

Dronabinol Versus Megestrol Acetate Versus Combination Therapy for Cancer-Associated Anorexia: A North Central Cancer Treatment Group Study

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Purpose: To determine whether dronabinol administered alone or with megestrol acetate was more, less, or equal in efficacy to single-agent megestrol acetate for palliating cancer-associated anorexia.

Patients and Methods: Four hundred sixty-nine assessable advanced cancer patients were randomized to (1) oral megestrol acetate 800 mg/d liquid suspension plus placebo, (2) oral dronabinol 2.5 mg twice a day plus placebo, or (3) both agents. Eligible patients acknowledged that loss of appetite or weight was a problem and reported the loss of 5 pounds or more during 2 months and/or a daily intake of less than 20 calories/kg of body weight.

Results: Groups were comparable at baseline in age, sex, tumor type, weight loss, and performance status. A greater percentage of megestrol acetate-treated patients reported appetite improvement and weight gain compared with dronabinol-treated patients: 75% versus 49% ($P = .0001$) for appetite and

11% versus 3% ($P = .02$) for $\geq 10\%$ baseline weight gain. Combination treatment resulted in no significant differences in appetite or weight compared with megestrol acetate alone. The Functional Assessment of Anorexia/Cachexia Therapy questionnaire, which emphasizes anorexia-related questions, demonstrated an improvement in quality of life (QOL) among megestrol acetate-treated and combination-treated patients. The single-item Uniscale, a global QOL instrument, found comparable scores. Toxicity was also comparable, with the exception of an increased incidence of impotence among men who received megestrol acetate.

Conclusion: In the doses and schedules we studied, megestrol acetate provided superior anorexia palliation among advanced cancer patients compared with dronabinol alone. Combination therapy did not appear to confer additional benefit.

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ANECDOTAL REPORTS and numerous small studies suggest that marijuana stimulates appetite. In one such study, Abel¹ observed seven marijuana-treated individuals devour a plate of marshmallows in a controlled investigation of marijuana's effects on memory, intellectual performance, and hunger. He concluded "marijuana increases the subjects' desire for food."

These preliminary observations led to further investigation of cannabinoids in the treatment of cancer-associated anorexia, a pervasive and devastating symptom among advanced cancer patients. More than half of patients with advanced cancer experience lack of appetite and/or weight loss.² Moreover, when queried about symptoms faced in the setting of advanced cancer, patients consistently rank anorexia as one of the most troublesome.³

In an effort to provide palliation for these patients, Nelson et al⁴ conducted a phase II study in which they administered delta-9-tetrahydrocannabinol (dronabinol) to 19 cancer patients with anorexia. Patients received dronabinol at a dose of 2.5 mg orally three times a day and were assessed for appetite improvement at 2 and 4 weeks. Observing that 13 patients reported an improvement in appetite, these investigators concluded that dronabinol holds promise as an appetite stimulant in cancer patients. In addition to this trial, at least 12 clinical trials have examined dronabinol for the treatment of chemotherapy-induced nausea and vomiting, as

recently reviewed by Voth and Schwartz.⁵ Some of these trials have suggested that dronabinol might control nausea, and four have also suggested a modest improvement in appetite. Coupled with similar information from AIDS patients,⁶⁻⁸ these data suggest that dronabinol may be effective in the treatment of cancer-induced anorexia.

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This study was conducted as a collaborative trial of the North Central Cancer Treatment Group and the Mayo Clinic.

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To date, no randomized trial has been undertaken to determine whether dronabinol is comparable with other orexigenic agents, such as megestrol acetate. A synthetically derived progesterone, megestrol acetate is the most extensively studied agent for treating cancer-associated anorexia and holds a well-established track record for alleviating this symptom and promoting weight gain in patients with advanced cancer.⁹⁻¹¹ Despite this track record, however, megestrol acetate does not benefit all patients with cancer-associated anorexia. In an earlier placebo-controlled trial among 133 patients from the North Central Cancer Treatment Group, 60% of patients who completed the anorexia questionnaire thought this hormone improved their appetite, compared with 42% of placebo-treated patients who also cited improvement.⁹ Fewer than 15% reported weight gain in the megestrol acetate arm. Such data demonstrate that, although megestrol acetate is effective in palliating anorexia, a large proportion of patients continue to suffer from anorexia despite treatment with this hormone. We therefore undertook this double-blind, randomized trial to define the role of dronabinol in the treatment of cancer-associated anorexia. The purpose of this study was to determine whether dronabinol administered either alone or in combination with megestrol acetate was more, less, or equal in efficacy when compared with megestrol acetate in palliating cancer-associated anorexia.

PATIENTS AND METHODS

Overview

Conducted through the North Central Cancer Treatment Group (NCCTG), this multi-institutional, double-blind, randomized trial involved 20 institutions. All 20 institutional review boards approved the study protocol, and all patients provided informed written consent before study enrollment.

Eligibility Criteria

Adult patients (≥ 18 years of age) with histologic evidence of an incurable malignancy other than brain, breast, ovarian, or endometrial cancer were eligible for study participation. Patients had to have an estimated life expectancy of ≥ 3 months and an Eastern Cooperative Oncology Group performance status of 0 to 2, as judged by their primary oncologist. Patients were also to have a self-reported weight loss of at least 5 pounds (2.3 kg) during the preceding 2 months and/or a physician-estimated caloric intake of less than 20 calories/kg of body weight per day. In addition, eligible patients had to believe that loss of appetite or loss of weight was an ongoing problem for them. Use of chemotherapy or radiation was permitted throughout the study period.

Exclusion Criteria

Exclusion criteria included (1) ongoing use of tube feedings or parenteral nutrition; (2) edema or ascites; (3) treatment with adrenal corticosteroids (except for short-term dexamethasone during the time of chemotherapy), androgens, progestational agents, or other appetite

stimulants within the previous month; (4) brain metastases; (5) insulin-requiring diabetes; (6) pregnancy or lactation or unwillingness to use oral contraceptives; (7) anticipated alcohol or barbiturate use during the study period; (8) poorly controlled hypertension or congestive heart failure; (9) history of thromboembolic disease; and (10) mechanical obstruction of the alimentary tract, malabsorption, or intractable vomiting.

Stratification and Randomization

Before randomization, patients were stratified on the basis of the following: (1) cancer type, lung cancer versus gastrointestinal cancer versus other malignancy; (2) severity of weight loss in the preceding 2 months, less than 10 pounds versus ≥ 10 pounds; (3) planned or ongoing chemotherapy at the time of recruitment, none versus cisplatin versus other; (4) sex, male versus female; (5) Eastern Cooperative Oncology Group performance status: 0 to 1 versus 2; (6) physician estimate of patient survival, less than 4 months versus 4 to 6 months versus more than 6 months; (7) planned concomitant radiation, yes versus no; (8) patient age, less than 50 years versus ≥ 50 years; and (9) medical center where patient was enrolled.

Patients were then randomized, in a double-blind manner, to one of three treatment arms: (1) megestrol acetate liquid suspension 800 mg orally daily plus capsule placebos; (2) dronabinol capsules 2.5 mg orally twice a day plus liquid placebo; or (3) a combination of both medications in the same dosages as noted previously.

Follow-Up

Before randomization and thereafter, a number of different parameters were assessed.¹² A history and physical examination, which included weight measurement in the office of the primary oncologist, was performed at study entry and monthly thereafter. Previously validated North Central Cancer Treatment Group questionnaires for appetite and weight were used at baseline, weekly for 4 weeks, and then monthly. For quality of life (QOL) assessment, the single-item Uniscale¹³ and the thirteen-item anorexia-specific Functional Assessment of Anorexia/Cachexia Therapy (FAACT) instrument¹⁴ were administered at the same times. These two tools were chosen for their brevity and specificity, respectively. Patients continued on treatment for as long as they and their healthcare providers thought it beneficial or until toxic side effects prompted study withdrawal.

Statistical Analyses

The megestrol acetate arm was viewed as the standard treatment arm, or reference group. The other two treatment arms were compared with this arm. Primary end points in the study included binary end points of whether patients' appetite improved and whether patients gained 10% of their baseline weight at some point during the study period. Patients rated their appetite with the use of previously validated appetite questionnaires.⁹⁻¹¹ Fisher's exact test was used to analyze differences between study groups in the categorical variables. For example, Fisher's exact test was used to compare percentages of patients who experienced a 10% weight gain or an improvement in appetite across the treatment arms. Data on weight were censored in patients with edema or ascites, and patients who dropped out of the study were considered to have experienced treatment failure. Repeated measures models were used to corroborate all conclusions with regard to patient-reported and physician-reported weight. Continuous variables, such as QOL ratings, ordinal baseline variables, and toxicity data were compared between treatment groups with Wilcoxon rank sum tests and

independent sample *t* tests. All hypothesis testing was carried out using a two-sided alternative hypothesis and a 5% type I error rate.

Sample Size Calculations

Sample size calculations demonstrated that 150 patients per treatment arm would enable detection of a 15% difference in appetite improvement between the study arms with 80% power. Similarly, a sample size of 135 patients per study arm took into account patient attrition and allowed for detection of a 10% difference in weight gain within one of the arms with 77% power. Finally, it was determined that 150 patients per arm allowed for 98% power to detect a shift in appetite improvement equivalent to one half of the SD of the interval level appetite scores. All sample size calculations anticipated a 6-week median time on study for patients, as is typical in clinical trials among advanced cancer patients with anorexia and/or weight loss.^{10,11}

RESULTS

A total of 485 patients were recruited onto the study between December of 1996 and December of 1999, and 469 of these patients (97%) were deemed assessable. Patients were not considered assessable on the basis of withdrawal before starting study drug (*n* = 14) and ineligibility as determined after randomization (*n* = 2). Patients completed a baseline questionnaire and at least one weekly questionnaire in the first follow-up. As expected and as consistent with earlier studies from our group, 45% of patients completed both a baseline and 1-month follow-up questionnaire.

Patients in all three arms were comparable at baseline with respect to weight, patients' rating of appetite, reduction in appetite, reported perception of food intake, nausea intensity, perception of current weight, and QOL assessment. (Tables 1 and 2)

The median time on study was not statistically different between the groups that received megestrol acetate, dronabinol, or the two-drug combination: 80 days versus 57 days versus 74 days (*P* = .21). Reasons for patient withdrawal included patient refusal and/or toxicity (45%, 58%, and 41%, respectively) and patient death (22%, 15%, and 26%, respectively). In addition, there were no statistically significant differences in patient survival within the three treatment arms: median survival, 123 days versus 141 days versus 113 days in the megestrol acetate versus dronabinol versus the combination arms, respectively (log-rank *P* = .66).

Within the megestrol acetate group, 75% of patients reported that this agent increased their appetite at some point during the study period, whereas only 49% of patients in the dronabinol group reported such improvement (Fisher's exact test, *P* = .0001). The combination arm resulted in 66% of patients' reporting an improvement in appetite (Fisher's exact test, *P* = .17) when compared with the megestrol acetate arm. As shown in Table 3, other appetite-related questions yielded a consistently favorable orexigenic effect of megestrol acetate when compared with dronabinol

Table 1. Baseline Patient Characteristics

Characteristic	Megestrol Acetate (n=159)	Dronabinol (n=152)	Megestrol Acetate + Dronabinol (n=158)	<i>P</i> (<i>t</i> test or χ^2)
Age, mean \pm SD, years	65 \pm 11	67 \pm 10	67 \pm 10	.3
Sex, %				
Male	65	66	66	.99
Female	35	34	34	
Malignancy, %				
Lung	44	45	44	
Gastrointestinal	29	30	30	.99
Other	27	26	25	
Weight loss in 2 months, %				
<10 pounds	39	40	40	.98
\geq 10 pounds	61	60	60	
Planned concurrent chemotherapy, %				
None	30	30	30	
With cisplatin	15	14	14	.99
Without cisplatin	55	56	56	
Planned concurrent radiation, %				
Yes	21	20	20	.97
No	79	80	80	
Physician estimate of survival, %				
<4 months	10	10	12	
4-6 months	35	36	34	.98
>6 months	55	54	54	
ECOG performance status, %				
0-1	70	69	69	.98
2	30	31	31	
FAACT total score				
Median	55	56	57	.67
Range	26-84	27-92	27-92	
QOL, UNISCALE				
Median	51	51	49	.94
Range	4-98	2-100	4-96	

alone and no statistically significant improvement with combination therapy when direct comparisons to the megestrol acetate arm were undertaken.

Eleven percent of patients in the megestrol acetate arm reported, from weights they obtained at home, a 10% or more weight gain above their baseline at some point during treatment, in contrast to 3% in the dronabinol arm (Fisher's exact test, *P* = .02). The combination of megestrol acetate and dronabinol resulted in 8% of patients' reporting a 10% increase in weight and was no different compared with the use of megestrol acetate alone (Fisher's exact test, *P* = .43). Physician-reported weight gain also demonstrated results in favor of the megestrol acetate arm: 14% of megestrol

Table 2. Baseline Response to Appetite Questionnaire

	Megestrol Acetate (n=159) (%)	Dronabinol (n=152) (%)	Megestrol Acetate + Dronabinol (n=158) (%)	P
How would you compare your appetite to what it was before your present illness?				
Markedly reduced (< 25% normal)	66	58	59	.46
Moderately reduced (about 50% of normal)	22	32	26	
Slightly reduced (about 75% of normal)	9	5	9	
The same	2	2	4	
Increased	1	3	2	
What is your current food intake in comparison to before your illness?				
Markedly reduced (< 25% normal)	64	59	56	.47
Moderately reduced (about 50% of normal)	24	29	32	
Slightly reduced (about 75% of normal)	9	8	7	
The same	1	3	3	
Increased	1	2	1	
How would you rate your appetite?				
Very good	1	1	1	.35
Good	3	5	4	
Fair	17	18	16	
Poor	32	38	36	
Very poor	48	39	44	
How do you presently feel about your weight status?				
I would like to stabilize or increase my weight	97	93	96	.06
My weight status is not a problem	1	6	3	
I would like to lose weight	0	0	1	
How much nausea have you had over the present week?				
None	48	45	42	.94
Mild, able to eat reasonably well	21	23	28	
Moderate, significantly, decreased food intake	23	27	26	
Severe, no significant oral intake	8	5	3	
How many times have you vomited over the present week?				
0 times	66	69	69	.82
1-3 times	26	24	19	
4-10 times	6	6	12	
> 10 times	2	1	0	

NOTE. Some percentages do not add up to 100% because of missing data.

acetate-treated patients gained 10% or more of their baseline weight, whereas only 5% of patients on the dronabinol arm manifested such a weight gain (Fisher's exact test, $P = .009$). Likewise, by office weights, the combination of megestrol acetate and dronabinol resulted in 11% of patients manifesting a 10% increase in weight, a percentage that was not statistically different compared with the use of megestrol acetate alone (Fisher's exact test, $P = .49$) (Table 4).

With regard to QOL, the Uniscale detected no significant differences between maximally improved QOL assessment over time in either of the three study arms. In contrast, the difference between baseline and maximum FAACT-AN scores was statistically significant between the megestrol acetate-treated and dronabinol-treated groups (median, 7.8 [range, 0 to 41] v 2.6 [range, 0 to 59]; Wilcoxon rank sum test, $P = .002$). Individually, the physical and the emotional

constructs of the FAACT-AN questionnaire were the only ones to yield statistically significant differences between the megestrol acetate-treated and dronabinol-treated groups, and these differences illustrated that patients on the megestrol acetate arm had better QOL within these constructs. In contrast, similar analyses yielded no significant QOL differences between patients who received combination treatment and those who received megestrol acetate alone, with the exception of the emotional construct for the FAACT. In the latter construct, the megestrol acetate arm had higher scores compared with the combination arm. Results are summarized in Fig 1.

Finally, 18% of male patients reported impotence with megestrol acetate, in contrast to 4% with dronabinol (Fisher's exact test, $P = .002$). Otherwise, toxicity incidence that included monitoring for nausea, vomiting, neurocortical dysfunction, edema, ascites, pleural effusion, or thrombo-

Table 3. Percentage of Patients Reporting a Best Follow-Up Response to Appetite Questions

	Megestrol Acetate Patients (n=159) (%)	Dronabinol Patients (n=152) (%)	P Compared With Megestrol Acetate*	Megestrol Acetate + Dronabinol Patients (n=158) (%)	P Compared With Megestrol Acetate
Q: How would you compare your appetite to what it was before your present illness?					
A: "Increased"	46	25	.0005	45	.94
Q: What is your current food intake in comparison to before your illness?					
A: "Increased"	46	25	<.0001	39	.37
Q: How would you rate your appetite?					
A: "Very good"	21	11	.001	19	.96
Q: How is your appetite now in comparison to before you started the study medications?					
A: "Increased very much"	16	8	<.05	15	.88
Q: What effect, if any, do you feel the study medications have had on your food intake?					
A: "I eat very much more"	15	5	.008	12	.5
Q: Do the study medications make food taste better?					
A: "Yes"	51	27	.0003	49	.48
Q: Do the study medications allow you to eat more at one time by preventing you from getting "full" soon after you start eating?					
A: "Yes"	65	44	.002	69	.29
Q: Do you feel the study medications are helping or hindering you?					
A: "Helping"	84	63	.0004	85	.79

* Missing data included in analysis.

embolic phenomena was not statistically different between treatment groups (Table 6).

DISCUSSION

This study is the first to compare megestrol acetate with dronabinol in the treatment of cancer-associated anorexia and/or weight loss. Our findings demonstrate that, in the doses and schedules mentioned above, megestrol acetate is superior to dronabinol in the treatment of cancer-associated anorexia and that the addition of dronabinol to megestrol acetate does not confer additional benefit.

These results are important because they may influence oncologists' viewpoint on the medical uses of cannabinoid derivatives. Although few oncologists prescribe dronabinol for nausea and vomiting, a recent survey completed by 1,122 American oncologists (75% reply rate) found that as many as 30% would favor rescheduling marijuana for medical purposes.¹⁵ In an earlier survey, 44% of respondents had recommended the use of marijuana to an oncology patient at some point in the past.¹⁶ Our findings that dronabinol does little to promote appetite or weight gain among advanced cancer patients compared with megestrol

Table 4. Maximum Weight Gain Over Baseline

Maximal Physician-Reported Weight Gain Over Baseline	Megestrol Acetate (n=159)* (%)	Dronabinol (n=152) (%)	P Compared With 10%+ Weight Gain Category With Megestrol Acetate	Megestrol Acetate + Dronabinol (n=158) (%)	P Compared With 10%+ Weight Gain Category With Megestrol Acetate
			.041		.84
0%	57	65		55	
1%-4%	23	23		23	
5%-9%	10	8		14	
≥ 10%	10	3		8	

* Data are reported as the percentage of patients under each treatment arm.

Table 5. Maximum QOL Minus Baseline Scores

	Megestrol Acetate (n=159)*	Dronabinol (n=152)	P Compared With Megestrol Acetate Arm	Megestrol Acetate + Dronabinol (n=158)	P Compared With Megestrol Acetate Arm
UNISCALE	15±19	12±8	.19	14±19	.72
FAACT-AN	10.3±11	7.2±10	.003	9±10	.30

* Score differences are presented as means ± SD.

acetate should dampen enthusiasm for the use of cannabinoids or their derivatives.

Although assessment of nausea and vomiting was not a major end point in our study, a noteworthy finding is that the severity of nausea and vomiting was not statistically different in direct comparisons between the megestrol acetate and dronabinol treatment arms. Prior data from our group and others have demonstrated that megestrol acetate has significant antiemetic potential among cancer patients^{9,17,18} The findings from this trial suggest that the antiemetic potential of dronabinol is comparable to that of megestrol acetate alone. Hence, these results suggest that even from an antiemetic standpoint, dronabinol appears to have little to add above and beyond megestrol acetate (Table 6).

Another noteworthy aspect of this trial is the improvement in specific aspects of QOL, as measured by the FAACT-AN instrument, with the use of megestrol acetate as compared with dronabinol alone. When analyzed in aggregate, multiple placebo-controlled trials have demonstrated that megestrol acetate does not improve overall QOL in advanced cancer patients with anorexia.¹⁹ However, our study clearly demonstrates that megestrol acetate promotes symptom-specific aspects of QOL in advanced cancer

patients with anorexia, as measured by the FAACT-AN instrument, compared with dronabinol alone. Because toxicity was not significantly different between the two groups, it is likely that this improvement in QOL is a direct reflection of the FAACT-AN instrument's heavy emphasis on anorexia. In effect, this improvement in QOL as measured by the FAACT-AN further validates the NCCTG anorexia questionnaire, which demonstrated an improvement in anorexia in the present trial.

One might question the dose of dronabinol that we chose in this study, and one might argue that a higher dose of this agent might have resulted in greater appetite-stimulatory effects. However, the phase II trial by Nelson and others, which suggested dronabinol at 2.5 mg three times a day resulted in improved appetite,⁴ found that this higher dose was also associated with notable side effects in approximately 20% of patients. Other trials have also reported that higher doses of dronabinol have had intolerable side effect profiles.^{20,21} On the basis of this information, we choose, in concert with the manufacturers of this drug, to study 2.5 mg twice a day orally in the current trial.

In short, our study demonstrates that megestrol acetate provided superior palliation of anorexia in advanced cancer patients than dronabinol alone and that combination therapy did not confer additional benefit.

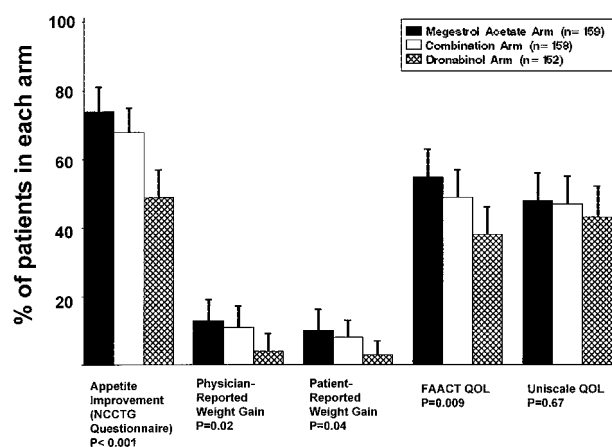


Fig 1. Megestrol acetate improved (1) appetite, (2) physician-reported weight, (3) patient-reported weight, and (4) FAACT QOL score (Fisher's exact test, $P < .001$, $.02$, $.04$, and $.009$, respectively). The UNISCALE found no significant differences in QOL. Bars represent 95% confidence intervals.

Table 6. Maximum Patient-Reported Toxicities

	Megestrol Acetate (n=159) (%)	Dronabinol (n=152) (%)	Combination (n=158) (%)	P Over All Groups
Male impotence	18	4	14	.0032
Vomiting	8	11	11	.44
Fluid retention	18	11	13	.19
Muddled thinking	21	24	21	.79
Drowsiness	33	36	39	.54
Loss of coordination	16	15	18	.82
Inappropriate behavior	3	1	4	.29

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