The Effects of Nabilone on Sleep in Fibromyalgia: Results of a Randomized Controlled Trial

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BACKGROUND: Sleep disorders affect many patients with chronic pain conditions. Cannabis has been reported by several patient populations to help sleep. We evaluated the safety and efficacy of nabilone, a synthetic cannabinoid, on sleep disturbance in fibromyalgia (FM), a disease characterized by widespread chronic pain and insomnia.

METHODS: We conducted a randomized, double-blind, active-control, equivalency crossover trial to compare nabilone (0.5–1.0 mg before bedtime) to amitriptyline (10–20 mg before bedtime) in patients with FM with chronic insomnia. Subjects received each drug for 2 wk with a 2-wk washout period. The primary outcome was sleep quality, measured by the Insomnia Severity Index and the Leeds Sleep Evaluation Questionnaire. Secondary outcomes included pain, mood, quality of life, and adverse events (AEs).

RESULTS: Thirty-one subjects were enrolled and 29 completed the trial (26 women, mean age 49.5 yr). Although sleep was improved by both amitriptyline and nabilone, nabilone was superior to amitriptyline (Insomnia Severity Index difference = 3.2; 95% confidence interval = 1.2–5.3). Nabilone was marginally better on the restfulness (Leeds Sleep Evaluation Questionnaire difference = 0.5 [0.0–1.0]) but not on wakefulness (difference = 0.3 [−0.2 to 0.8]). No effects on pain, mood, or quality of life were observed. AEs were mostly mild to moderate and were more frequent with nabilone. The most common AEs for nabilone were dizziness, nausea, and dry mouth.

CONCLUSIONS: Nabilone is effective in improving sleep in patients with FM and is well tolerated. Low-dose nabilone given once daily at bedtime may be considered as an alternative to amitriptyline. Longer trials are needed to determine the duration of effect and to characterize long-term safety.

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Fibromyalgia (FM) is a chronic pain syndrome characterized by diffuse body pain with associated pressure allodynia. The diagnosis is clinical with no confirmatory test and is based on a history of widespread pain and the presence of tenderness at 11 of 18 specific tender point sites.[1] This condition, predominantly affecting adult women, is worldwide and common with a prevalence of 2% in North America.[2–4]

Although the pathophysiology of FM is not clearly understood, evidence is emerging of widespread central nervous system sensitization,[5] which may be mediated by dopaminergic,[6] serotonergic,[7] and glutamatergic[8] mechanisms. Autonomic dysregulation has also been postulated in FM.[9–11]

In addition to the report of pain, patients with FM experience numerous other somatic symptoms such as fatigue, mood disorder, and sleep disturbance that have an important effect on well-being. Insomnia has been reported in >75% of patients with FM.[12] Unique sleep patterns have been identified in patients with FM, for example, increased α non-rapid eye movement (REM) spindles on electroencephalogram recordings.[13] The use of antidepressant therapy has been shown to improve sleep quality in patients with FM.[14]

Pregabalin has been shown to be effective for pain in FM[15] and was recently approved by the United States Food and Drug Administration for the management of pain associated with FM. Before this, standard treatment for FM has included low-dose tricyclic antidepressants such as amitriptyline, cardiovascular

exercise, cognitive behavioral therapy, and patient education.[16,17] Nabilone, a synthetic cannabinoid, has been observed in a small case series to improve sleep in patients with chronic pain.[18] A recent small randomized controlled trial of nabilone in FM was shown to reduce pain, but sleep changes were not reported.[19] To our knowledge, no study has specifically evaluated sleep quality as a primary outcome in FM. This study was therefore designed to investigate the effects of nabilone on sleep in patients with FM.

METHODS

We conducted a randomized, active-control, equivalency clinical trial using a 2-period crossover design. Each period was of 2 wk duration separated by a 2-wk washout phase. The total study period was for 10 wk, including the initial and final 2-wk washout periods.

Participants

Subjects were recruited from the Pain Clinic of the McGill University Health Centre. Eligible subjects were adult men and nonpregnant women aged 18 yr or older with a diagnosis of FM[1] who had self-reported chronic insomnia. Insomnia was defined as disturbed sleep either every night or every other night for the past 6 mo.[20] Subjects remained on stable analgesic therapy and had to have a negative urine screen for cannabinoids at the baseline visit. Subjects who were using a cannabinoid or amitriptyline at screening underwent a 2-wk washout period before entering the study. Subjects were excluded if they had cancer pain, unstable cardiac disease, a history of psychotic disorder, schizophrenia, or recent manic episode (within the past year), seizure disorder, glaucoma, urinary retention, hypersensitivity to cannabinoids, amitriptyline, or related tricyclic antidepressants, or were taking monoamine oxidase inhibitors.

Eligible and consenting subjects underwent a medical history, physical examination, and chart review. Vital signs and concomitant medications were recorded, and urinary drug screening, full blood counts, and renal and liver function tests were performed and required to be negative or normal. At the baseline visit, eligible subjects completed questionnaires on pain, mood, and quality of life (see below), and underwent a urine drug test before randomization.

Study Drug

Doses of nabilone 0.5 mg or amitriptyline 10 mg were prepared by an independent pharmacy in sealed opaque capsules. Subjects received either nabilone 0.5 mg or amitriptyline 10 mg at the start of the treatment cycle of the study according to the randomization schedule. On Day 7 of each treatment cycle, the study physician evaluated whether the subject might benefit from an increase in dose. If an increase was indicated, the dose of the assigned medication was doubled (to either nabilone 1 mg or amitriptyline 20 mg) for the second week. At the end of the second week, subjects stopped the study medication for a 2-wk washout period and began the second treatment cycle on the other study drug following the same procedures as above.

Objectives

The primary objective of this study was to determine whether nabilone is equivalent to amitriptyline in improving quality of sleep in patients with FM. The secondary objective was to describe the effects of nabilone on the other clinical variables of pain, mood, quality of life, and global satisfaction. Adverse events (AEs) were recorded.

Study Outcomes

Primary Outcome

The primary outcome was the quality of sleep. Two measures were used to assess sleep, the Insomnia Severity Index (ISI) and the Leeds Sleep Evaluation Questionnaire (LSEQ). The ISI is a reliable and valid instrument used to quantify perceived insomnia severity and is used as an outcome measure in insomnia treatment research.[21] A score of <8 on the ISI implies no clinical insomnia, 8–14 implies moderate insomnia, and >15 implies severe insomnia. The LSEQ is a well-validated instrument that has been used to monitor subjectively perceived changes in sleep during psychopharmacological investigations with a variety of psychoactive drugs including sedative hypnotics, anxiolytics, central nervous system stimulants, and antihistamines.[22] The LSEQ comprises ten 100-mm visual analog scales measuring 4 characteristics of sleep: getting to sleep, quality of sleep, awakening from sleep, and behavior after wakefulness. We used the full LSEQ at clinic visits and in a study diary. During telephone interviews, patients responded to the questions on a 0–10 numerical scale. Sleep diaries were completed daily and returned at the end of each 2-wk cycle. Sleep data were also collected on 3 occasions by telephone during each week of the study including the washout period.

Secondary Outcomes

The secondary outcomes were pain, mood, quality of life, global satisfaction with treatment, and AEs. Pain was measured with the McGill Pain Questionnaire, a widely used and validated instrument frequently used in clinical trials of analgesic medications.[23] Mood was assessed using the short-form Profile of Mood States.[24] Quality of life was assessed using the Fibromyalgia Impact Questionnaire, a validated and disease-specific questionnaire for FM.[25] Patient global satisfaction was assessed using the question "Would you wish to continue with this medication?" (Y/N). Data on pain, mood, quality of life, and satisfaction were collected on Days 1 and 14 of each treatment cycle. At the end of the third and last washout phase, patients were asked to give their preference (if any) for 1 of the study

medications. Vital signs were recorded at each clinic visit. AEs were recorded throughout the study.

Urine samples were obtained at the screening visit and on Days 1 and 14 of each treatment cycle and tested by semiquantitative assay for the principal urinary metabolite (9-COOH-THC) of tetrahydrocannabinol (THC) to ensure that no other cannabinoid was used during the study.

Sample Size Estimation

The LSEQ has demonstrated differences in sleep quality from baseline of >1.5 on a 10-cm scale with samples of 30 subjects or fewer.[22] An equivalence study comparing the analgesic efficacy of amitriptyline with gabapentin concluded equivalence with 24 subjects. There are no specific data on sleep scores after amitriptyline therapy. We therefore estimated that a sample of 30 subjects would be sufficient to conclude equivalence based on within-subject SD of 1.0 around the primary outcome, because this would provide a confidence interval (CI) width for the between-treatment difference of approximately ±0.7 on the LSEQ scale. To account for a dropout rate of up to 25%, we aimed to recruit 40 subjects for this trial for a final sample size of at least 30 subjects. No interim analyses were planned.

Randomization

The randomization schedule was prepared (ralloc procedure, Stata version 8.0, Houston, TX) using randomly assigned block sizes ranging from 2 to 8. The schedule was kept by the study pharmacist away from the investigators. Study subjects were consecutively assigned to treatment order by the study nurse based on the randomization schedule. A coded script was given to the subject with instructions on the use of the allocated treatment. The subject then collected the medication from the study pharmacy and began taking the medication the same night.

Blinding

The study physician, study nurse, and subjects were blinded to the allocated treatment order. At the end of the study, the subjects were asked to estimate the order of allocated drugs as a means of estimating the success of blinding.

Statistical Analyses

The principal hypothesis for this study was that nabilone at a dose of 0.5–1 mg is equivalent to amitriptyline at a dose of 10–20 mg in improving sleep quality in patients with FM. The primary outcome of sleep quality was derived from the average scores obtained during the second week of each cycle of the ISI and of the sleep quality items (questions 4 and 5 on restfulness and wakefulness, respectively) from the LSEQ. The sleep scores during nabilone therapy were compared with those during amitriptyline using CIs of the within-subject difference in scores. Regression models were created with treatment, period, and
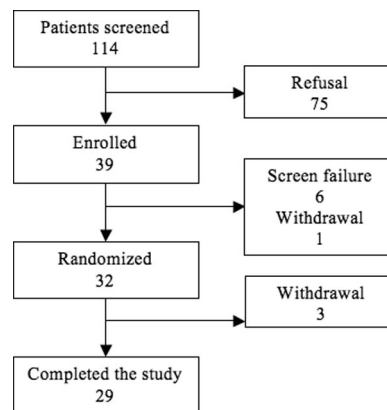

Figure 1. Trial flow diagram.

Table 1. Baseline Demographic Characteristics of Trial Participants ($n = 32$)

Characteristic	
Mean age (SD), range (yr)	49.5 (11.2), 26–76
Gender	
Female	26
Male	5
Education level attained	
University/college	25
Secondary/high school	6
Primary/elementary	1
Employment status	
Full time employed	12
Retired	6
Long term disability	4
Short term disability	4
Part time employed	2
Home maker	2
Other	2

order as terms in the model. Examination of treatment by period interactions was included to assess potential carryover effects. For inferences, 95% CIs were generated for all parameters. Secondary outcomes were assessed using similar procedures for each variable. AEs were tabulated by severity and study drug.

Ethics and Trial Registration

Ethics approval was obtained from the McGill University Health Centre Research Ethics Board; all subjects provided written informed consent. Approval to use the study drugs was obtained through a Clinical Trial Application to the Therapeutic Products Directorate of Health Canada (Clinical Trial Application number 099547). The trial was conducted following Good Clinical Practice guidelines and was registered at www.clinicaltrials.gov (registration number NCT00381199).

RESULTS

One hundred fourteen subjects were screened, 39 were enrolled, and 32 were recruited and randomized to study drug (Fig. 1). Enrollment began in August 2005 and the last enrolled subject completed follow-up

Table 2. Baseline Self-Reported Symptom Data for Study Participants (n = 32)

Variable	Mean	SD
Insomnia severity index	18.3	5.2
McGill pain questionnaire		
Present pain intensity (PPI)	2.3	0.8
Sensory	15.8	9.0
Affective	4.7	3.1
Evaluative	2.3	1.3
Miscellaneous	6.0	3.0
Fibromyalgia impact questionnaire total score	62.6	15.2
Rested	81.6	15.3
Fatigue	80.5	20.2
Stiffness	74.5	19.5
Pain	69.3	20.5
Do work	66.4	25.1
Anxiety	51.6	30.1
Depression	37.5	32.5
Feel good	5.3	1.6
Physical impairment	1.4	0.8
Work missed	0.4	0.5
Profile of mood states total score	29.5	16.6
Fatigue	10.6	4.3
Tension/anxiety	7.3	3.7
Depression	5.8	4.4
Confusion	5.6	2.9
Anger	5.2	4.0
Vigor	4.6	3.3

Note the Leeds Sleep Evaluation Questionnaire is not measured at baseline because it requires a comparison with normal sleep.

in January 2007. Three subjects withdrew after randomization, 1 for noncompliance with study protocol, 1 for lack of effect, and 1 because of side effects after a single dose (edema of arms and legs, decreased concentration, dizziness, nausea, hyper-alert state, and insomnia). Twenty-nine subjects completed the study per protocol; there were no dropouts. All randomized subjects' data were included in the safety analysis.

Of the 32 randomized subjects, 26 were women and 5 were men (1 missing data). The mean age was 49.5 yr (SD 11.2) with a range of 26–76 yr. Baseline demographic and clinical data of recruited subjects are shown in Tables 1 and 2. Five subjects were taking tricyclic antidepressants at screening (4 amitriptyline and 1 nortriptyline), and all successfully withdrew from these medications before randomization. No subject was taking cannabinoid medications at screening, and all baseline urine tests were negative for THC.

Primary Outcome

Although both drugs improved sleep, after controlling for period effects, nabilone was found to have a greater effect on sleep than amitriptyline on the ISI (adjusted difference = −3.25; CI, −5.26 to −1.24) (Fig. 2). Based on the LSEQ sleep quality outcomes, there was no evidence of superiority of either drug, although subjects had a more restful sleep taking nabilone compared with amitriptyline (difference = 0.48; CI, 0.01–0.95) (Fig. 3). There were no marked differences in other scales of the LSEQ between the 2 drugs, although there was a suggestion of nabilone performing better than amitriptyline for ease (difference = −0.7; CI, −1.4 to 0.02) and speed (difference = −0.7; CI, −1.36 to 0.03) of falling asleep.

Other Outcomes

No differences were noted between treatments for pain (McGill PPI difference = −0.1; 95% CI = −0.3 to 0.2; other scales of McGill Pain Questionnaire also not significant), mood (Profile of Mood States difference = 1.4; 95% CI = −4.3 to 7.2), or quality of life (Fibromyalgia Impact Questionnaire difference = −0.7; 95% CI = −7.3 to 5.8).

## Satisfaction and Preference

At the completion of the trial, preference for nabilone was reported by 41% (12 of 29) and for amitriptyline by 32% (9 of 28) of subjects (difference = 9%; 95% CI = −16% to 32%).
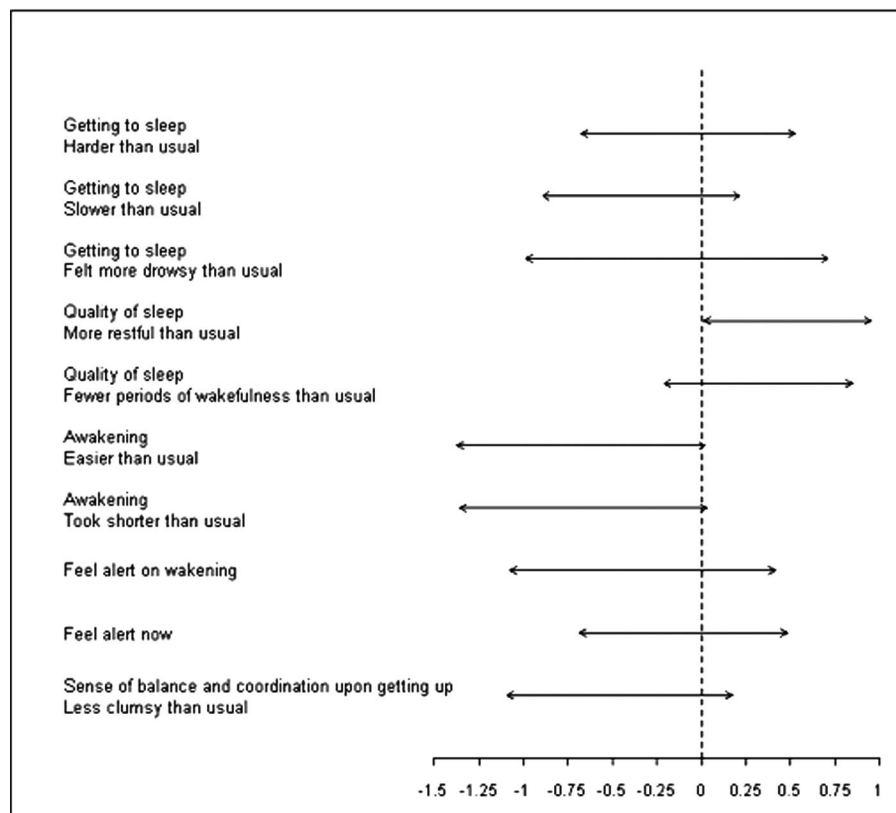
Dose Adjustment

The dose of amitriptyline was more frequently increased at 1 wk (26 of 28; 92%) compared with nabilone (21 of 29; 72%) (difference = 20%; 95% CI = −2%–43%).

Figure 2. Effects of nabilone and amitriptyline on the Insomnia Severity Index (ISI).

Insomnia severity index scores
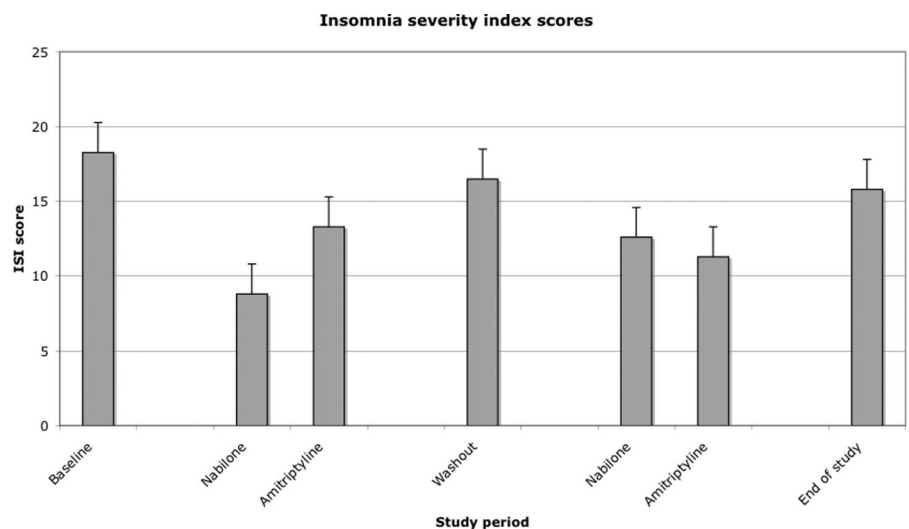
**Treatment Effect
[LSEQ]**

Figure 3. Treatment effects of nabilone compared with amitriptyline on sleep items in the Leeds Sleep Evaluation Questionnaire (LSEQ). Note that treatment effects shifted to the right favor nabilone, whereas effects shifted to the left favor amitriptyline. The x axis is the magnitude of the effect on a scale from 0 to 10. Shifts to the right represent improvements on the sleep subscales (shown on the y axis).

Table 3. Absolute Number of Adverse Events Occurring on >1 Occasion During the Trial

Description	Nabilone	Amitriptyline	Total
Dizziness	10	4	16
Headache	4	6	14
Nausea	9	1	14
Dry mouth	7	3	10
Drowsiness	6	1	7
Constipation	4	1	5
Diarrhea	2	2	4
Insomnia	3		3
Vomiting	3		3
Blurred vision	2	3	5
Fatigue	2	1	3
Cognitive impairment	2		2
Disorientation	2		2
Migraine	2		2

Discernment

When asked at the end of the study to guess which treatment had been administered, 8 subjects (29%) correctly identified the period in which they received amitriptyline, and 12 (41%) correctly identified the period in which they received nabilone.

Adverse Events

A total of 187 AEs were reported during the trial of which 120 were mild, 64 were moderate, and 3 severe. Of the 3 severe AEs, 2 occurred during amitriptyline therapy (headache and insomnia) and 1 occurred

during nabilone (drowsiness). No serious AEs occurred during the trial. Fifty-three AEs were deemed possibly or probably related to amitriptyline therapy, and 91 AEs were deemed possibly or probably related to nabilone therapy. The most common AEs reported for nabilone and amitriptyline are shown in Table 3. AEs occurring in >2 subjects, which were more common for nabilone, were dizziness (10 subjects), nausea (9), dry mouth (7), drowsiness (6), constipation (4), insomnia (3), and vomiting (3).

DISCUSSION

We have observed that both the synthetic cannabinoid nabilone and the tricyclic antidepressant amitriptyline had a favorable effect on sleep in patients with FM, with nabilone showing overall superiority to amitriptyline for sleep quality. The effects of nabilone on pain, mood, and quality of life were similar to those seen with amitriptyline. Adverse effects were more common with nabilone, particularly drowsiness and dizziness, although global satisfaction with both drugs was similar.

The effects of cannabinoids on sleep have been recognized for many years. The hypnotic effects of THC were evaluated in the 1970s, and it was shown that THC increased Stage 3 sleep and reduced REM sleep[26]; amitriptyline has not been found to have any effect on non-REM sleep in patients with FM.[27]

Researchers conducting clinical trials of cannabinoids for other chronic pain disorders have reported improved sleep as secondary outcomes.[28] Endogenous cannabinoids have also been postulated to have an effect on normal sleep induction.[29] To our knowledge, this is the first study to evaluate sleep as a primary outcome for a chronic noncancer pain condition.

Our study has several important strengths. First, because both drugs cause similar side effects (e.g., drowsiness and dry mouth), we postulated that amitriptyline would be a suitable active control for nabilone, and therefore would preserve the blinded nature of the trial. Our data on blinding suggest that blinding was preserved, suggesting that amitriptyline is a good active control for further trials of nabilone. Second, because amitriptyline is frequently used for promoting sleep in FM, and because we have observed improvement of sleep among subjects taking amitriptyline, we believe that the study has demonstrated internal and external validity and was sufficiently powered to show clinically meaningful sleep improvements. For these reasons, we believe that the effects of nabilone on sleep quality are valid.

There are a number of limitations to this study that require comment. First, because the exposure to each drug was for a single 2-wk period, we are unable to extrapolate any conclusions regarding the long-term safety and efficacy of nabilone for sleep disturbance in FM. Because FM is a chronic condition, favorable treatments will likely require prolonged administration. Second, because both study drugs were used in relatively low dosage, this may have influenced the final outcome either favorably for nabilone (if nabilone was more effective at lower doses) or unfavorably for amitriptyline (if amitriptyline was more effective at higher doses). Because no other equivalency studies have previously been conducted with these drugs, the selected doses of the study drugs were based on clinical experience. Further dose-finding studies, specifically for nabilone, may be needed to explore safety and efficacy if higher doses are to be considered.

The mainstay of management for FM remains a multidisciplinary treatment approach, which includes exercise, education, pharmacological interventions, and behavioral therapies.[17,30] Sleep disturbances in FM are associated with poor quality of life and function, and increased pain and fatigue.[31] Although nabilone has been shown to have analgesic effects on pain in FM,[19] the effects of nabilone on sleep have not hitherto been addressed in this population.

In conclusion, we report that the synthetic cannabinoid nabilone is an effective drug in promoting sleep in patients with FM who have chronic insomnia and may be superior to amitriptyline, which is currently widely used for this purpose. Further studies on the effects of nabilone on sleep architecture and long-term safety and efficacy in FM and other pain conditions are warranted.

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