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EFFECTS OF DRONABINOL ON ANOREXIA AND DISTURBED BEHAVIOR IN PATIENTS WITH ALZHEIMER'S DISEASE

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SUMMARY

A placebo-controlled crossover design, with each treatment period lasting 6 weeks, was used to investigate effects of dronabinol in 15 patients with a diagnosis of probable Alzheimer's disease who were refusing food. Eleven patients completed both study periods; one patient who died of a heart attack 2 weeks before the end of the study was also included in the analysis. The study was terminated in 3 patients: one developed a grand mal seizure and 2 developed serious intercurrent infections. Body weight of study subjects increased more during the dronabinol treatment than during the placebo periods. Dronabinol treatment decreased severity of disturbed behavior and this effect persisted during the placebo period in patients who received dronabinol first. Adverse reactions observed more commonly during the dronabinol treatment than during placebo periods included euphoria, somnolence and tiredness, but did not require discontinuation of therapy. These results indicate that dronabinol is a promising novel therapeutic agent which may be useful not only for treatment of anorexia but also to improve disturbed behavior in patients with Alzheimer's disease. © 1997 John Wiley & Sons, Ltd.

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Anorexia is quite common in the cognitively intact elderly (Morley *et al*., 1988). It has many causes including social, physical and mental factors. Physical changes associated with ageing which could precipitate development of anorexia are decreased taste and smell, decreased feeding drive because of decreased effectiveness of endogenous opioids, and increased satiety because of increased sensitivity to the effect of cholecystokinin (Morley *et al*., 1988). Abnormality of other neurotransmitters may also play a role, especially in demented individuals. Brain levels of neuropeptide Y and norepinephrine, which stimulate appetite, have been found to be reduced in patients suffering from dementia of the Alzheimer type (DAT) (Morley *et al*., 1988).

Dementia of the Alzheimer type leads to a progressive loss of learned behaviors including the ability to feed oneself, and some patients also start refusing food during the course of the disease (Volicer *et al*., 1989). Several different factors may contribute to the refusal of food by demented individuals, including: dislike of hospital food, failure to recognize edible objects as food (agnosia), or loss of sense of thirst and/or hunger (anorexia). Some patients develop food refusal when they start choking on food or liquids and the refusal could be a consequence of dysphagia. This can be corrected by diet modifications. Other patients refuse food, even though swallowing is unimpaired. This refusal may be a symptom of depression, which is difficult to diagnose in this patient population (Emery and Oxman, 1992). Treatment with antidepressants improves food

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intake even in patients with severe dementia (Volicer *et al.*, 1994b). However, some patients do not improve and are at risk for development of malnutrition. Therefore, additional therapeutic modalities are needed to deal with this problem.

Smoking marijuana has been found to cause appetite stimulation in normal humans (Struwe *et al.*, 1993). One of the main components of marijuana, dronabinol, was associated with increased food intake when used as an antiemetic in cancer patients (Sallan *et al.*, 1980). It also improved appetite and sense of well-being, as well as causing weight gain (Regelson *et al.*, 1976). In a pilot study of 10 AIDS patients, dronabinol treatment was associated with weight gain and improvement in mood or sense of well-being without euphoria (Gorter, 1991). In a double-blind study of 12 AIDS patients, dronabinol treatment increased % of body fat, decreased symptom distress and tended to cause weight gain, increased prealbumin and improved appetite scores (Struwe *et al.*, 1993). A multicenter trial (Beal *et al.*, 1995), including 139 AIDS patients, showed that dronabinol improved appetite and mood, and that euphoria was the most common side-effect in dronabinol-treated patients, occurring in 13% of patients. Other side-effects occurred in less than 10% of patients and included dizziness, abnormal thinking, sinusitis and somnolence.

The above studies indicate that dronabinol may be effective in treatment of anorexia of demented individuals even in the absence of nausea. However, nausea as a cause of anorexia in these individuals cannot be excluded, since they are unable to complain about it, and some develop periodic bouts of vomiting. Therefore, we investigated the effect of dronabinol on food refusal in DAT patients. In addition, we also monitored the effect of dronabinol on disturbed behavior.

SUBJECTS AND METHODS

Subjects were 15 patients hospitalized on the Dementia Study Unit, with the diagnosis of 'probable' DAT made by a neurologist according to DSM-III-R and NINCDS–ADRDA criteria (McKhann *et al.*, 1984), who exhibited simple food refusal. Simple food refusal was characterized as refusal of feeding by keeping the mouth shut, turning the head away, pushing away the spoon or feeding hand, or by spitting food, in the absence of choking on food and/or liquids. Informed consent was obtained from the guardians or the next-of-kin of patients who did not have capacity to make health care decisions.

The patients were identified by a survey of nursing staff. They received physical examination and laboratory examination including complete blood count with differential, liver function tests, thyroid function tests including TSH, iron binding capacity, albumin, BUN, creatinine and electrolytes. Patients who were choking on food or liquids, had hypersensitivity to dronabinol or sesame oil or had significant laboratory abnormalities were not eligible for the study.

The severity of dementia was measured by the Mini-Mental State Examination (MMSE) (Folstein *et al.*, 1975), Katz Activity of Daily Living scale (Katz ADL) (Katz *et al.*, 1963) and Bedford Alzheimer Nursing Scale—Severity (BANS-S) (Volicer *et al.*, 1994a). The study used a double-blind placebo-controlled crossover design with each study period lasting 6 weeks. Dronabinol or placebo was administered on a fixed dose schedule, 2.5 mg capsule (Marionol, Roxane Laboratories) or identical looking placebo capsule every morning and noon. This administration schedule was a modification from that recommended for AIDS patients because DAT patients usually eat most of their daily food during breakfast and lunch. Subjects were randomly assigned to placebo first or dronabinol first groups. Possible side-effects were determined every week by asking the primary caregivers if the patient experienced any of a list of possible symptoms.

Baseline measurements were taken the week prior to randomization and treatment initiation. Plasma albumin and lymphocyte count were also obtained at the end of each treatment period. Body weights, skin fold thickness, caloric intake and behavior measures were obtained weekly for the 12-week duration of the trial. Repeated measures on these variables were therefore available for 6 weeks on dronabinol and 6 weeks on placebo for each subject. Complete data were obtained for 11 subjects and for 10 weeks for the one subject who died before the end of the study. For that individual, who was assigned to the placebo for the last 6 weeks of the study, values for the last 2 weeks were estimated by taking the average of measures for the previous 4 weeks.

Nutritional status was monitored by weekly measurements of body weight and triceps skin fold thickness, and by measurement of plasma albumin and lymphocyte count at the beginning and end of

each study period. The caloric intake was calculated from the fraction of prescribed diet and dietary supplements consumed during 2 days each week. The diet was kept constant during the study. Body mass index (BMI) was calculated from body weight and height measured either in a standing position or by a knee caliper as weight (kg) divided by height (m) squared.

The extent of disturbed behavior exhibited by each patient was determined each week by interview with primary caregivers who were familiar with patients' behavior and with rating scales. The disturbed behavior was measured by the Cohen-Mansfield Agitation Inventory (CMAI) (Cohen-Mansfield *et al.*, 1989), which is a widely used instrument with good psychometric properties. Twenty-nine items of this instrument are rated by frequency (from 1 = never to 7 = constantly or almost constantly) and by disruptiveness (from 1 = not at all to 5 = extremely). For each observation period, the total score was calculated by multiplying the frequency and disruptiveness of individual items and adding the products. Patients' affect was measured using the Lawton Observed Affect Scale—Past (Lawton *et al.*, 1996). This scale consists of six items, three measuring positive affect (pleasure, interest and contentment) and three negative affect (anger, anxiety/fear and depression/sadness) on a five-point scale (from 1 = never to 5 = more than three times a day). The negative and positive affect scores were calculated by adding scores of the appropriate items.

Statistical analysis was performed using Statistix 4.1 (Analytic Software). Repeated measures ANOVA for the 12 weeks of the study was done to test for effects of order, time and treatment on study variables. In this analysis, time and treatment were repeated measures and order (dronabinol first vs placebo first) was a non-repeated measure. The repeated measures ANOVA was done for body weight, triceps skin fold thickness, caloric intake, disturbed behavior and negative and positive affect.

RESULTS

Of the 15 patients enrolled in the study, 11 patients completed both study periods. One patient who died of a heart attack 2 weeks before the end of the study, while on placebo, was also included in the analysis. The study was terminated in three patients: one developed a grand mal seizure after the first dronabinol dose and two developed serious intercurrent infections. Of the 12 patients included in the analysis, six received placebo for 6 weeks followed by dronabinol for 6 weeks, and six received dronabinol for 6 weeks followed by placebo for 6 weeks.

Table 1. Characteristics of study population

Characteristic	Mean ± SD	Range
Age (yr)	72.7 ± 4.9	65–82
Gender	11 males, 1 female	
Duration of DAT (yr)	7.0 ± 4.1	2–16
Duration of long-term care before beginning of study (months)	17.4 ± 21.9	2.6–81.0
Mini-Mental State Examination score	4.0 ± 7.4	0–20
Katz Activity of Daily Living score	5.7 ± 0.6	4–6
Bedford Alzheimer Nursing Scale—Severity score	17.5 ± 3.0	13–22
Body mass index (kg/m^2)	22.6 ± 2.5	16.9–26.2
Plasma albumin (g/dl)	3.7 ± 0.4	3.1–4.5
Lymphocyte count (thousand/mm^3)	1.7 ± 0.4	0.8–2.3

Note: The numbers are means ± SD.

The subjects included in the analysis were all 65 years old or older and all but one were males (Table 1). Duration of DAT varied from 2 to 16 years and most patients had been in institutional long-term care for many months before the onset of the study. Most also suffered from severe dementia; the MMSE score was 0 in eight subjects. Patients were also severely impaired in activities of daily living: nine were dependent in all six activities. BANS-S score, which detects progression of the disease even in the severe stage (Volicer *et al.*, 1994a), indicated moderate to severe impairment. The mean BMI was in a low normal range and only one patient had BMI lower than 20. The mean plasma albumin was in the normal range and no patient had plasma albumin less than 3 g/dl. The mean lymphocyte count was also in the normal range and two patients had a count lower than 1200 cells/mm^3.

Body weight increased during the 12-week study period, regardless of the order in which the treatment was given (Fig. 1) (F(time) = 3.64, df = 5,143, p = 0.006). The effect of dronabinol on weight gain was greater for those who received dronabinol first than for those who received the placebo first (F(order × treatment) = 8.4 for interaction between order and treatment, df = 1, 143, $p < 0.017$). Patients on dronabinol gained 7.0 ± 1.5 lb and 2.3 ± 1.7 lb in the first and second

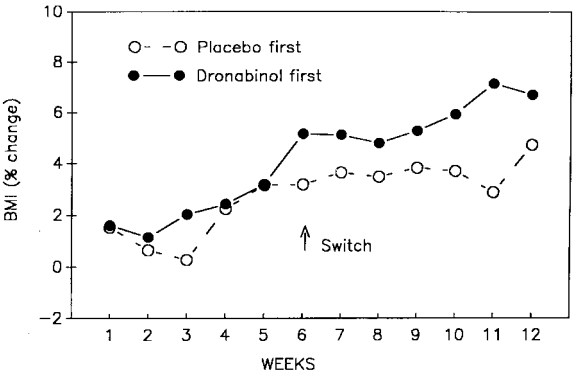

Fig. 1. Changes of the body mass index (BMI) during the placebo and dronabinol phases of the study. The treatment was switched after 6 weeks. For statistical analysis see text

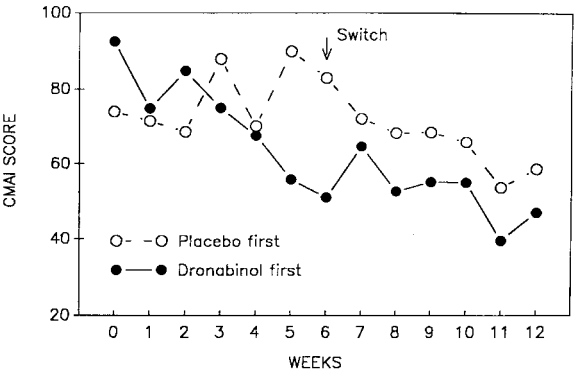

Fig. 2. Changes of the Cohen-Mansfield Agitation Inventory (CMAI) (14) score during the placebo and dronabinol phases of the study. For statistical analysis see text

period respectively, while patients on placebo gained 4.6 ± 1.3 lb and 1.7 ± 2.3 lb. These body weight changes expressed as changes of the body mass index are shown in Fig. 1. Triceps skin fold thickness also increased during the 12-week study period (F(time) = 3.12, df = 5, 143, $p = 0.016$), but was not affected by order or treatment. Caloric intake did not change during the study period and was similar in placebo (2200 ± 128 kcal and 2190 ± 227 kcal) and dronabinol (2219 ± 647 kcal and 2299 ± 227 kcal) periods. Plasma albumin and lymphocyte counts did not change significantly.

Disturbed behavior decreased during both dronabinol treatment periods (F(order × treatment) = 2.78, df1, 143, $p = 0.12$) and this decrease in disturbed behavior persisted during the placebo period following dronabinol treatment (Fig. 2). When the CMAI scores were expressed as percentage of the baseline, there was a significant order × time interaction (F = 2.35(order × time), df = 5, 143, $p = 0.05$).

Negative affect decreased during the 12-week study period as shown in Fig. 3 (F(time) = 2.46, df = 5, 143, $p = 0.045$) and it decreased more while patients were on dronabinol than during the placebo periods (F(time × treatment) = 3.98, df = 5, 143, $p = 0.004$). Further, the decrease was greater for those who received dronabinol first compared to those who received placebo first (F(order × time) = 5.45, df = 5, 143, $p < 0.0005$). In contrast, positive affect remained similar during both treatments and treatment periods.

Eleven of the patients were on a psychoactive medication before the beginning of the dronabinol study and were maintained on the same

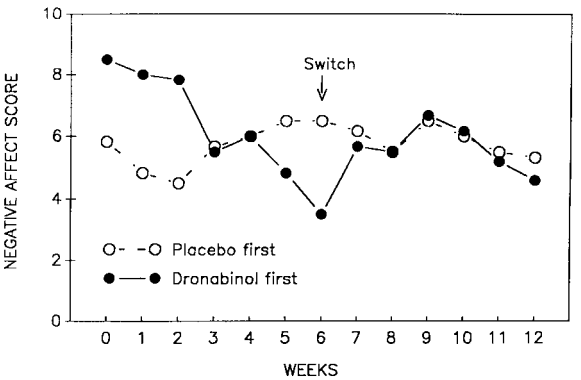

Fig. 3. Changes of the negative affect score (15) during the placebo and dronabinol phases of the study. For statistical analysis see text

medication during the study period. Four patients were receiving regular doses of neuroleptics (perphenazine, thiothixene, haloperidol or thioridazine), four patients were receiving regular doses of benzodiazepines (three lorazepam and one alprazolam) and eight patients were receiving regular doses of antidepressants. The antidepressants included sertraline (eight patients), trazodone (four patients) and desipramine (one patient). Three patients were on both sertraline and trazodone, and one patient was switched from trazodone to doxepin. Antidepressant treatment was initiated at least 4 weeks before the start of the study and the mean duration of antidepressant treatment before study initiation was 7 months. Eleven patients had orders for psychoactive medications as needed (PRN). These included lorazepam in four patients

Table 2. Adverse reactions reported during the study

Symptom	Dronabinol				Placebo			
	Patients		Weeks		Patients		Weeks	
	N	%	*N*	%	*N*	%	*N*	%
Anxiety/nervousness	11	92	37	53	12	100	43	61
Emotional lability	11	92	32	46	10	83	36	51
Tiredness	9	75	25	36	5	42	15	21
Somnolence	8	67	29	41	4	33	12	17
Euphoria	7	58	31	44	5	42	16	23
Paranoid reaction	4	33	16	23	5	42	18	26
Hallucination	4	33	11	16	5	42	16	23
Depression	2	16	4	6	2	16	4	6
Ataxia	2	16	6	8	2	16	3	4
Muscle pain	2	16	7	10	1	8	3	4
Diarrhoea	2	16	3	4				
Flushing	1	8	2	3	2	16	2	3
Increased confusion	1	8	2	3	2	16	2	3
Sweating	1	8	2	3	1	8	1	1
Increased speech difficulty					1	8	1	1
Headache	1	8	1	1				
Nightmares					1	8	1	1

Note: There were totals of 12 patients and 70 weeks of observation. In addition to the listed effects, one incidence of seizure in a dronabinol-treated patient was observed.

and alprazolam, trazodone, doxepin, haloperidol, perphenazine and thioridazine in one patient each. The patients received these medications very rarely, on average, 9.7 doses/6 weeks during placebo administration and 7.2 doses/6 weeks during dronabinol administration.

With the exception of a seizure which occurred in one patient, no serious adverse reactions to dronabinol were detected. Some reactions, eg emotional lability, anxiety/nervousness, hallucinations and paranoid reactions, were observed in most patients, but were not associated with treatment. More patients exhibited tiredness, somnolence and euphoria during the dronabinol treatment than during placebo periods (Table 2). The number of weeks during which euphoria and somnolence were observed during the dronabinol therapy was also much larger than the number of weeks during the placebo periods. In no case was dronabinol treatment discontinued because of these side-effects.

DISCUSSION

Food refusal in DAT patients leads to considerable stress among health care providers and families (Lo and Dornbrand, 1984) because of its emotional and ethical implications (Callahan, 1995). Providing nourishment is one of the basic components of care which is often seen as necessary to maintain comfort of the patient. If the problem is not openly discussed, the staff are forced to choose between allowing the patient to deteriorate physically because of inadequate intake or forcing the patient to take nourishment against his or her will. As a result, conflicts arise with regard to the perceived obligation to keep the patient alive, the desire not to cause pointless suffering and respect for the patient's wishes (Norberg *et al*., 1980). Alternatively, tube feeding is instituted, which deprives the patient of the taste of food and contact with caregivers during the feeding process, and may require restraining the patient to prevent tube removal.

Antidepressant treatment is often effective in decreasing food refusal in patients with advanced dementia (Volicer *et al*., 1994b). However, the present study indicates that weight gain could be further promoted by administration of dronabinol even in patients on antidepressant therapy. Body weight actually increased in both patients who were on dronabinol and placebo. This could have been caused either by a delayed effect of antidepressants or by more intensive feeding efforts. Since the antidepressants were started several weeks before initiation of the study, it is unlikely that they caused this weight gain. We felt that stopping antidepressant treatment would not be ethical in these

nutritionally compromised patients. Changes in the patient feeding practices may be a more likely explanation of this general weight gain. Although the study was double-blind, the staff knew the objectives of the study and might have made more intensive efforts to get the patients to eat.

Surprisingly, the caloric intake was similar during the placebo and dronabinol periods. It is possible that the weight gain was partly caused by decreased agitation of the patients, which could have decreased their caloric requirements. Decreased agitation was observed using two scales: CMAI and Observed affect Scale. The negative part of the Observed Affect Scale includes two items (anger and anxiety/fear) which are commonly present in patients during agitated behaviors. The third item, depression/sadness, was rarely observed, as can be seen from Table 2. Thus both scales measured similar disruptive behaviors. It is possible that this effect was partly due to somnolence, which was twice as common in patients treated with dronabinol as in patients on placebo.

The possibility that the weight gain was partly caused by decreased agitation is supported by the restriction of the effect of dronabinol on body weight to the first treatment period. Since the effect of dronabinol on disturbed behavior carried over to the following placebo period, there was no difference in the disturbed behavior in the second treatment period. This prolonged change in disturbed behavior could be due to a long-term effect of dronabinol. It has been reported that tetrahydrocannabinol metabolites are present in the urine as long as 77 days after ingestion of marijuana (Ellis *et al*., 1985). Dronabinol pharmacokinetics can be described by a four-compartment model, with initial half-life of 4 hours and terminal half-life of 25–36 hrs (Agurell *et al*., 1986). However, low levels of dronabinol metabolites have been detected in the urine and feces for 2–5 weeks after initiation of a supervised abstinence (Dackis *et al*., 1982).

Dronabinol treatment did not change the positive affect (Lawton *et al*., 1996), although euphoria as an adverse reaction was reported more frequently and in more patients during the dronabinol treatment than during placebo periods. It is possible that the positive affect items represent more a degree of patient's engagement than patient's mood (Lawton *et al*., 1995).

The main adverse reaction, possibly caused by dronabinol, was occurrence of a seizure in one patient shortly after receiving the first dose of dronabinol. This seizure could have been caused by dronabinol because it has been reported that tetrahydrocannabinol lowers seizure threshold in rats (Chiu *et al*., 1979). In a study involving 809 patients receiving dronabinol as an antiemetic, two patients (0.24%) developed myoclonic jerking and one patient (0.12%) developed grand mal seizures (Devine *et al*., 1987). However, it is important to note that recurrent seizures also develop without any precipitating event in 20% of patients with advanced DAT (Volicer *et al*., 1995). In the patient who developed a seizure after the first dose of dronabinol, the seizure did not recur despite the lack of anticonvulsant treatment, but the follow-up was limited to 2 months because the patient died of causes unrelated to participation in the study. Therefore, it is not clear if the seizure observed in this study was caused by dronabinol or by progression of DAT. A larger trial of dronabinol in DAT patients is necessary to address whether the incidence of seizures is increased during dronabinol therapy. It is also possible that a lower dose than the one used in this study would be effective and safer in this patient population.

Other possible side-effects included tiredness, somnolence and euphoria, which were observed more frequently and in more patients during dronabinol treatment than during the placebo period. These side-effects were not unexpected considering the pharmacological profile of dronabinol, and were not severe enough to require discontinuation of the study. In contrast, the study indicates that dronabinol did not increase paranoid reactions and hallucinations, although perception distortions have been observed in previous trials (Devine *et al*., 1987). There was also no evidence of increased confusion, ataxia and speech difficulties which would impair cognitive or functional abilities of Alzheimer patients.

Results of this study indicate that dronabinol may be a useful addition to drugs used for management of patients with DAT and other dementias. There are, however, several questions which need to be further investigated. This study used a single fixed dose, which may not be optimal in this patient population. The study was also not designed specifically to investigate behavioral and affective changes after dronabinol administration. Results of this further investigation are needed before the place of dronabinol in the treatment of anorexia and behavioral problems in DAT patients can be clearly delineated. None the less, these early results are promising and a larger-scale study of dronabinol in patients with DAT is warranted.

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