fibromyalgia Impact Questionnaire (FIQ).

Materials and Methods

Setting

The study was conducted in the Outpatient Musculoskeletal Clinic at the Rehabilitation Hospital, Health Sciences Centre (HSC), Department of Physical Medicine and Rehabilitation, in Winnipeg, Manitoba, Canada, from April 2006 to November 2006. Patients were recruited from the musculoskeletal practices of attending Physiatrists and Rheumatologists at the Rehabilitation Hospital.

Inclusion Criteria

Inclusion criteria for the study included the subject meeting The American College of Rheumatology (1990) criteria for the classification of fibromyalgia[38]; patients between 18 and 70 years of age; having continued pain despite the use of other oral medications; and no previous use of oral cannabinoids for pain management.

Exclusion Criteria

Subjects were excluded from participating in the study if their pain was better explained by a diagnosis other than fibromyalgia; for abnormalities on routine baseline blood work including electrolytes, urea and creatinine, a complete blood count, and liver function tests; heart disease; schizophrenia or other psychotic disorder; severe liver dysfunction; history of untreated nonpsychotic emotional disorders; cognitive impairment; major illness in another organ system; pregnancy; nursing mothers; a history of drug dependency; or a known sensitivity to marijuana or other cannabinoid agents.

Protocol

Subjects met the eligibility criteria through a structured interview process, and participants provided informed consent. HSC Research ethics board, HSC Impact Committee and Health Canada approval was obtained prior to proceeding with the study.

Subjects were randomly assigned by the HSC pharmacy into treatment and control groups, each consisting of 20 participants (Fig 1). The examining physicians and the subjects were blinded to the randomization process. All of the study medication was provided by Valeant Canada Limited (Montreal, Quebec, Canada) and was identical to placebo. Subjects in both groups were seen at baseline, after 2 weeks and 4 weeks of treatment and after a 4-week washout period. Subjects in the treatment group received 0.5 mg nabilone PO at bedtime for a 1-week period, with instructions to increase to 0.5 mg BID after 7 days. At the 2-week visit, subjects were evaluated for the presence of side effects and drug tolerance, and if they consented to continue, had the prescription increased to nabilone 0.5 mg PO in the morning and 1 mg PO at bedtime, with instructions to increase to 1 mg BID after 7 days. Subjects in the control group received a corresponding placebo. Subjects were assessed for the safety and efficacy of their prescription based on the outcome measures at the 2-, 4-, and 8-week follow-up visits. Subjects were asked to continue any current treatment for fibromyalgia, including breakthrough pain medications, but not to begin any new therapies.

Outcome Measures

The primary outcome measure was a 10 cm VAS for pain. The secondary outcome measures included the number of positive tender points; the average tender point pain threshold; and the subject's score on the FIQ.

At each visit, subjects were asked to rate their current level of pain on the 10 cm VAS, (0 = no pain; 10 = worst pain imaginable), a valid and reliable scale for rating pain intensity.[26] Subjects then filled out the FIQ, which is a validated, self-administered test, scored out of 100, that evaluates physical function, work status, depression,

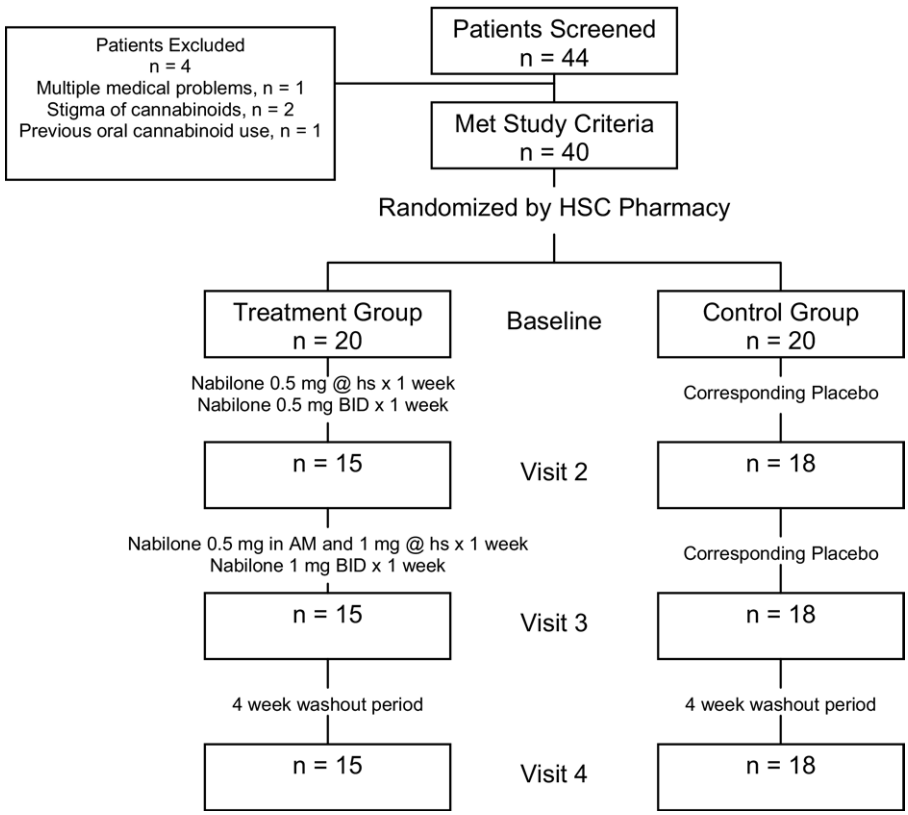

Figure 1. Study design. A randomized, double-blind, placebo-controlled trial.

anxiety, sleep, pain, stiffness, fatigue, and well-being in patients with fibromyalgia.[7,23] The higher the score on the FIQ, the greater the impact of fibromyalgia on the subject's quality of life.[7] Subjects were then assessed for the number of positive tender points by digital palpation over the 18 characteristic tender point sites in the ACR criteria for the diagnosis of fibromyalgia,[38] which has been previously shown to have both good intrarater and interrater reliability.[33] The subjects were asked to identify if a given point was painful as slow steady digital pressure was applied. The same evaluation of the tender points was then repeated with a hand-held Fischer algometer. This test has also demonstrated good interrater and test-retest reliability.[33] Pressure was applied over each tender point at a rate of 1 kilogram per square centimeter per second, and subjects were asked to identify the moment the pressure became painful. The pain threshold at each of the 18 tender points was recorded and an average tender point pain threshold for each visit was calculated. During each visit, any reported side effects as well as weight, blood pressure, and heart rate were recorded.

Statistical Analysis

Based on the previous case series investigating nabilone use in fibromyalgia,[18] we calculated that 16 patients would be necessary in each group to detect a change of 2 cm on the 10 cm VAS, using an α of <0.05 and a power of 80%. Allowing for dropouts, our aim was to have 20 subjects in each group start the study. Statistical analysis was conducted, and we considered $P < .05$ to be statistically significant for all of our outcome measures. The mean and standard deviation was calculated for each outcome measure at each visit and a Student's *t* test was performed to compare the change in the mean from baseline within and between groups.

Results

Forty-four subjects were screened to participate in the study between April and November of 2006. Four subjects did not meet the entrance requirements for the study. Reasons for their exclusion included a history of multiple medical problems (n = 1); subjects did not like the stigma associated with the use of cannabinoids (n = 2); and previous oral cannabinoid use (n = 1).

The remaining 40 subjects were randomly assigned by the HSC pharmacy into either the nabilone or placebo group (Fig 1). The examining physicians and patients were blinded to the randomization process. The baseline demographic data and baseline outcome measures are presented for both groups (Table 1). No significant differences in baseline demographic data or primary and secondary outcome measures were present. The percentage of subjects employed and the use of opioid medications for pain were not significantly different between the 2 groups.

A total of 5 subjects from the treatment group and 2

Table 1. Baseline Demographics and Outcome Measures for the Nabilone and Placebo Groups (Mean ± SD)

Patient Demographics and Baseline Outcome Measures	*Treatment Group N = 20 (20 F:0 M)*	*Placebo Group N = 20 (17 F:3 M)*	*Mean Difference*	*P Value Significant < .05*
Age (years)	47.6 ± 9.13	50.11 ± 5.96	2.51	> .15
Height (inches)	64.30 ± 1.86	64.74 ± 4.24	0.44	> .25
Weight (kg)	89.42 ± 24.54	79.85 ± 14.36	9.57	> .10
VAS (cm)	6.86 ± 2.14	6.2 ± 1.46	0.66	> .15
Number of tender points	15.73 ± 3.01	15.67 ± 2.03	0.06	> .25
Pain threshold (kg/cm^2)	1.41 ± 0.51	1.51 ± 0.60	0.1	> .25
FIQ score	66.45 ± 12.76	66.53 ± 16.21	0.08	> .25
Anxiety score	5.87 ± 1.72	5.39 ± 2.14	0.48	> .20
Depression score	5.47 ± 2.33	5.28 ± 2.42	0.19	> .25
Fatigue score	8.20 ± 1.51	7.50 ± 2.65	0.70	> .20

Abbreviations: FIQ, Fibromyalgia Impact Questionnaire; VAS, visual analog score.

from the placebo group dropped out of the study before its completion. All of the subjects who withdrew from the study did so at or before the first follow-up visit. In the control group, one subject discontinued the medication after 4 days because of headaches; the other withdrew at the first follow-up visit, after 2 weeks, although no side effects or reason for dropping out was stated. Of the subjects in the treatment group, 3 withdrew before the first follow-up visit. Two of these subjects did not state a reason for withdrawal and listed no side effects, whereas the other subject experienced dizziness, disorientation, and nausea. The remaining 2 subjects in the treatment group to withdraw did so at the first follow-up visit, after 2 weeks. One subject stated poor coordination, dizziness, headache, and nausea as the reasons for withdrawing from the study, whereas the other experienced drowsiness and fatigue. All patients in the treatment group that continued with the study achieved a nabilone dose of 1 mg BID.

There was a significant increase in the weight of subjects treated with nabilone for 2 weeks, (1.13 kg, $P < .01$). This effect, however, was transient, as there was no significant difference in weight change observed between the 2 groups during the 4-week and 8-week visits.

When compared with baseline, at the 2-, 4-, and 8-week visits, no statistically significant differences were observed in any of the outcome measures in the placebo group.

There were no statistically significant differences from baseline in the outcome measures in the nabilone treated subjects, at a dose of 0.5 mg BID, after 2 weeks of treatment. However, at the 4-week follow-up visit, at a nabilone dose of 1 mg BID, statistically significant improvements were seen in the VAS, FIQ, and FIQ anxiety scale. The VAS scores for pain decreased from baseline at 4 weeks (−2.04, $P < .02$) (Fig 2). Fibromyalgia Impact Questionnaire scores also significantly decreased (−12.07, $P < .02$) (Fig 3). The 10-point anxiety scale within the FIQ was the final outcome to be statistically improved from baseline after 4 weeks of treatment (−1.67, $P < .02$) (Fig 4). The remaining outcomes we assessed including number of tender points, tender point pain threshold, and

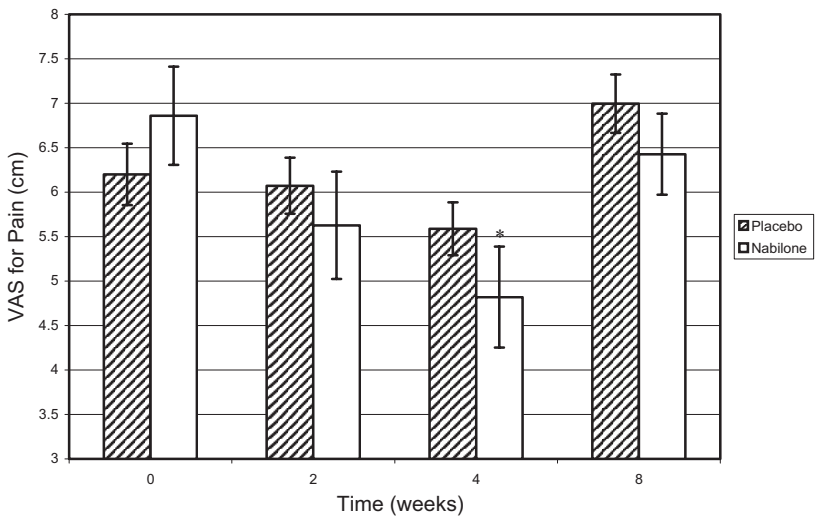

Figure 2. VAS scores, nabilone vs placebo, mean ± SE. When compared with baseline, nabilone-treated patients had significantly improved VAS scores at 4 weeks (−2.04, $P < .02$*).

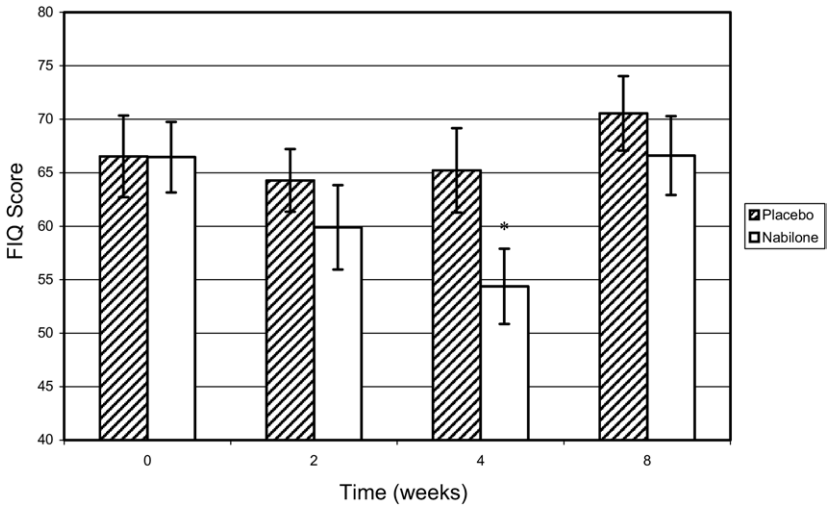

Figure 3. FIQ scores, nabilone vs placebo, mean ± SE. When compared with baseline, nabilone-treated patients had significantly improved FIQ scores at 4 weeks (−12.07, $P < .02$*).

the depression and fatigue scales on the FIQ were not significantly different from baseline values.

Comparing the treatment and placebo groups at 2 weeks of treatment, no significant differences were seen in VAS, number of tender points, tender point pain threshold, or FIQ. Of the 3 separately analyzed questions in the FIQ concerning anxiety, depression, and fatigue, only anxiety was significantly less at the 2-week visit in the nabilone group. The score on the 10-point scale for anxiety decreased in the treatment group at a nabilone dose of 0.5 mg BID (−1.92, $P < .025$).

At the 4-week visit, statistically significant differences between the treatment and placebo groups were also present. The change from baseline in visual analogue scale pain scores (−1.43, $P < .05$) (Fig 5), FIQ scores (−10.76, $P < .01$) (Fig 6), and the FIQ anxiety scale (−2.20, $P < .01$) (Fig 7) all showed significant improvement when compared with the placebo group.

No significant differences were seen between the treatment and placebo groups after the 4-week washout period at the 8-week visit.

Side effects were more common in the nabilone-treated subjects compared with placebo controls at both 2 and 4 weeks of treatment, (1.58, $P < .02$ and 1.54, $P < .05$), respectively. The frequency of the most common side effects for both groups is listed in Table 2. The most common side effects reported by subjects in the nabilone group include drowsiness (7/15), dry mouth (5/15), vertigo (4/15), and ataxia (3/15). No serious adverse events occurred during the study.

Discussion

Our study was conducted to investigate the possible benefits of the synthetic cannabinoid nabilone on pain reduction and quality of life improvement in patients

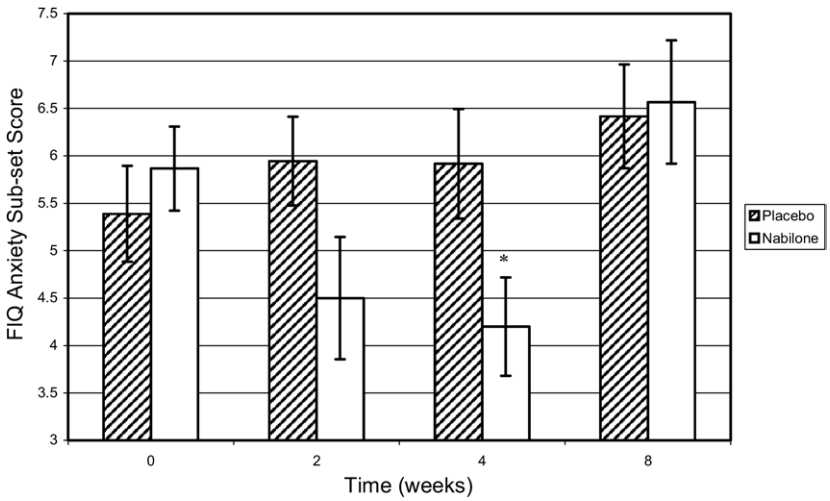

Figure 4. FIQ anxiety subset scores, nabilone vs placebo, mean ± SE. When compared with baseline, nabilone-treated patients had significantly improved FIQ scores at 4 weeks (−1.67, $P < .02$*).

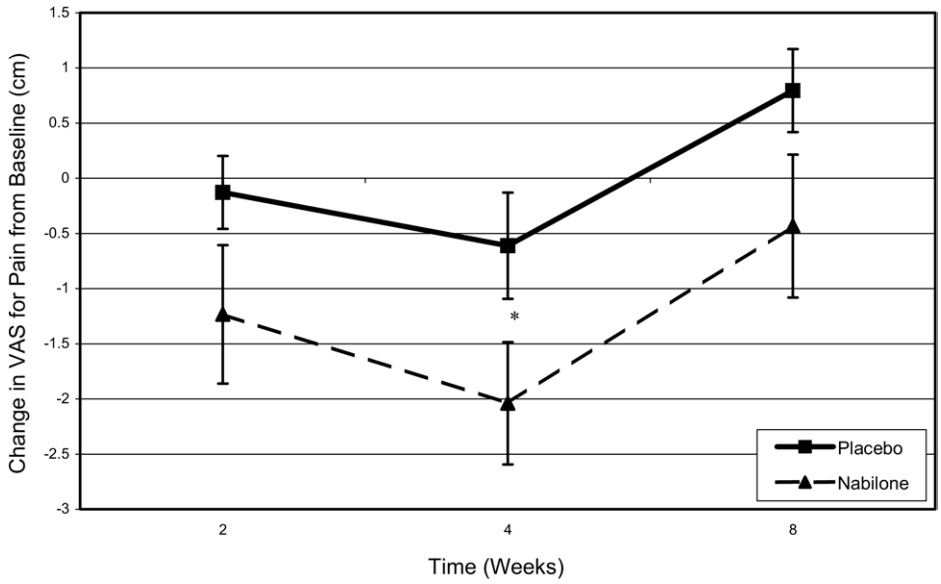

Figure 5. Change in VAS score, nabilone vs placebo, mean ± SE. There was a significant improvement in the change in VAS score in the nabilone group compared with placebo at 4 weeks (−1.43, $P < .05$*).

with fibromyalgia. Significant reductions in VAS score for pain, FIQ score, and FIQ anxiety score were seen in the treatment group at the 4-week visit. These significant reductions are found both when comparing the treatment group with their baseline values and when comparing the change from baseline to the placebo group at 4 weeks. None of the study participants achieved a total remission of their fibromyalgia symptoms.

Although improvements in VAS and FIQ scores were present after 4 weeks of treatment, there was no significant change in the number of tender points or tender point pain threshold, which is supported by other studies.[2,23]

Subjects in the placebo group did not obtain any significant benefit in the outcome measures at any time during the study. After a 4-week washout period, out-

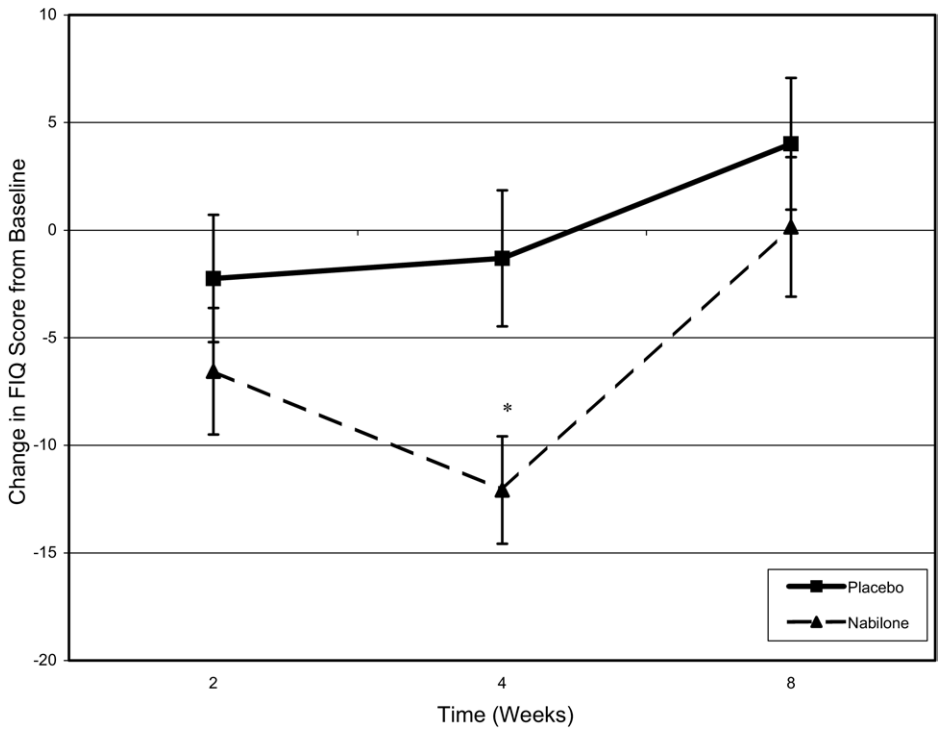

Figure 6. Change in FIQ score, nabilone vs placebo, mean ± SE. There was a significant improvement in the change in FIQ score in the nabilone group compared with placebo at 4 weeks (−10.76, $P < .01$*).

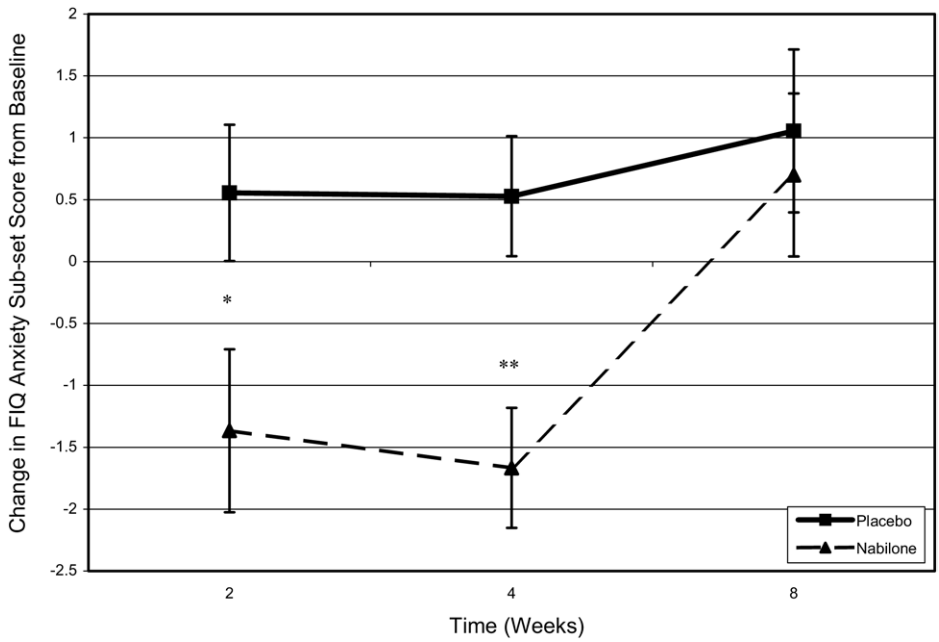

Figure 7. Change in FIQ anxiety subset scores, nabilone vs placebo, mean ± SE. There was a significant improvement in the change in anxiety score in the nabilone group when compared with placebo at 2 and 4 weeks of treatment, with differences of (-1.92, $P < .025$*) and (-2.20, $P < .01$**), respectively.

come measures were not significantly different from baseline in both groups. Nabilone does not appear to have any lasting benefit in subjects when treatment is discontinued.

Comparing the baseline FIQ scores in our study to some recent studies that used the FIQ, our subjects scored on average 12 to 22 points higher,[2,5,30] indicating their quality of life was more severely affected by fibromyalgia.[23] As our recruitment practices were similar, the reason for the disparity in the baseline FIQ scores and its effect on our results is unclear.

The significant drop in the VAS (-2.04, $P < .02$) in our treatment group was similar to those of other drug trials, which ranged from 1.2 to 2.2.[2,5,17] Our finding of a significant drop in the FIQ score (-12.07, $P < .02$) was also similar to other drug trials whose drop in FIQ score ranged from 5.53 to 15.8.[2,3,5,17,30] Despite the poorer baseline quality of life of our subjects, they still managed a significant improvement in FIQ scores on par with other studies. This suggests that nabilone is an effective treatment even for those with severe cases of fibromyalgia with marked functional impairment.

Although statistically significant reductions in VAS score for pain, FIQ score, and FIQ anxiety score were observed in this study, the question remains whether these findings are clinically significant? With the current lack of understanding of the pathophysiology of fibromyalgia, and options in its medical management,[13] the statistically significant benefits obtained in this study are promising and require consideration as an adjunct to the current medical management of fibromyalgia.

The analgesic benefits of cannabinoids in the treatment of acute and chronic pain have already been estab-

Table 2. Side Effects Reported in the Treatment and Placebo Groups at 2 and 4 Weeks

	Placebo		Nabilone			Placebo		Nabilone	
Side Effect	2 Week	4 Week	2 Week	4 Week	Side Effect	2 Week	4 Week	2 Week	4 Week
Drowsiness	3/20	1/18	7/18	7/15	Blurred vision	1/20	0/18	1/18	0/15
Dry mouth	5/20	1/18	5/18	5/15	Dysphoria	0/20	0/18	2/18	1/15
Vertigo	0/20	0/18	2/18	4/15	Depression	0/20	1/18	0/18	0/15
Ataxia	0/20	1/18	3/18	3/15	Euphoria	0/20	1/18	0/18	1/15
Confusion	0/20	1/18	3/18	2/15	Lightheaded	0/20	0/18	1/18	0/15
Decreased concentration	0/20	1/18	1/18	2/15	Psychological high	1/20	0/18	1/18	0/15
Disassociation	0/20	0/18	2/18	2/15	Nightmares	0/20	1/18	1/18	0/15
Orthostatic hypotension	0/20	1/18	1/18	2/15	Sensory disturbance	0/20	0/18	1/18	1/15
Anorexia	0/20	1/18	1/18	2/15	Tachycardia	0/20	1/18	0/18	0/15
Headache	2/20	3/18	3/18	1/15	Hallucination	0/20	0/18	0/18	0/15

lished,[10] so their benefit in fibromyalgia patients is not surprising. Whether this benefit is secondary to a clinical endocannabinoid deficiency in fibromyalgia patients as has been suggested[28] or the synergistic relationship with endogenous opioids,[27] it is clear from previous studies that cannabinoids act at many sites along pain transmission pathways.

Other known actions of cannabinoids including inhibition of prostaglandin E-2 synthesis,[8] its anti-inflammatory effect,[12] experimental increases in β-endorphins,[34] and the regulation of substance P and enkephalin mRNA levels in the basal ganglia[22] could all contribute to less pain experienced in the nabilone-treated patients.

Anxiety on the FIQ was also decreased in the treatment group at the 4-week visit, which is not exclusive to our study. A trial assessing the effects of tramadol and acetaminophen on patients with fibromyalgia found similar improvements in VAS, FIQ, and anxiety, without significant improvements in depression or fatigue.[5] Although part of the benefit obtained in pain reduction and quality-of-life improvement in these patients may be secondary to reduced anxiety, other studies have not shown a change in anxiety despite significant functional improvements.[30] Further studies with validated scales for anxiety need to be conducted to explore this issue.

Nabilone was generally well tolerated by participants throughout the study. This is reassuring, as it is well known that patients with fibromyalgia are sensitive to most medications and have difficulty tolerating medication side effects.[15] Although there were significantly more side effects per person in the treatment group at 2 and 4 weeks (1.58, $P < .02$ and 1.54, $P < .05$), respectively, no serious adverse effects were seen in the nabilone-treated subjects during the study. Three-quarters of the subjects in the treatment group tolerated the medication well and completed the study. Those who withdrew from the study did so at or before the first follow-up visit at 2 weeks. The reported side effects of nabilone were generally mild, and nabilone did not appear to have adverse interactions with any of the concomitant medications patients were taking, including antidepressants, muscle relaxants, nonsteroidal anti-inflammatories, and opioids. This supports the findings from the previously conducted case series with nabilone and fibromyalgia patients.[18] Slowing the titration of the medication in longer studies may further reduce treatment side effects.

When prescribing nabilone, cost must be taken into consideration. Participants using nabilone at the dose we found to be effective in the study should expect to pay over four thousand dollars for a year's supply of the medication in Canada. Patients must weigh these costs against the potential benefits of pain reduction and improved quality of life. As the medication's cost may be prohibitive to some patients, nabilone probably would not be the first line therapy prescribed to patients with fibromyalgia but should be considered if other treatments have been ineffective.

The current study is not without its limitations. Participants in both groups were allowed to continue any treatments for pain, with the use of nabilone as an adjunctive therapy. Despite the benefit in pain and anxiety reduction and quality of life improvement in the treatment group, it cannot be definitively concluded that the benefit was not a result of the combination of therapies. We thought that allowing both groups to continue their ongoing pain therapies controlled for this variable, and as fibromyalgia patients using complementary therapies ranges in studies from 60 to 90 percent,[4] the use of nabilone as an adjunct is clinically relevant. Future studies could be done using nabilone as a single agent to determine its effect on pain and quality of life alone.

Given the fluctuating nature of fibromyalgia symptoms,[15] our study was limited by its short duration and limited number of visits. To control for the fluctuating nature of fibromyalgia symptoms a pain journal could be given to subjects; however, this requires more effort on their behalf and may lead to decreased adherence to the protocol.

Subjects were only trialed on nabilone for a total of 4 weeks, of which only the last week of treatment was at 1 mg BID. The long-term effect of nabilone in alleviating pain and improving quality of life in patients with fibromyalgia cannot be determined based on the short duration of the study. As this study was the first randomized, controlled trial to assess the benefits of nabilone in subjects with fibromyalgia, it was reasonable to conduct this study for a shorter duration. Now that our study has shown significant improvements for fibromyalgia patients, future studies should involve a longer duration of the treatment, at a stable dose.

Although anxiety, depression, and fatigue were assessed in this study with single questions on the FIQ, these single questions are not validated scales for the respective symptoms. As the outcome measures in our study focused on pain and quality of life, the VAS for pain and FIQ were the scales used to assess them. Reports exist for[19,24] and against[1] the incidence of depression and anxiety being higher in the fibromyalgia population, and this area is still up for debate. Chronic fatigue syndrome is associated with fibromyalgia,[6] and it has been reported that patients with fibromyalgia have less restorative sleep.[11] Future studies to evaluate the effect of nabilone on anxiety, depression, and fatigue in patients with fibromyalgia should use validated scales for each.

To our knowledge, this is the first randomized, controlled trial to demonstrate the benefit of nabilone on pain and quality of life in subjects with fibromyalgia. The significant reductions in VAS, FIQ, and anxiety seen in the treatment group, coupled with minimal side effects, suggest that nabilone may be a beneficial, well-tolerated, treatment option in patients with fibromyalgia. Future studies are still necessary to assess the long-term benefit of nabilone on pain and quality of life, and secondary outcome measures such as anxiety, depression, and

fatigue should be further explored with validated assessment tools.

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References

1. Ahles TA, Khan SA, Yunus MB, Spiegell DA, Masi AT: Psychiatric status of patients with primary fibromyalgia, patients with rheumatoid arthritis and subjects without pain: A blind comparison of DSM-III diagnoses. Am J Psychiatry 148:1721-1726, 1991

2. Arnold LM, Hess EV, Hudson JI, Welge JA, Berno SE, Keck PE: A randomized, placebo-controlled, double-blind, flexible-dose study of fluoxetine in the treatment of women with fibromyalgia. Am J Med 112:191-197, 2002

3. Arnold LM, Lu Y, Crofford LJ, Wohlreich M, Detke MJ, Iyengar S, Goldstein DJ: A double-blind, multicenter trial comparing duloxetine with placebo in the treatment of fibromyalgia patients with or without major depressive disorder. Arthritis Rheum 50:2974-2984, 2004

4. Assefi NP, Sherman KJ, Jacobsen C, Goldberg J, Smith WR, Buchwald D: A randomized clinical trial of acupuncture compared with sham acupuncture in fibromyalgia. Ann Intern Med 143:10-19, 2005

5. Bennett RM, Kamin M, Karim R, Rosenthal N: Tramadol and acetaminophen combination tablets in the treatment of fibromyalgia pain: A double-blind, randomized, placebo-controlled study. Am J Med 114:537-545, 2003

6. Buchwald D, Garrity D: Comparison of patients with chronic fatigue syndrome, fibromyalgia and multiple chemical sensitivities. Arch Intern Med 154:2049-2053, 1994

7. Burckhardt CS, Clark SR, Bennett RM: The fibromyalgia impact questionnaire: Development and validation. J Rheumatol 18:728-733, 1991

8. Burstein S, Levin E, Varanelli C: Prostoglandins and cannabis, II: Inhibition of biosynthesis by the naturally occurring cannabinoids. Biochem Pharmacol 22:2905-2910, 1973

9. Corchero J, Manzanares J, Fuentes JA: Cannabinoid/opioid crosstalk in the central nervous system. Crit Rev Neurobiol 16:159-172, 2004

10. Cravatt BF, Lichtman AH: The endogenous cannabinoid system and its role in nociceptive behavior. J Neurobiol 61: 149-160, 2004

11. Edinger JD, Wohlgemuth WK, Krystal AD, Rice JR: Behavioral insomnia therapy for fibromyalgia patients: A randomized clinical trial. Arch Intern Med 165: 2527-2535, 2005

12. Evans FJ: Cannabinoids: The separation of central from peripheral effects on a structural basis. Planta Med 57:S60-S67, 1991

13. FDA News: FDA approves first drug for treating fibromyalgia. Available from: www.fda.gov/bbs/topics/NEWS/2007/NEW01656.html, 2007. Accessed April 19, 2007

14. Gibson SJ, Littlejohn GO, Gorman MM, Helme RD, Granges G: Altered heat pain thresholds and cerebral event-related potentials following painful CO2 laser stimulation in subjects with fibromyalgia syndrome. Pain 58:185-193, 1994

15. Gilliland RP: Fibromyalgia. Emedicine. Available from: www.emedicine.com/pmr/topic47.htm, 2004. Accessed April 19, 2007

16. Goldenberg DL, Burckhardt C, Crofford L: Management of fibromyalgia syndrome. JAMA 292:2388-2395, 2004

17. Holman AJ, Myers RR: A randomized, double-blind, placebo-controlled trial of pramipexole, a dopamine agonist, in patients with fibromyalgia receiving concomitant medications. Arthritis Rheum 52:2495-2505, 2005

18. Ko G, Wine W: Chronic pain and cannabinoids: A survey study of current fibromyalgia treatment approaches together with an overview and case studies of a new "old" treatment approach. Pract Pain Manage 1-8, 2005

19. Kraj NJ, Norregaard J, Larsen JK, Danneskiold-Samsoe B: A blinded controlled evaluation of anxiety and depressive symptoms in patients with fibromyalgia, as measured by standardized psychometric interview scales. Acta Psychiatrica Scandinavica 89:370-375, 1994

20. Littlejohn GO: Balanced treatments for fibromyalgia. Arthritis Rheum 50:2725-2729, 2004

21. Littlejohn GO, Weinstein C, Helme RD: Increased neurogenic inflammation in fibrositis syndrome. J Rheumatol 14: 1022-1025, 1987

22. Mailleux P, Vanderhaeghen JJ: Delta-9-tetrahydrocannabinol regulates substance P and enkephalin mRNAs levels in the caudate-putamen. Eur J Pharmacol 267:R1-R3, 1994

23. Marques AP, Ferreira EAG, Matsutani LA, Pereira CA, Assumpcao A: Quantifying pain threshold and quality of life of fibromyalgia patients. Clin Rheumatol 3:266-271, 2005

24. Martinez JE, Ferraz MB, Fontana AM, Atra E: Psychological aspects of Brazilian women with fibromyalgia. J Psychosom Res 39:167-174, 1995

25. Pertwee RG: Cannabis and cannabinoids: Pharmacology and rationale for clinical use. Forsch Komplementarmed Suppl 3:12-15, 1999

26. Price DD, Bush FM, Long S, Hawkins SW: A comparison of pain measurement characteristics of mechanical visual analogue and simple numerical rating scales. Pain 56:217-226, 1994

27. Pugh G, Mason DJ, Combs V, Welch SP: Involvement of dynorphin B in the antinociceptive effects of the cannabinoid CP55, 940 in the spinal cord. J Pharmacol Exp Ther 281:730-737, 1997

28. Russo EB: Clinical endocannabinoid deficiency (CECD): Can this concept explain therapeutic benefits of cannabis in

migraine, fibromyalgia, irritable bowel syndrome and other treatment-resistant conditions? Neuroendocrinol Lett 25: 31-39, 2004

29. Salio C, Fischer J, Franzoni MF, Mackie K, Kaneko T, Conrath M: CB1-canabinoid and mu-receptor co-localization on postsynaptic target in the rat dorsal horn. NeuroReport 12:3689-3692, 2001

30. Sayar K, Aksu G, Ak I, Tosun M: Venlafaxine treatment of fibromyalgia. Ann Pharmacother 37:1561-1565, 2003

31. Schafer CF, Brackett DJ, Gunn CG, Dubowski KM: Decreased platelet aggregation following marihuana smoking in man. J Okla State Med Assoc 72:435-436, 1979

32. Svendsen KB, Jensen TS, Bach FW: Does the cannabinoid dronabinol reduce central pain in multiple sclerosis? Randomised double blind placebo controlled crossover trial BMJ 329:253-260, 2004

33. Tunks E, McCain GA, Hart LE: The reliability of examination for tenderness in patients with myofascial pain, chronic fibromyalgia and controls. J Rheumatol 22:944-952, 1995

34. Wiegant VM, Sweep CG, Nir I: Effect of acute administration of delta 1-tetrahydrocannabinol on beta-endorphin levels in plasma and brain tissue of the rat. Experientia 43: 413-415, 1987

35. Wolfe F, Cathey MA: Prevalence of primary and secondary fibrositis. J Rheumatol 10:965-968, 1983

36. Wolfe F, Cathey MA: The epidemiology of tender points. J Rheumatol 12:1164-1168, 1985

37. Wolfe F, Ross K, Anderson J, Russell IJ, Herbert L: The prevalence and characteristics of fibromyalgia in the general population. Arthritis Rheum 38:19-28, 1995

38. Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, Tugwell P, Campbell SM, Abeles M, Clark P, Fam AG, Farber SJ, Fiechtner JJ, Franklin CM, Gatter RA, Hamaty D, Lessard J, Lichtbroun AS, Masi AT, McCain GA: The American College of Rheumatology 1990 criteria for the classification of fibromyalgia: report of the Multicenter Criteria Committee. Arthritis Rheum 33:160-172, 1990