Original Article

Dronabinol as a Treatment for Anorexia Associated with Weight Loss in Patients with AIDS

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Abstract

The effects of dronabinol on appetite and weight were evaluated in 139 patients with AIDS-related anorexia and ≥2.3 kg weight loss in a multi-institutional study. Patients were randomized to receive 2.5 mg dronabinol twice daily or placebo. Patients rated appetite, mood, and nausea by using a 100-mm visual analogue scale 3 days weekly. Efficacy was evaluable in 88 patients. Dronabinol was associated with increased appetite above baseline (38% vs 8% for placebo, P = 0.015), improvement in mood (10% vs −2%, P = 0.06), and decreased nausea (20% vs 7%; P = 0.05). Weight was stable in dronabinol patients, while placebo recipients had a mean loss of 0.4 kg (P = 0.14). Of the dronabinol patients, 22% gained ≥2 kg, compared with 10.5% of placebo recipients (P = 0.11). Side effects were mostly mild to moderate in severity (euphoria, dizziness, thinking abnormalities); there was no difference in discontinued therapy between dronabinol (8.3%) and placebo (4.5%) recipients. Dronabinol was found to be safe and effective for anorexia associated with weight loss in patients with AIDS. J Pain Symptom Manage *1995;10:89–97.*

Key Words

Dronabinol, cachexia, urine cannabinoid–creatinine ratio

Introduction

Severe anorexia and wasting are common problems in patients with advanced human immunodeficiency virus (HIV) infection. Weight loss of >10% of body weight is the index diagnosis for almost one-fifth of AIDS cases.[1] In immunosuppressed patients, there are many possible etiologies for cachexia. Processes that result in intestinal malabsorption are common and can be secondary to gastrointestinal parasites (cryptosporidium or microsporidium), viruses (cytomegalovirus), neoplasms (Kaposi's sarcoma), or the pathogenic effects of HIV

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itself. Lesions of the buccal cavity or esophagus can make eating difficult and are caused by a number of opportunistic pathogens such as viruses of the herpes family or fungi, of which the most prominent is *Candida albicans.* Nausea and accompanying loss of appetite are important side effects of many chemotherapeutic agents frequently used clinically to manage patients with AIDS. In addition, metabolic disturbances, hypermetabolism, and elevated levels of certain cytokines such as tumor necrosis factor have all been associated with cachexia in the setting of HIV.[2,3] Maintaining appetite and normal body weight is an important clinical goal in the management of HIV infection. Death in some AIDS patients with cachexia has been linked to body cell mass depletion.[4,5] In addition, enhanced appetite can profoundly improve quality of life.

Preliminary investigations indicate that dronabinol (Marinol) may increase appetite and weight in patients infected with HIV.[6,7] In a pilot study of AIDS patients, dronabinol at a dose of 2.5 mg twice daily was found to enhance appetite and cause weight gain in six of eight patients. Higher doses were not as effective nor as well tolerated.[8] A lower dose, 2.5 mg daily, had been less effective than 2.5 mg twice daily in a pilot study.[9] Therefore, we endeavored to study the effects of dronabinol 2.5 mg twice daily on appetite, weight, mood, and nausea in patients with AIDS who had lost at least 2.3 kg of their normal body weight in a multicenter, randomized, double-blind, placebo-controlled trial.

Methods

Patients

Of 404 patients screened for participation, 221 (55%) were determined to be eligible. Of those who satisfied the selection requirements, 139 patients (63%) were enrolled. The protocol stipulated the following inclusion criteria: at least one AIDS-defining event according to the 1987 Center for Disease Control definition,[1] a loss of at least 2.3 kg from normal body weight, and ability to feed oneself and to consume a normal diet. Commercially available or investigational antiretrovirals were allowed if the patient had tolerated the medication for at least 4 weeks and was on the same dose for at least 2 weeks prior to the start of the baseline period. Patients presenting with any of the following were excluded: acute infections, diabetes mellitus, *Candida* esophagitis, ascites, pleural effusion, edema, uncontrolled diarrhea, dementia, and/or biliary, pancreatic, or gastrointestinal obstruction. Megestrol acetate, tube feedings, and corticosteroids were not allowed during the trial. Patients who had used marijuana within 30 days prior to beginning the trial were not eligible. Participants agreed not to use marijuana throughout the course of the trial.

Baseline characteristics were determined during a 4-day period before starting therapy. Patients underwent physical exam, ECG, Karnofsky performance evaluations, and T^{b4} analysis. Biweekly evaluations included weight, physical exam, and Karnofsky score. Hematology and chemistry profiles were obtained at baseline and day 42.

Study Design

The study was a multicenter, double-blind, placebo-controlled, parallel-group trial. Eighteen centers enrolled patients. Duration was 6 weeks, encompassing the baseline visit and three biweekly follow-up evaluations. The protocol was approved by the Investigational Review Board at each participating institution, and all patients provided written informed consent. Patients randomized to the treatment arm received capsules containing 2.5 mg dronabinol (Marinol) twice daily 1 hr before lunch and 1 hr before supper. Placebo recipients were given identical capsules containing no dronabinol to be taken according to the same schedule. Patients who could not tolerate the full dronabinol dose were eligible for rechallenge with a reduced dose of 2.5 mg once daily after toxicity resolved. Compliance was measured by capsule counts at each office visit and was calculated as the ratio of number of capsules taken to number of capsules required to be taken.

Measurements

The primary efficacy parameters in this study were change in appetite as measured by VAS and change in weight. Secondary measures of efficacy were changes in Karnofsky performance status score, as well as mood and nausea and vomiting as measured by VAS.

A 100-mm visual analogue scale (VAS) was used by patients to quantify levels of mood, appetite, and nausea at baseline and to assess changes during 3 days of the baseline period and 3 days weekly at home throughout the course of the trial. Patients were asked to reflect the degree of each parameter by recording a mark on a continuous 100-mm line with the 0 end representing no appetite, no nausea, and terrible mood, and 100 representing the opposites, respectively. On appropriate days, three hunger cards (one at each meal time) and one each for nausea and mood were completed. The mean VAS scores were calculated for the baseline period and for each 2-week on-study period. Changes were calculated by subtracting the mean score for the baseline period from that of each on-study period (days 0–14, 15–28, and 29–42). Change to end point was the difference between the last period in which the patient was evaluable and the baseline mean. Second-morning voiding urine samples were tested for urinary cannabinoids by using Abbott ADx fluorometric assay, and creatinine was measured in the same spot urine. Patients were evaluated for performance status according to the Karnofsky scale. A score of 100 represents normal activity, 50 represents the need for considerable assistance and frequent medical care, and 0 represents death.

Statistical Analysis

All statistical analyses for this study were performed using SAS version 6.06 (SAS Institute, Cary, NC, 1989). Means, medians, standard deviations, and minimum and maximum values were derived using the statistical procedure PROC UNIVARIATE. Each response (mood, appetite, and weight) was examined using an analysis of variance (ANOVA) linear model with factors site, treatment, and their interaction. No correction was made for the multiple time points tested. ANOVA techniques were carried out using the procedure PROC GLM, and the Cochran–Mantel–Haenszel-2 test was performed using the procedure PROC FREQ. Student's *t*-tests to investigate the significance from baseline were also performed using PROC UNIVARIATE.

Results

Study Patients

A total of 72 patients were randomized to receive dronabinol 2.5 mg twice a day, and 67 received matching placebo. Patient characteristics are listed in Table 1. Patients were randomized by center to treatment. There were no statistically significant differences in baseline characteristics between patients treated with dronabinol versus placebo. Gender, race, source of HIV infection, and prior marijuana use were analyzed for treatment differences by the Cochran–Mantel–Haenszel-2 test, adjusting for site. Of the trial participants, 93% were male and 78% were Caucasian; average age was 38.8 years (range, 22–64 years). Exposure to HIV was by homosexual contact for 87.5% of dronabinol and 80.6% of placebo-treated patients. There was a trend toward greater pretherapy rate of weight loss in all dronabinol patients, but not in those evaluable for efficacy. Actual and percent loss from usual body weight was well matched in the two groups with a mean weight loss of ~10 kg (13% of usual body weight). The mean initial T^{b4} cell count was 50 mm^3 in evaluable patients. There was a trend toward lower T^{b4} counts in all dronabinol as compared with placebo patients, but this was not seen in the evaluable patients. Mean T_4 cell count at baseline was 39 cells/mm^3 for patients randomized to dronabinol and 56 cells/mm^3 for those who received placebo ($P = 0.14$). Treatment groups were similar with respect to weight loss, duration of HIV symptoms, antiretroviral use, and prior marijuana use.

Patients were considered evaluable if they were observed for at least 4 weeks, took 75% of planned study medication (correcting for dose modification), and committed no major protocol violations. Of the 139 patients entered, 88 (63%) were evaluable; 50 (69%) of 72 were randomized to dronabinol, and 38 (57%) of 67 received placebo (difference NS). Table 2 lists reasons patients were considered unevaluable. The single most common reason for unevaluability was presence of cannabinoids in the urine of patients receiving placebo; this accounted for 10 of 13 on-study protocol violations in the placebo group. Nine of these 10 patients experienced a worsening of appetite during the course of the study despite presumed use of

Table 1
Patient Characteristics

	Dronabinol	Placebo	*P*
Patients *N*	72	67	
Age (years)			0.56
Mean ± SD	38.3 ±8.54	39.3 ± 7.79	
Gender *N* (%)			0.92
Male	67 (93.1)	62 (92.5)	
Female	5 (6.9)	5 (7.5)	
Race *N* (%)			0.76
Caucasian	59 (81.9)	50 (74.6)	
Black	4 (5.6)	6 (9.0)	
Hispanic	9 (12.5)	11 (16.4)	
Source of HIV *N* (%)			0.056
Homosexual contact	63 (87.5)	54 (80.6)	
Heterosexual contact	6 (8.3)	1 (1.5)	
IV drug abuser	1 (1.4)	3 (4.5)	
Transfusion	1 (1.4)	3 (4.5)	
Multiple sources	1 (1.4)	5 (7.5)	
Other	0 (0.0)	1 (1.5)	
Duration of HIV symptoms (months)			0.42
Mean ± SD	33.8 ± 21.0	30.8 ± 24.3	
Pretherapy loss from usual body weight (kg)			0.67
Mean ± SD	10.3 ± 5.3	9.5 ± 4.6	
Percent usual body weight			0.74
Mean ± SD	86.4 ± 5.8	87.2 ± 5.7	
Initial T_4 cell count			0.14
Mean ± SD	38.7 ± 67.2	55.9 ± 82.6	
Past marijuana use *N* (%)			0.35
None	30 (41.7)	32 (47.8)	
< Once monthly	19 (26.4)	16 (23.9)	
1–3 Times monthly	10 (13.9)	8 (11.9)	
≥4 Times monthly	13 (18.1)	11 (16.4)	

SD, standard deviation.

marijuana as indicated by the presence of cannabinoids in the urine. Only six patients (8.3%) receiving dronabinol and three (4.5%) receiving placebo discontinued treatment due to perceived drug toxicity (NS).

Efficacy

Evaluable patients treated with dronabinol experienced improvements in appetite and mood, decreased nausea, and stabilized weight. Improvement in appetite was statistically significant for all patients and for evaluable patients. Decrease in nausea was statistically significant in evaluable patients. There was a trend toward weight stabilization in evaluable patients randomized to dronabinol (+0.1 kg), while those in the placebo group continued to lose weight (–0.4 kg) (P = 0.14). Improvements in mood among evaluable patients who received treatment approached significance at end point (P = 0.06).

Appetite

As measured by VAS cards, there was a significant improvement in appetite for dronabinol-treated patients as compared with controls, both for all patients (P = 0.05), as well as for evaluables (P = 0.015); data for evaluable patients are shown in Figure 1. Appetite had increased slightly for both groups at day 14, but plateaued at that point for the placebo group, while it continued to increase in patients receiving dronabinol. For all patients, the mean increase in appetite from baseline to end point was 37% and 17% in the dronabinol and placebo groups, respectively (P = 0.05). The mean increase in appetite to end point for

Table 2
Patient Evaluability

	Dronabinol	Placebo	*P*
Patients *N*	72	67	
Patient considered evaluable for efficacy *N* (%)			
Yes	50 (69.4)	38 (56.7)	0.11
No	22 (30.6)	29 (43.3)	
If no, reason *N* (%)			
Entry criteria protocol violation	0 (0.0)	2 (3.0)	0.14
On-study protocol violation	1 (1.4)	13 (19.4)	0.001
Inadequate treatment: reason	21 (29.2)	14 (20.9)	0.26
Lost to follow-up	0 (0.0)	4 (6.0)	0.033
Refused further treatment	2 (2.8)	0 (0.0)	0.19
Toxicity	6 (8.3)	3 (4.5)	0.29
Intercurrent illness	4 (5.6)	3 (4.5)	0.80
Noncompliance with study medications	8(11.1)	3 (4.5)	0.17
Other	2 (2.8)	1 (1.5)	0.62
Duration of therapy (days)			
Median	43.0	43.0	0.929
Mean ± SD	35.2 ± 13.8	36.1 ± 12.6	

SD, standard deviation.

evaluable patients receiving dronabinol was 38% over baseline, compared with 8% for those receiving placebo ($P = 0.015$). Interestingly, in the 11 patients who, due to side effects, decreased their dose of dronabinol to 2.5 mg once daily, the appetite increase was the same as for those taking medication twice daily. The average increase in appetite was not related to CD4 count. The subgroup of patients with a mean baseline CD4 count of 2.3 cells/mm^3 (range, 0–10) on the lowest end of the spectrum had a mean VAS increase of +16 mm.

The subgroup on the highest end, mean baseline CD4 count of 114.8 cells/mm^3 (range, 38–306), had a mean VAS increase of +18 mm.

Weight Gain

Evaluable patients who received dronabinol showed a mean weight gain of 0.1 kg versus a mean loss of 0.4 kg in the placebo group ($P = 0.14$). These results are shown in Figure 2: 22% of evaluable dronabinol patients versus 10.5% of placebo patients gained 2 kg (4.4 lb) by end of study ($P = 0.11$). No correlation was found between urinary cannabinoid–creatinine ratios and weight gain.

During the course of the study, 35 patients developed significant intercurrent illnesses. The adverse events are defined as moderate, severe, or life-threatening and not related to treatment. Figure 3 shows weight changes in

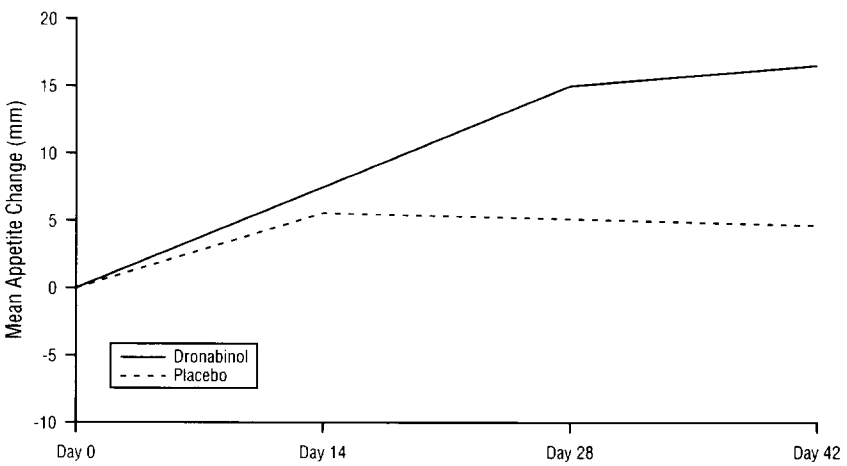

Fig. 1. Mean change in appetite from baseline, evaluable patients. Number of evaluable dronabinol-treated patients was 46 at day 14, 45 at day 28, and 43 at day 42. Number of evaluable placebo-treated patients was 37 at day 14, 36 at day 28, and 33 at day 42.

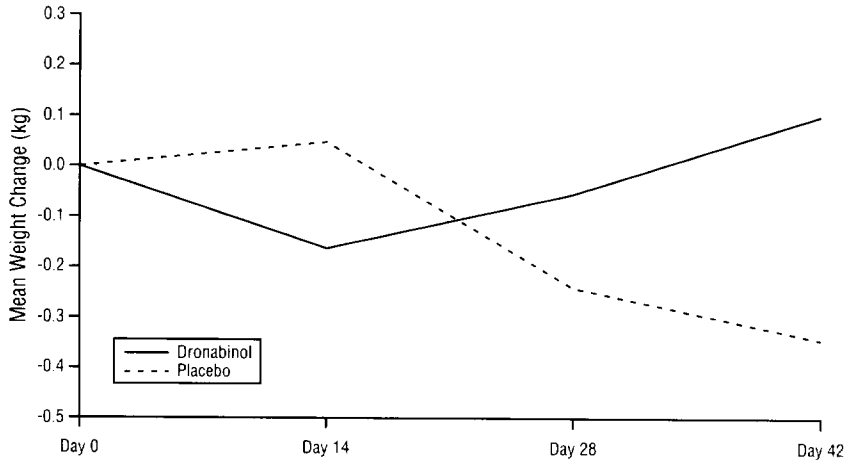

Fig. 2. Mean change in weight from baseline, evaluable patients. Number of evaluable dronabinol-treated patients was 50 at day 14, 49 at day 28, and 48 at day 42. Number of evaluable placebo-treated patients was 38 at day 14, 38 at day 28, and 35 at day 42.

those patients who did not develop significant intercurrent illness. In this subgroup, the dronabinol group gained a mean of 1.1 kg versus a mean loss of 0.1 kg in the placebo group ($P = 0.12$).

Mood and Nausea

Dronabinol-treated patients noted improved mood in the absence of overt euphoria. Mood, as measured by VAS, was improved at all time points in the dronabinol group versus stable or worse in the placebo group and approached statistical significance for evaluable patients. For all patients, improvement in mood by end point was noted in 7% of patients treated with dronabinol and 2% of patients treated with placebo ($P = 0.14$). For evaluable patients, mood had improved 10% in the dronabinol group versus a 2% decline in the placebo group ($P = 0.06$).

Nausea was generally mild at baseline. Improvement in nausea was statistically significant in evaluable patients who were treated with dronabinol. For all patients, nausea had decreased 22% by end point in the dronabinol group and 4% in the placebo group ($P = 0.26$). For evaluable patients, there was a 20% decrease in nausea in the dronabinol group as compared with 7% in placebo-treated patients ($P = 0.05$).

Karnofsky Performance Evaluations

At each clinic visit, patients were evaluated for Karnofsky performance status with 100 representing normal activity and 0 representing death. For all patients, Karnofsky scores had decreased by 2.5 points in the dronabinol group versus no change in the placebo group ($P = 0.18$). In evaluable patients, Karnofsky scores decreased a mean of 1 point in dronabi-

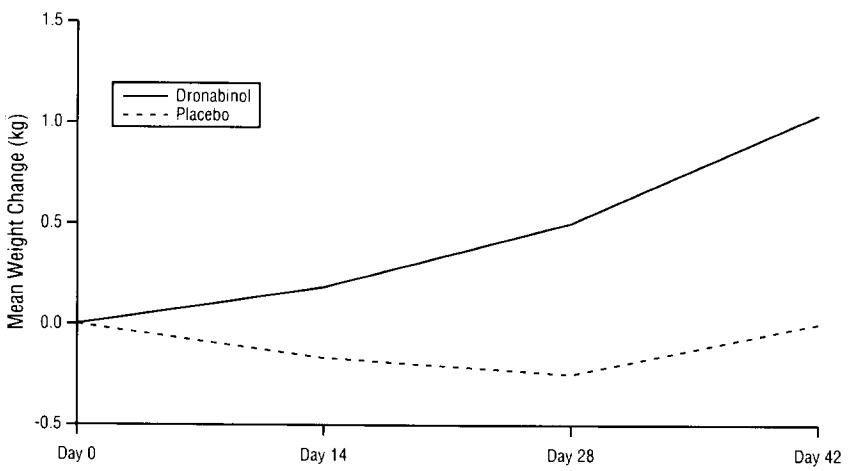

Fig. 3. Mean change in weight from baseline, evaluable patients. Excludes patients with moderate, severe, or life-threatening drug-nonrelated adverse events. Number of dronabinol-treated patients was 29 at day 14, 29 at day 28, and 27 at day 42. Number of placebo-treated patients was 24 at day 14, 24 at day 28, and 22 at day 42.

Table 3
Treatment-Related Adverse Events

	Dronabinol *N* (%) (*N* = 72)				Placebo *N* (%) (*N* = 67)				
Body system	Mild	Moderate	Severe	All drug related	Mild	Moderate	Severe	All drug related	*P*
Body as a whole	1 (1.4)	4 (5.6)	0 (0.0)	5 (6.9)	0 (0.0)	1 (1.5)	0 (0.0)	1 (1.5)	0.030
Cardiovascular	0 (0.0)	0 (0.0)	1 (1.4)	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.22
Digestive	4 (5.6)	1 (1.4)	1 (1.4)	6 (8.3)	2 (3.0)	0 (0.0)	0 (0.0)	2 (3.0)	0.165
Nervous	8 (11.1)	13 (18.1)	4 (5.6)	25 (34.7)	2 (3.0)	4 (6.0)	0 (0.0)	6 (9.0)	<0.001
Integument	0 (0.0)	0 (0.0)	1 (1.4)	1 (1.4)	0 (0.0)	2 (3.0)	0 (0.0)	2 (3.0)	0.64
Special senses	0 (0.0)	0 (0.0)	1 (1.4)	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.22
Total	9 (12.5)	16 (22.2)	6 (8.3)	31 (43.1)	3 (4.5)	6 (9.0)	0 (0.0)	9 (13.4)	<0.001

nol patients versus an increase of 0.3 points in those receiving placebo ($P = 0.07$).

Adverse Events

Three-quarters of all dronabinol-treated patients and one-half of those who received placebo experienced one or more adverse events during the study. Many of these were related to underlying disease. All adverse events related to study medication resolved without sequelae on decreasing dose or discontinuing treatment. In most cases, patients could continue treatment at a lower dose. Table 3 shows adverse events, by COSTART category, felt to be possibly or probably related to treatment: 43% of dronabinol and 13% of placebo recipients noted treatment-related adverse events ($P < 0.001$). The one cardiovascular event noted in the dronabinol group was tachycardia, which resolved without sequelae on discontinuation of therapy.

The difference between treatment groups is due to the incidence of nervous system events: 35% in the dronabinol group versus 9% in the placebo group ($P < 0.001$). In most cases, these were mild or moderate and in all cases resolved without sequelae on discontinuation of treatment. The most common nervous system adverse events in the dronabinol group were euphoria (nine patients), dizziness (five), thinking abnormalities (five), and somnolence (four). Dizziness was noted in two and the other experiences in one patient each in the placebo group. There was no significant difference in the patient dropout rates between treatment arms (dronabinol 8.3%, and placebo 4.5%; $P = 0.29$).

There was no clinically significant interaction between dronabinol and either opioid analgesics or benzodiazepines in terms of adverse events. The incidence of adverse events was the same for patients receiving dronabinol with or without these concomitant medications. No treatment-related toxicity was found on physical examinations or laboratory tests, such as hematology and chemistry profiles. There was no correlation between urine cannabinoid–creatinine ratios and adverse events.

Discussion

The effects of dronabinol on appetite, weight, nausea, and mood were examined in this study of 139 AIDS patients. Based on results from an earlier pilot study, we treated patients with a low dose of dronabinol, 2.5 mg twice a day, administered 1 hr before lunch and supper.[9]

In the present study, dronabinol caused a marked, statistically significant increase in appetite in severely immunosuppressed patients with AIDS-related anorexia. Positive effects were seen in 2–4 weeks, and differences between drug and placebo recipients were significant after 4 weeks of treatment and sustained until the end of the 6-week study. Improvements were also seen in parameters related to anorexia, such as nausea and mood, in treated patients. The earliest response to treatment was reflected in mood and was evident 14 days into the trial. Mood improvement was not dependent on overt euphoria, which was reported by only nine dronabinol recipients. Differences in appetite and nausea became apparent at 28 days. This delay was not

due to gradual buildup of cannabinoid blood levels. Urine cannabinoid–creatinine ratios actually declined somewhat over the three study periods, indicating that a steady state had been reached in the first 2-week period.

Because appetite improvement did not occur until between weeks 2 and 4, there was only a limited amount of time for patients to gain weight in this 6-week study. Further data on weight change from the open-label, follow-up study indicate a continued weight gain (data not shown; will be reported separately). Nevertheless, the two groups reflect divergent trends, with dronabinol-treated patients tending toward weight stabilization and placebo recipients continuing to lose weight. A subset of evaluable patients who did not develop opportunistic infections exhibited weight gain, whereas the treated group as a whole was stable. The patients in this trial were at advanced stages of HIV disease. Dronabinol recipients had HIV-related symptoms for an average of 33.8 months, and placebo recipients had symptoms of HIV disease for 30.8 months on average. The mean T^{b4} count was <50 cells/mm^3, indicating that these patients were at high risk for developing life-threatening opportunistic infections such as those caused by cytomegalovirus, *Mycobacterium avium* complex, and *Toxoplasma gondii.* In fact, 35 (44%) of 88 evaluable patients developed significant intercurrent illness during the 42-day trial. Further study is needed to determine whether dronabinol would be even more efficacious in patients with early HIV infection who are at risk for developing nutritional deficiencies and weight loss.

Dronabinol was well tolerated. The majority of side effects reported were central nervous system disturbances that are commonly associated with cannabinoids. In most cases, they were not severe enough to warrant intervention. There was no significant difference between both treatment groups in the patient dropout rates due to adverse reactions. Six dronabinol versus three placebo recipients discontinued therapy due to any adverse effect thought to be possibly or probably related to treatment. These numbers are small and attest to the safety and tolerance of treatment.

Most patients who required dose reduction were able to tolerate the half-dose (one 2.5-mg capsule in the evening). Of 17 patients who received a reduced dose, 11 were evaluable for efficacy and showed a similar appetite increase compared with those patients treated with dronabinol twice a day.

Based primarily on this study, dronabinol was approved, under the trademark Marinol, by the Food and Drug Administration (FDA) as a treatment for anorexia associated with weight loss in patients with AIDS. It was the first drug to receive such an indication.

Megestrol acetate has also demonstrated efficacy as a treatment for AIDS-related anorexia and cachexia.[10,11] In one trial of 270 patients with AIDS and significant weight loss, patients randomized to placebo lost an average of 2 lb, while patients receiving 100, 400, and 800 mg/day of megestrol acetate gained a mean of 2, 4, and 8 lb, respectively, over the 12 weeks of the study.[10,11] A second study compared 800 mg megestrol acetate with placebo in 100 patients with AIDS.[10,11] Patients receiving placebo lost an average of 2 lb while treated patients gained 11 lb. Three starting daily doses were used in the first clinical trial: 100, 400, and 800 mg. The 800-mg dose was associated with the highest efficacy rates and is the recommended starting dose. However, there was an apparent dose-related increase in the incidence of impotence—100 mg, 4%; 400 mg, 6%; and 800 mg, 14%. Other common side effects (all clinical trials) included loss of libido (2%), and gastrointestinal (diarrhea, 11%) and skin (rash, 7%) reactions.[10]

As the mechanism of action and toxicity of each drug are different, combination therapy may provide increased benefits as compared with either agent alone. This is currently being studied in a randomized multi-institutional clinical trial.

In conclusion, dronabinol is a safe and effective treatment for anorexia in patients with weight loss due to AIDS. A further longer-term study is now under way to determine the effects of prolonged treatment. By improving appetite and mood, decreasing nausea, and stabilizing weight, dronabinol may significantly improve the quality of life of patients infected with HIV.

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Appendix

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