The Journal of Pain, Vol 9, No 3 (March), 2008: pp 254-264
Available online at www.sciencedirect.com

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Efficacy of Dronabinol as an Adjuvant Treatment for Chronic Pain Patients on Opioid Therapy

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Abstract: We assessed the efficacy of dronabinol (Marinol capsules; Solvay Pharmaceuticals, Brussels, Belgium), a synthetic Δ^9-THC (tetrahydrocannabinol), in 30 patients taking opioids for chronic pain to determine its potential analgesic effects as an adjuvant treatment. Phase I of this 2-phase study was a randomized, single-dose, double-blinded, placebo-controlled, crossover trial in which subjects were randomly administered either 10 mg or 20 mg of dronabinol or identical placebo capsules over the course of three, 8-hour visits. Baseline self-report measures, hourly ratings of pain intensity, pain relief, pain bothersomeness, treatment satisfaction, mood, side effects, and blood serum levels were obtained. Phase II was an extended open-label titrated trial of dronabinol as add-on medication to patients on stable doses of opioids. Results of the Phase I study showed that patients who received dronabinol experienced decreased pain intensity and increased satisfaction compared with placebo. No differences in benefit were found between the 20 mg and 10 mg doses. In the Phase II trial, titrated dronabinol contributed to significant relief of pain, reduced pain bothersomeness, and increased satisfaction compared with baseline. The incidence of side effects was dose-related. Overall, the use of dronabinol was found to result in additional analgesia among patients taking opioids for chronic noncancer pain.

***Perspective:** This study examines the effect of adding a cannabinoid to the regimen of patients with chronic pain who report significant pain despite taking stable doses of opioids. The results of our preliminary study suggest that dronabinol, a synthetic THC, may have an additive effect on pain relief.*

***Key words:** Chronic pain, Marinol, dronabinol, cannabinoids, endocannabinoids, opioids.*

Although the use of opioids in the treatment of chronic cancer and noncancer pain has grown, there is a limit to the efficacy of these drugs, and there has been considerable interest in investigating other compounds to help control pain. Clinicians treating chronic noncancer pain with opioids often note that some patients report a modest benefit from the medication but still experience moderate to severe pain. Studies of random urine screens among patients with chronic noncancer pain demonstrate that marijuana is the 1 illicit substance detected most often in the urine.[13,30] Although this is a troubling finding among prescribing physicians, this may also reflect an efficacious property of cannabinoids to potentiate opioid analgesia.

The identification of cannabinoid receptors in mammals has triggered studies exploring the endocannabinoid system in treating a number of health conditions.[36,50] Exogenous cannabinoids in humans have been found to be useful in treating symptoms of Parkinson's and Huntington's disease,[35] multiple sclerosis,[39,48,49,55] myocardial infarction, stoke, and hypertension.[35] Another area of study is use of cannabinoids for treatment of persistent pain.[1,26,47] Cannabinoids are known to have important pain-modulating effects.[25] Cannabinoid receptors are highly localized in brain sites that subserve analgesia,[28] and cannabinoids have been shown to reduce hypersensitivity associated with neuropathic pain in rats.[18] Cannabinoids also appear to have peripheral

Received August 20, 2007; Revised October 16, 2007; Accepted October 26, 2007.

Supported in part by an investigator-initiated grant from Solvay Pharmaceuticals, Inc.

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1526-5900/$34.00

doi:10.1016/j.jpain.2007.10.018

pain-modulation effects in these animals.[21] Other recent animal studies have found a synergistic interaction between cannabinoids and opioids, although the translation of the results of animal studies cannot always be applied to clinical pain in humans.[8,46]

Despite the controversy related to cannabinoid use due to its association with substance abuse disorders, a large body of anecdotal data points toward the possible pain-relieving properties of cannabinoids in humans.[53] In a recent survey of patients with chronic noncancer pain, 34.5% of responders admitted to have used cannabis, and 44% of these reported using it for pain relief.[52] In an earlier study, treatment of chronic pain was the second most common medical use of marijuana after nausea and vomiting.[25] Several case series show that patients frequently cite pain relief as a consequence of marijuana use.[11] However, until recently, few well-designed studies with humans existed.[5,20,44] It is known that opioids are helpful in controlling chronic neuropathic pain[26] and pain due to multiple sclerosis,[55] but limitations exist due to tolerance and the adverse effects of these drugs.[25] An Institute of Medicine report suggested that cannabis might be a useful modality to treat pain if it has synergistic interactions with opioid analgesics or if its use improves the efficacy of pain treatment in patients with a tolerance to opioids.[25]

The aim of this preliminary investigation is to examine the analgesic effects of cannabinoids among patients with chronic noncancer pain who report moderate to severe pain while taking stable doses of opioids. We designed a controlled trial comparing 2 single doses of dronabinol (Marinol; Solvay Pharmaceuticals, Brussels, Belgium) with placebo and an open-label, multidose extension. We hoped to understand whether patients taking adjuvant dronabinol would demonstrate significant reductions in pain and improvements in sleep and mood over placebo and whether the side effects of higher doses of dronabinol would outweigh the benefits in pain control compared with lower doses in an open trial.

Materials and Methods

Patient Selection

The Hospital Human Research Committee approved this study. Subjects were recruited through Brigham and Women's Hospital and other affiliated teaching hospitals of Harvard Medical School. Permission to enroll subjects was obtained from their treating physicians and all subjects gave written informed consent. Patients with chronic noncancer pain were included in this study if they were taking stable doses of opioid analgesics for longer than 6 months and reported pain of at least 4 on a 0 to 10 numeric rating scale. Female patients with reproductive capacity were eligible if they agreed to use birth control measures during the study and had negative urine pregnancy tests. Patients who admitted to using marijuana in the past were required to abstain for 1 month before participation in the study, although no formal testing was done to evaluate ongoing marijuana use. Subjects were excluded from this study if they had (1) pain due to cancer, (2) been using a transdermal fentanyl patch or intrathecally administered opioid treatment, because subjects would not be able to easily titrate their opioid dose during the trial, (3) required opioid dosing more frequently than every 8 hours, (4) an unstable psychiatric disorder per investigator judgment, (5) current substance abuse by self-report, (6) involvement in active litigation, compensation, or disability issues, or (7) significant depression and/or anxiety (scores higher than 11 on the Hospital Anxiety and Depression Scale).[56]

Procedures

The research design includes 2 studies; a double-blinded, randomized, placebo-controlled, single-dose study (Phase I) followed by an open-label, multidose extension study (Phase II; Fig 1). At a subject's first visit, enrollment criteria were verified, informed consent was obtained, and a history and physical examination was performed. At this time, baseline questionnaires were

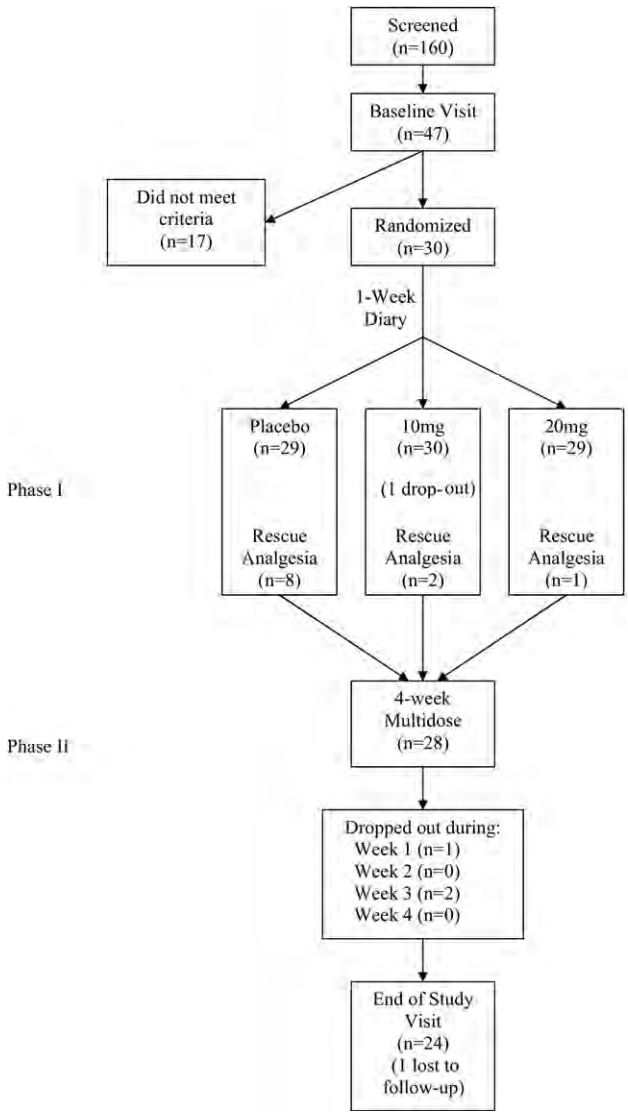

Figure 1. Research design and schema for the single-dose, blinded Study I and multidose, open-label Phase II trials.

administered and a urine pregnancy test was done, if indicated. To better assess functional change as an outcome measure, the concept of evoked pain was introduced to the subjects. This was defined as a movement, action, or position that caused a transient increase in pain, lasting for not more than 10 to 15 minutes. It was explained as an optional study procedure, useful for the purpose of the study but not mandatory.

Subjects who met enrollment criteria and were willing to participate in the study were given a 1-week paper diary and were asked to record their usual pain, the amount of pain relief, and the extent of pain bothersomeness on a daily basis before presenting for their first treatment visit. The diary also tracked their medication use and their satisfaction with their current regimen of pain management. A history and medical examination were completed during the baseline visit to ensure the suitability of the entering subjects. Height, weight, and vital signs (pulse, sitting blood pressure, and temperature) were also recorded at baseline and at the end-of-study visit. During all treatment visits, vital signs were recorded at hourly intervals. Adverse events were reported according to Institutional Review Board policy. The Investigational Drug Service (IDS) Pharmacy of the hospital generated the randomization scheme (www.randomization.com). Study personnel and subjects were blinded until all the subjects had completed the Phase I trial. Serum samples were sent for analysis after all subjects had completed Phase I and results were not examined until the subjects had finished both phases of the study.

Phase I Double-Blinded, Single-Dose Design

The single-dose phase was a double-blinded, randomized, 3-treatment, 3-period, crossover trial. Subjects each received identically appearing placebo, 10 mg or 20 mg dronabinol capsules in 1 of 6 randomly allocated sequences (Fig 1). The 3 treatment visits were separated by a minimum of 3 days between each visit. Subjects were asked to reschedule their study visit if their pain was less than 4/10 on the morning of the anticipated treatment. Subjects were instructed to fast, except for clear liquids, and abstain from taking their usual pain medications on the morning of each treatment. On arrival, subjects answered questions about their pain and satisfaction levels, completed a set of questionnaires, and had blood drawn. In addition, blood was drawn 4 and 8 hours after receiving the study drug. Subjects then received the study drug together with the morning dose of their regular prescribed opioid medication. Subsequently, they had breakfast and answered questions about their pain and satisfaction levels every hour for 8 hours. At the completion of each treatment session, subjects completed an assessment to evaluate blinding and recorded their satisfaction with the treatment of their pain. The use of breakthrough pain medication was allowed during the 8-hour study period; however, further study measurements were stopped once breakthrough medication was taken. At that time, subjects were observed to ensure that they achieved adequate relief of their pain and then discharged home. Three treatment sessions, using placebo, 10 mg of dronabinol, or 20 mg of dronabinol, were conducted for each subject. Subjects who participated in this trial were compensated $75 for participating in each Phase I treatment session. At the end of the third treatment session of Phase I, subjects were offered entry into the 4-week, open-label extension (Phase II).

Table 1. Stepwise Multidose Dronabinol Regimens

Dosage Level	AM Dose	PM Dose	Nighttime Dose
Level 1	–NIL–	–NIL–	5 mg
Level 2	5 mg	–NIL–	5 mg
Level 3	5 mg	5 mg	5 mg
Level 4	10 mg	5 mg	10 mg
Level 5	10 mg	10 mg	10 mg
Level 6	20 mg	20 mg	20 mg

Phase II Open-Label Multidose Design

Subjects who chose to enter the open-label extension were given a 4-week prescription of dronabinol. They were instructed in a stepwise dosage schedule (Table 1). The starting dose was 5 mg twice a day, but subjects could take as little as 5 mg once a day and as much as 20 mg 3 times a day. Subjects were allowed to titrate upward after having been on a particular dose level for a minimum of 2 days. Subjects could reduce their dose at any time if they experienced severe adverse effects. Subjects were asked to maintain a stable dronabinol regimen during the last week of the study. The subjects were instructed to complete a daily diary at the same time each day during the 4 weeks detailing their level of pain intensity and amount of pain relief on a 0 to 10 numeric rating scale. The study manager monitored compliance. The amount of dronabinol used and the amount and type of opioid pain medication taken were also recorded daily.

Subjects could reduce their opioid intake during Phase II if their pain improved while taking dronabinol. Subjects were contacted by telephone at the end of each week and were asked about any adverse events or side effects. Dose adjustments were made if needed and the subjects were encouraged to complete their study diaries. By the end of the fourth week of Phase II, all subjects, including those who withdrew from the study early, were scheduled for a final end-of-study visit. This included a review of the subject's medication use, a history and physical examination, and the same assessment battery used in the baseline visit. Subjects who desired to continue taking dronabinol were referred back to their treating physician for further treatment.

Measurement Tools

Baseline and study diary levels of pain intensity were assessed on a numeric rating scale from 0 = no pain to 10 = worse pain imaginable. Pain relief was assessed on a scale from 0 = no relief to 10 = complete relief, and

pain bothersomeness was assessed on a 5-point categorical scale from 0 = not at all bothersome to 4 = extremely bothersome. Subjects also rated their degree of satisfaction on an 11-point scale from 0 = completely unsatisfied to 10 = completely satisfied.

Subjects were asked to complete a battery of pain and quality-of-life measures during their participation in this study. The following 5 questionnaires were administered during the first visit of Phase I of the study and at the final visit at the completion of Phase II of the study: Brief Pain Inventory-Short Form (BPI),[9] Hospital Anxiety and Depression Scale (HADS),[56] Symptom Checklist, RAND 36-Item Health Survey, and the Medical Outcomes Study (MOS) Sleep Scale.

The BPI is a well-known, self-report, multidimensional pain questionnaire. The BPI provides information about pain history, intensity, and location as well as the degree to which the pain interferes with daily activities, mood, and influences enjoyment of life. Scales (rated from 0–10) indicate the intensity of pain at its worst, at its least, average, and pain "right now." Test-retest reliability for the BPI reveals correlations of .93 for worst pain, .78 for usual pain, and .59 for pain now. Research suggests the BPI has adequate validity and has been adopted in many countries for clinical pain assessment and in studies of the effectiveness of pain treatment. Although originally developed to assess cancer pain, the BPI has been validated for use for patients with chronic noncancer pain.[45]

The Hospital Anxiety and Depression Scale is a 14-item, self-report questionnaire constructed to measure comorbid depression and generalized anxiety. It was developed for use in patient populations with physical illnesses. Subjects are asked to choose 1 of 4 responses on each item. The HADS has been shown to have good psychometric properties in a variety of medical populations, in terms of factor structure, subscale intercorrelation, homogeneity, and internal consistency.[4,31] Cronbach's α for the HADS anxiety and depression scales average .83 and .82, respectively, and elevated scores have a high sensitivity and specificity for a DSM-IV Major Depression or Generalized Anxiety Disorder.[4]

The 29-item symptom Side Effect Checklist[24] was used to evaluate the presence or absence of side effects pertaining to different systems of the body. It was adapted from the original Side Effect Checklist[23] and expanded to include known side effects of dronabinol and of nonsteroidal anti-inflammatory drugs. All items are presented as a checklist, the symptom being either present or absent.

The RAND 36-Item Health Survey[51] is a 36-item questionnaire that measures 8 health-related domains: Physical functioning, role-physical (role limitations due to physical impairments), bodily pain, role-emotional (role limitations due to personal or emotional problems), mental health, social functioning, vitality/fatigue, and general health. Higher scores on the RAND represent a more favorable health status. It is scored using the RAND method, which uses the same items as the MOS SF-36,[29] but with simplified algorithms for scoring the bodily pain and general health subscales. Validation studies conducted with data from the MOS have shown that the RAND and MOS scoring methods produce equivalent forms of these 2 subscales (r = .99).[14,15] The value of the RAND is that it allows comparisons of quality of life experienced by people with chronic illnesses with healthy adults. To do this, raw scores are converted to standardized T-scores (mean = 50, SD = 10) using US general population norms reported in the test manual.[51] Accordingly, a score of 50 represents the national average for healthy adults, whereas a score of 40 is 1 standard deviation below the national norm.

The MOS Sleep Scale[16] is a 12-item self-report sleep measure that has been evaluated extensively among individuals with chronic illness. The MOS Sleep Scale has shown good psychometric properties, with adequate test-retest reliability (r = .79–.91) and internal consistency (Cronbach's α, .64–.87). The MOS Sleep Scale was found to be responsive to change in clinical trials and found to be particularly useful in patients with neuropathic pain.[38]

All patients consented to give blood samples periodically during the Phase I trials. Approximately 3 mL of blood was taken from each subject and centrifuged to obtain serum, which was preserved at −20°C. When all samples had been collected, they were sent to RTI International laboratories (www.rti.org) for analysis. Levels of tetrahydrocannabinol (THC) were quantified by using radioimmunoassay with a lower limit of detection of 2.5 ng/mL.[12] This measure would help to determine the presence or absence of sufficient drug levels to affect pain. The National Institute of Drug Abuse (NIDA) arranged for the analysis of the serum THC levels.

Outcome Measures

In the single-dose Phase I part of the trial, the primary outcome measure was Total Pain Relief at 8 hours (TOTPAR). To calculate TOTPAR, integral relief scores ranging from 0 = no relief of pain to 10 = complete relief of pain were summed. Subjects in Phase I were also evaluated for average pain intensity and for the sum of pain intensity difference (SPID) for 8 hours after receiving the test drug. In the multidose Phase II of the trial, the primary outcome measure was the change in pain intensity from baseline (average pain over last week), as measured on a numerical scale ranging from 0 = no pain to 10 = worst pain imaginable. For both Phases I and II, secondary outcome measures included patient satisfaction, side effects, dropout rate, adverse events, pain bothersomeness, changes in mood, changes in evoked pain (0–10), evaluation of subject blinding, and plasma levels of THC. Other covariates that were analyzed included previous marijuana use, baseline HADS score, opioid use (morphine equivalent), pain type, pain location, pain duration, and duration of opioid treatment. Finally, pre- and post-study scores for the BPI, RAND-36, and MOS scales were also examined for statistical significance.

Statistical Analysis

All data were analyzed with SPSS (Statistical Package for the Social Sciences, v 13.0; Chicago, IL). For Phase I

of the study, fixed-effects regression was used to assess longitudinal drug-related change in TOTPAR as a primary measurement of dronabinol efficacy. For Phase II, additional fixed-effects regression models were used to assess reported pain scores from baseline and to assess secondary outcome measurements (Pain intensity differences, SPID; evoked pain differences, ESPID; changes in mood, HADS; and satisfaction). Frequency of each side effect on the Symptom Checklist was assessed using McNemar's exact test. Paired *t* tests were calculated for baseline versus end-of-study scores for HADS, vital signs, BPI, RAND-36, and MOS Sleep Scale measurements. Previous marijuana use was compared with patients' estimated dronabinol dose to assess the study's blinding using Fisher's exact test. Ancillary comparisons of potential covariates (baseline HADs, pain type, previous marijuana use, and morphine equivalence units) and primary outcomes were assessed with Fisher's exact tests or Pearson's correlations as appropriate. All statistical tests were considered significant at a 2-tailed α of 0.05. Missing time-series data (for time points after a rescue dose) were accommodated using a last point carried forward technique, which on average should be biased toward the absence of effect. All analyses were also replicated by using all available observations without imputation.

Results

One hundred sixty (N = 160) subjects were screened for enrollment via telephone (Fig 1). Of these, 47 met preliminary inclusion criteria and presented for a baseline visit. Thirty subjects met final enrollment criteria and began participation in the study. Of the 30 subjects who started the single-dose, blinded phase of the study, 29 subjects completed the study. One subject completed only the first treatment of Phase I and dropped out of the study due to a reported inability to concentrate.

Twenty-eight subjects entered the open-label multidose phase. One subject did not qualify to enter the Phase II trial because she had discontinued opioid therapy. One subject dropped out after 1 day, stating the medication precipitated migraine headaches. Two additional subjects dropped out during week 3: One had a flare-up of regular pain unrelated to the study and the other stopped because of side effects. One subject was lost to follow-up. Eventually, of the 28 who began, 27 were seen for an end-of-study visit, and 24 successfully completed the multidose Phase II trial.

The original 30 subjects were classified as having neuropathic (N = 7), nociceptive (N = 7), mixed neuropathic and nociceptive (N = 11), and uncategorized (N = 5) pain. Fifty-seven percent had had back or neck surgery, and most subjects had chronic pain in more than one location. Low back pain (66.7%) was most common, and other pain locations included lower extremity (46.7%), cervical (43.3%), abdominal/pelvic (43.3%), shoulder (36.7%), upper extremity (10.0%), and head (2.0 %). Other patient demographic and descriptive characteristics are presented in Table 2.

Table 2. Patient Demographic and Descriptive Characteristics (N = 30)

Variable	
Age (median)	43.5 (±11.8; range, 21–67)
Gender (% female)	53.3
Race (% Caucasian)	96.7
Pain site (% low back)	66.7
Pain duration (% >5 y)	66.7
Opioid duration (% >2 y)	70.0
Morphine equivalent (oral mg/d)	68.1 (SD = 57.2; range, 7.5–228)
Current opioid medication (% of subjects)	
RTC	
Methadone	30.0
Morphine – long-acting	30.0
Oxycodone – long-acting	16.7
PRN	36.7
Oxycodone – short-acting	36.7
Morphine – short-acting	16.7
Hydrocodone	6.7
Hydromorphone	6.7
Baseline levels:	
Prestudy Diary (0–10)	
Pain Intensity	6.9 (±1.3)
Pain Relief	3.9 (±1.7)
Pain Bothersomeness (0–4)	2.7 (±0.6)
Satisfaction baseline (0–10)	3.7 (±2.0)
Brief Pain Inventory (0–0)	
Interference with Sleep	6.7 (±3.2)
RAND-36 (0–100)	
Energy/Fatigue	37.1 (±20.8)
Pain	26.6 (±15.2)
Social Functioning	47.8 (±24.6)
MOS Sleep Scale (0–100)	
Sleep Disturbance	59.7 (±27.7)
Sleep Problems I	48.3 (±17.5)
Sleep Problems II	51.9 (±17.6)
Sleep Adequacy	32.7 (±27.7)
HADS	
Anxiety	6.7 (±2.9)
Depression	6.0 (±3.3)

Abbreviations: RTC, return to clinic; PRN, as needed; RAND-36, RAND 36-Health Survey; MOS, Medical Outcomes Study; HADS, Hospital Anxiety and Depression Scale.

Forty-seven percent of the subjects were prescribed more than 1 type of opioid medication. Most (75%) were prescribed both long- and short-acting opioid medication and had been taking opioids for more than 2 years. The median morphine equivalent dose per day was 47.5 mg, with a range from 7.5 mg to 228.0 mg. Nineteen subjects (63.3%) admitted to using marijuana in the past, 8 of whom had used it within the last year. All subjects were required to abstain from use for 1 month before and during enrollment.

Phase I Results

In the single-dose Phase I trial, 8 subjects took a rescue opioid dose: One subject took a rescue dose in all 3 treatments (placebo, 10 mg dronabinol, and 20 mg dronabinol), 1 subject on both placebo and low-dose treatments,

Table 3. Results of Phase I Trial (Single-Dose Dronabinol Versus Placebo)

Variables	Placebo	10 mg Dronabinol	20 mg Dronabinol
Total pain relief (TOTPAR)	31.1	39.7*	41.7†
Pain intensity difference (SPID)	−6.4	−17.4†	−19.7†
Evoked pain differences (ESPID)	−9.6	−18.7*	−18.1*
Pain Bothersomeness (sum)	17.2	13.2†	11.6†
Anxiety (SPID)	−5.2	−7.8	−1.5
Depression (SPID)	−2.0	−6.2	−4.0
Irritability (SPID)	−2.2	−10.7	−6.5
Global Satisfaction	3.9	5.9*	5.9*

Abbreviations: TOTPAR, total pain relief; SPID, sum of pain intensity difference; ESPID, evoked pain differences.

*Significant from placebo at $P < .05$.

†Significant from placebo at $P < .01$.

and 6 subjects during their placebo treatment day only. Five percent of all relief scores were missing mostly due to rescue doses in the placebo treatment (two-thirds of all missing points).

Total pain relief at 8 hours (TOTPAR) in Phase I was found to be significantly greater in subjects receiving both the 20 mg and 10 mg dronabinol treatments compared with placebo (20 mg vs placebo at $P < .01$, 10 mg vs placebo at $P < .05$; Table 3 and Fig 2). An analysis of group effect (order of treatment) was calculated, and no significant order-of-treatment effect was found. Significant differences were also found in the single-dose Phase I trial in the SPID for subjects receiving dronabinol 10 mg versus placebo and dronabinol 20 mg versus placebo ($P < .05$; Table 3). In the measure of evoked pain (ESPID), a significant decrease in pain was found in subjects receiving 10 mg and 20 mg dronabinol versus placebo, but there was no difference in evoked pain relief between subjects receiving the 10 mg and 20 mg doses (Table 3). Significant differences were found between the 2 treatment arms and placebo on average hourly pain relief (Fig 3) and average pain intensity (Fig 4). No significant differences in anxiety, depression, or irritability levels were found in the treatment groups when compared with the placebo group. Blood plasma levels of THC were generally higher in subjects after taking the higher dose of dronabinol. However, 5 subjects did not have detectable THC in their system on 1 of the days they took dronabinol. One subject had no detectable serum THC on any of the study dates in spite of

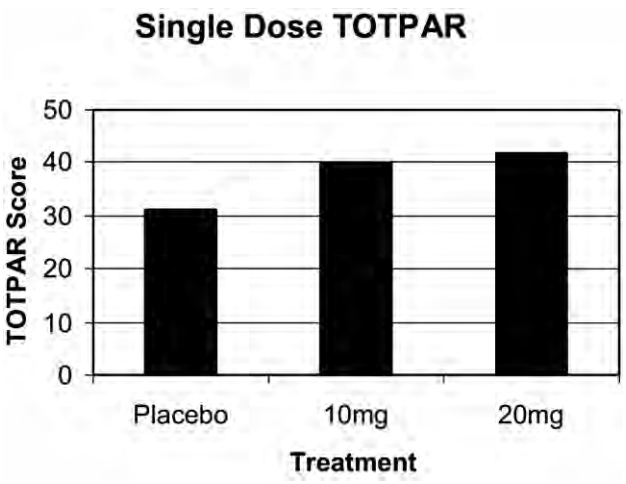

Figure 2. Phase I comparisons of pain intensity differences (TOTPAR) with 10 mg and 20 mg dronabinol compared with placebo ($P < .05$ and $P < .01$).

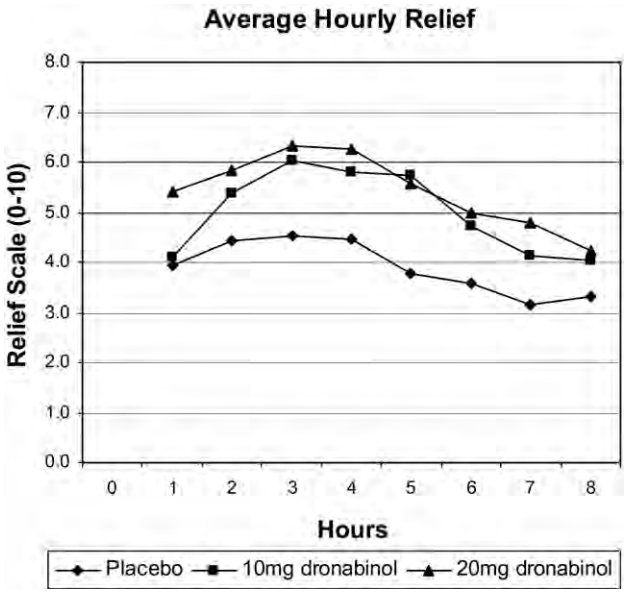

Figure 3. Average hourly pain relief in subjects receiving either dronabinol (10 mg or 20 mg) or placebo (Phase I trial; $P < .01$).

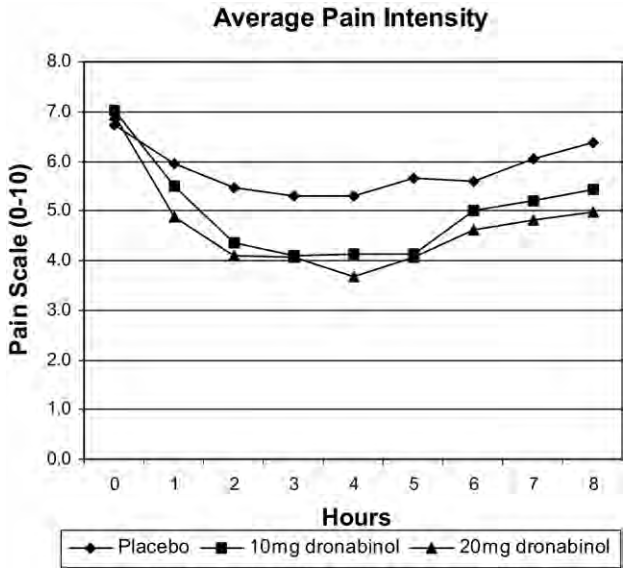

Figure 4. Average hourly pain intensity ratings for subjects receiving dronabinol or placebo (Phase I trial; $P < .001$).

Table 4. Incidence of Medication Side Effects During Phase I Trial (N = 30)

Side Effect	20 mg Dronabinol	10 mg Dronabinol	Placebo
Drowsiness	20	16	8
Sleepiness	16	12	10
Dizziness	15	14	1
Dry mouth	14	15	2
Confusion	12	3	1
Anxiety-nervousness	12	5	1
Change in vision	12	8	3
Tiredness	11	13	7
Euphoria	11	14	1
Abnormal thinking	11	7	1
Forgetfulness	10	12	1
Difficulty balancing	8	6	2
Eye irritation	8	5	1
Facial flushing	8	5	1
Difficulty speaking	7	9	0
Headache	7	6	1
Fast heartbeat	7	4	0
Upset stomach	6	5	1
Nausea	6	3	1
Ringing in the ears	6	4	0
Weakness	6	6	3
Itching	6	4	4
Depression	4	3	2
Sweating	3	5	4
Heartburn	2	1	0
Abdominal pain	2	0	1
Vomiting	0	1	0

receiving dronabinol, whereas 4 subjects had evidence of THC while receiving placebo.

Occurrence of side effects on the Symptom Checklist increased as the dose of dronabinol increased. The most frequent symptoms during the 20 mg treatment of Phase I were drowsiness, sleepiness, dizziness, and dry mouth (Table 4). All side effects subsided, on average, within 2 hours of dosing except for sleepiness and drowsiness, which lasted for 2.1 and 3.1 hours, respectively, in the subjects who received the 20 mg dose. The most frequently reported side effects of dronabinol during Phase II of the study were dry mouth, tiredness, sleepiness, and drowsiness (Table 5). Of these side effects, dry mouth, tiredness (both $P < .0001$), and drowsiness ($P < .05$) showed a significantly higher occurrence at the 20 mg dronabinol dose compared with placebo.

Certain adverse effects were significant only in the high-dose treatment versus the placebo and not significant in the high dose treatment versus the low-dose treatment or the low-dose treatment versus placebo. These were drowsiness, abnormal thinking, anxiety, facial flushing, eye irritation, headache, and ringing in the ears ($P < .05$). Similarly, other adverse effects were seen in both treatment arms versus placebo, such as dry mouth, difficulty speaking, forgetfulness, confusion, dizziness, and euphoria ($P < .01$).

On the 0 to 10 Satisfaction Scale, the mean scores for subjects receiving placebo, 10 mg of dronabinol, and 20 mg doses of dronabinol were 3.85, 5.93, and 5.93, respectively. Despite the side effects for each treatment, a statistically significant difference in satisfaction was found both between 20 mg and placebo and between 10 mg and placebo ($P < .01$). No distinguishable differences were found between the 20 mg and 10 mg doses.

At the end of each single-dose trial, the subjects were asked what dose of dronabinol they thought they received. Of the 88 total treatments, subjects guessed correctly 51 times (58.0%). Those who guessed correctly did not achieve significantly greater analgesia. Ten of 29 subjects thought they received an active dose when they actually received the placebo. Previous use of marijuana did not serve as an advantage in estimating dose; marijuana use within the past year actually increased the chances of misidentification of the 10 mg and 20 mg doses ($P < .05$). Compared with nonusers, those with a history of marijuana use did not have significantly greater analgesia at any dose or time point in either Phase I or II.

Pain duration was negatively correlated with TOTPAR levels (those patients with longer pain duration had lower TOTPAR levels, $P < .05$). Despite this effect, the

Table 5. Incidence of Medication Side Effects During Phase II Trial at Time of Weekly Phone Interview (N = 30)

Side Effect	Week 1 (N = 25)	Week 2 (N = 20)	Week 3 (N = 18)
Dry mouth	13	10	8
Tiredness	13	10	9
Sleepiness	13	7	6
Drowsiness	11	9	8
Anxiety/nervousness	8	4	4
Headache	5	5	4
Difficulty balancing	5	5	3
Dizziness	5	3	3
Abdominal pain	5	4	3
Nausea	5	1	1
Forgetfulness	4	2	2
Eye irritation	4	2	2
Weakness	4	2	2
Upset stomach	4	2	2
Diarrhea	4	1	2
Depression	3	4	2
Sweating	3	2	1
Ring in the ears	3	2	0
Euphoria	3	1	2
Itching	3	1	0
Fast heartbeat	2	2	1
Difficulty speaking	2	1	2
Abnormal thinking	2	1	1
Vomiting	2	1	1
Heartburn	2	0	1
Confusion	1	2	3
Facial flushing	1	2	2
Change in vision	1	0	1

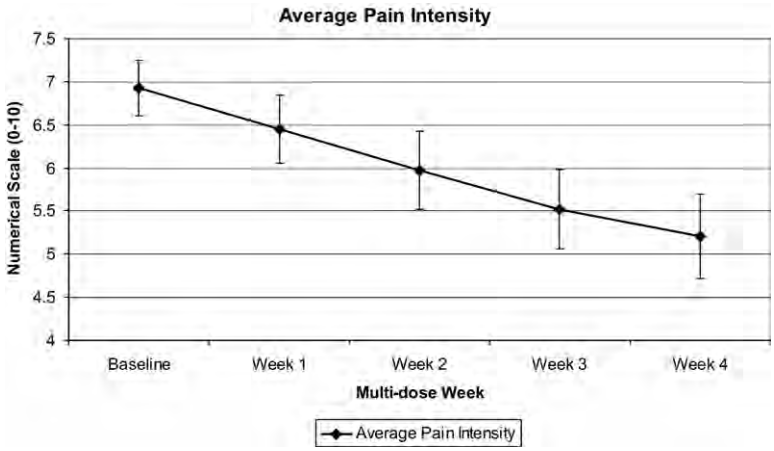

Figure 5. Average pain intensity ratings and standard error of measurement over the course of the 4-week open-label trial of dronabinol (Phase II trial).

treatment satisfaction ratings were significantly higher with active treatment versus placebo, regardless of pain duration ($P < .01$).

Phase II Results

In Phase II, there was a statistically significant decrease in average pain scores from baseline ($P < .001$; Fig 5). Although no significant changes comparing consecutive weeks were found, biweekly comparisons showed a significant reduction of pain for subjects taking dronabinol (baseline vs week 2, $P < .01$; week 1 vs week 3, $P < .05$; week 2 vs week 4, $P < .05$). There was also a significant change from baseline measures of pain, pain relief, bothersomeness, and satisfaction ($P < .01$). Pain relief and patient satisfaction increased from baseline to week 4 by 1.7 and 1.8 points, respectively, whereas bothersomeness decreased by 0.74.

Differences were examined between the initial and end of study scores. In the Brief Pain Inventory (BPI) question "How much does pain interfere with sleep," a significant decrease of 1.48 points ($P < .05$) was found. RAND-36 scores showed improvement by the end of the study in Energy/Fatigue, Pain, and Social Functioning ($P < .05$, $P < .01$, and $P < .01$, respectively). Baseline and end of study MOS Sleep Scale scores showed a decrease in sleep disturbance and sleep problems (Phases I and II; $P < .01$) and an increase in sleep adequacy ($P < .05$). No significant differences were found on the HADS.

Adverse Events

There were 2 adverse events during the study, both relating to heightened anxiety. One subject reported anxiety, tremors, dizziness, and inability to concentrate. The event resolved within 3 hours. The second adverse event occurred in a subject who reported high anxiety and dizziness that lasted for the duration of the treatment day. Both events occurred in subjects who received 20 mg of dronabinol. No one reported any psychosis or hallucinations.

Discussion

This preliminary study attempted to assess the effects of dronabinol as an adjuvant therapy for patients with chronic noncancer pain who are taking stable doses of opioids. The results of the single-dose Phase I trial demonstrated that pain relief was significantly greater in subjects who received either the 10 mg and 20 mg treatments compared with placebo. No differences in pain relief, however, were found between the 2 active treatments. Pain intensity and evoked pain (SPID and ESPID) were also significantly reduced in subjects who received active treatments compared with placebo. In the open-label Phase II trial, a significant decrease in pain scores was also found compared with baseline pain levels. Over the course of the 4-week, open-label trial, pain bothersomeness decreased, and pain relief and satisfaction significantly increased. The results imply that dronabinol may be a useful adjuvant analgesic for patients with persistent pain in spite of taking stable doses of opioids.

These positive results do not address the controversy about the long-term use of cannabinoids for pain, particularly as an adjunct medication for patients with noncancer pain on opioid therapy. Although cannabis has been used around the world for thousands of years for its medicinal properties, it is known that the use of THC among certain individuals can contribute to poor outcome and can trigger an addiction disorder. Results from the National Household Survey on Drug Abuse suggest that use of marijuana, particularly among youth, has a potential to lead to use of other illicit substances such as cocaine and heroin.[41] Also, there is some recent evidence that the chronic use of cannabis can contribute to psychosis,[7,17,42] particularly among individuals who had previously experienced psychotic symptoms and those at high genetic risk of developing schizophrenia. Although this study was not designed to address problems that may arise from the long-term use of THC, addiction and psychosis are known risk factors that must be considered before a cannabinoid can be offered as part of a treat-

ment regimen. Although subjects in this study were carefully screened, the findings of THC in the serum samples of subjects receiving placebo suggests possible illicit use of marijuana by some subjects. Since the prevalence of substance abuse disorders is high in a chronic pain population, potential candidates for cannabinoid therapy would need to be closely monitored and cautioned about its potential for abuse and addiction.[6]

Significant side effects, such as dry mouth and tiredness, were seen more frequently in active treatment groups, occurring most often with higher doses of dronabinol. The most frequent side effects reported in our study were also reported in other studies investigating cannabinoids.[3,22,32,40,44] Despite these side effects, subjects' overall satisfaction with treatment was significantly higher (54%) on active doses than placebo. In general, the number of occurrences of each side effect decreased with continued use of dronabinol (Phase II) compared with single-dose administration (Phase I). Unlike past studies, the results of our study showed no significant changes in mood (anxiety, depression, and irritability) either over the 8-hour Phase I period or during the Phase II trial. Reports of cognitive changes such as confusion and abnormal thinking were evident in the single dose trial but did not represent significant interference in the open-label multidose phase. Future studies would benefit from the use of formal neuropsychological evaluations of those patients taking THC as an additive therapy.

Patients with chronic pain typically experience sleep disturbances[2] and may experience more difficulties with sleep than patients with insomnia who do not have chronic pain.[54] The results of this study showed that sleep disturbances due to pain significantly decreased and sleep adequacy increased during prolonged use of dronabinol (Phase II). Twenty of the 30 subjects in this study had low back pain, and it has been shown that there is a significant correlation between pain intensity and sleep quality in patients with chronic low back pain.[27] These results suggest that dronabinol has a positive effect on sleep quality as well as pain.

The maintenance of placebo blinding in the single-dose trial was effective and did not seem to influence the results. At the end of each treatment, subjects recorded what dose of drug they thought they had received and the subjects were found to guess correctly a little better than chance (58%). At no dose level were the 19 former users of marijuana more able to identify active drug than were nonusers. In fact, at high doses there was a nonsignificant trend in the opposite direction (nonusers more accurately guessing their dosages). Some of this may be due to the fact that only 2 of the 19 previous users admitted to having used cannabis recently, and most reported having tried marijuana many years ago. Future studies, however, may consider including an active placebo with a similar side effect profile to dronabinol (eg, diphenhydramine) improving blinding.

The literature is mixed about the efficacy of cannabinoids for pain. In acute pain studies, Raft et al.[37] found no effect of THC on dental extraction pain. Jain et al[22] found that in 56 patients with severe postoperative or post-traumatic pain, levonantradol (a THC analog) was significantly more effective than placebo. In the chronic pain literature, the studies with cannabis have mostly included patients with cancer pain. Noyes et al[34] compared single doses of placebo and 5, 10, 15, and 20 mg of THC in 10 subjects with cancer pain and found that THC at 15 and 20 mg produced substantial analgesia, but at the expense of significant sedation and mental clouding. In a larger study, the same group found that THC had similar analgesic properties to codeine with similar side effects. The THC-treated patients, however, reported improved mood, sense of well-being, and less anxiety.[33] Two single-dose studies of a nitrogen analog of THC were conducted in patients with cancer pain. The THC analog was found to have analgesic properties when compared with the use of placebo, codeine, and secobarbital, but also had side effects.[43] No clinical trial has examined the long-term use of THC for chronic noncancer pain. Future studies need to examine whether the benefits and the side effects of THC among chronic pain patients change with prolonged use.

Endocannabinoid systems in the brain, spinal cord, and periphery have been shown to modulate pain processing. An extensive body of literature supports the efficacy of exogenously administered cannabinoids as analgesics in both animal and human models.[19] Injections of the cannabinoid receptor antagonist rimonabant in experimental animal studies have also been found to suppress environmentally induced antinociception.[10] Our study is the first clinical investigation to demonstrate the effectiveness of cannabinoids as useful adjuvants to opioids for chronic, noncancer pain.

There are a number of limitations in the design of this study that deserve mention. First, this is a preliminary study with a limited number of subjects of a heterogeneous pain patient population on various opioid doses. Although these subjects may reflect a typical clinical population in a pain medicine practice, studies of subjects with homogenous diagnoses taking the same opioid and followed for a longer period of time are needed. Future studies may also examine the usefulness of adjunctive dronabinol among cancer pain patients as a breakthrough medication. Second, many of the subjects were not naive to use of marijuana, and subjects were included only if they reported significant pain despite the use of opioids. We did not have a comparison group of chronic pain patients who were not taking opioids for pain. Future studies are needed to determine the effects of dronabinol on patients with chronic pain who do not have a history of exposure to opioids and THC. Also, adverse symptom measures that assess severity of each symptom should be used to investigate the effect of tolerance to THC over time. Third, lack of an active placebo may have contributed to expectations for treatment in Phase I. Also, the titrated-dose, open-label Phase II trial had no control group or crossover arm, making it difficult to determine whether the subjects' reduction in pain was due to dronabinol or due to the nonspecific effects of treatment. Fourth, the serum blood levels were ana-

lyzed by using radioimmunoassay rather than gas chromatography–mass spectrometry (GCMS), which may have resulted in false negative findings for THC. Finally, patients with high levels of anxiety and depression were excluded from this study, and further investigations are needed to determine the role of dronabinol on patients who have chronic pain and high levels of emotional distress.

Despite these limitations, the results of this preliminary study suggest that dronabinol may have additional analgesic efficacy among patients taking opioids for chronic noncancer pain. Although a number of side effects were reported, subjects were still more satisfied with their treatment while taking dronabinol than during placebo dosing. Subjects also showed improvements in quality of sleep. Although the use of cannabinoids is controversial, we believe that more research is needed to further evaluate the efficacy of THC as adjuvant therapy when treating chronic noncancer pain.

Acknowledgments

We would like to thank Margaret Beste, Margaret Daly, Alexandra Flynn, Evan Freiberg, Lauren Koranteng, Patricia McHugh, Biljana Miljanovic, and Rebecca Rosser for their invaluable contributions. Special thanks to Nathanial Katz, who had initial input in the design of this study. Nathanael Hevelone, MPH, Biostatistician, Department of Anesthesiology and Center for Surgery and Public Health, helped to make sense of the data. We appreciate the efforts of the pharmacists and staff of the Brigham and Women's Hospital Investigational Drug Service Pharmacy, and we would also like to thank the National Institute of Drug Abuse and RTI International for performing all blood serum analyses.

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