The Impact of Δ⁹-THC on the Psychological Symptoms of Anorexia Nervosa: A Pilot Study

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ABSTRACT

Background: Δ⁹-Tetrahydrocannabinol (Δ⁹-THC) is the active compound of *Cannabis sativa* with appetite-stimulating properties. This study evaluated the effect of low doses of oral Δ⁹-THC on self-reported symptoms of patients suffering from chronic anorexia nervosa (AN).

Methods: Nine female subjects over 18 years of age participated in the study. Six were diagnosed according to DSM-IV criteria with AN restrictive type and three with active AN binge-purge type. Their mean age was 45.0±3.2 years and their BMI was 16.1±1.6 kg/M². They completed questionnaires before and after treatment with Δ⁹-THC (1 mg/day for one week and 2 mg/day for three weeks). The primary outcome was improvement in the way patients perceived their eating behavior.

Results: Significant improvements were found in self-reported body care, sense of ineffectiveness, asceticism and depression. There were no significant changes in BMI.

Conclusions: Δ⁹-THC may be an effective component in treating the psychological symptoms of AN.

INTRODUCTION

Anorexia nervosa (AN) is a psychiatric illness characterized by an abnormally low body weight, intense fear of gaining weight and a distorted perception of body weight. Diagnostic criteria also include refusal to maintain weight at or above a minimally normal weight for age and height, or failure to reach expected weight; fear of gaining weight despite being underweight; disturbances in body perception, or undue influence of weight and shape on self-evaluation, or denial of the seriousness of low weight, and amenorrhea (DSM-IV, 1994). AN usually starts as a restricting subtype, with 30-60% of restricting patients progressing to binge-purging AN or bulimia nervosa (BN) (1, 2). The prevalence of AN in young females is 0.3-0.5% (3).

AN is associated with high rate of DSM-IV Axis I comorbidities. Between 40-70% of these patients have lifetime affective (mainly depressive) and anxiety (mainly obsessive compulsive and social phobia) disorders, and similar rates of patients with bingeing/purging AN have lifetime substance use disorders (SUDs) (4). The lifetime mortality rate in AN is between 5-20% (5), higher than that reported for most psychiatric disturbances (5).

AN is a chronic disorder with recovery occurring usually after 4-10 years (1, 2). Recovery - defined in terms of achieving normal weight, regular menstrual cycles and normal eating patterns for a period of at least one year - occurs in 40-50% of AN patients (1, 2). Despite treatment, around 20% of patients with AN show a chronic non-remitting pattern over time. Such a disease course may be associated with a long duration of illness until receiving treatment, refusal to accept and maintain treatment, severe disturbances in body image, obsessional-ritualistic eating and physical exercise, presence of purging/bingeing and comorbid disorders, maladaptive relations with family members, dysfunctional social skills, and a history of childhood sexual abuse (1, 2).

The etiological underpinnings of AN are complex and multifactorial, including social, genetic, psychological and biological predispositions (6). Understanding how severe

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weight loss might affect brain function may assist in better understanding the etiology and lead to the development of new therapeutic strategies. In order to accomplish it we have developed three experimental animal models of AN which represent different aspects of the disorder: diet restriction, activity wheel and separation stress (7-9).

The plant Cannabis sativa and its active ingredient, Δ^9- tetrahydrocannabinol (Δ^9-THC) are known appetite stimulators (8, 9). Following the discovery of the endocannabinoids anandamide and 2-arachidonoylglycerol (2-AG) (amide and ester of the essential fatty acid arachidonic acid respectively that bind to the cannabinoid receptors), we tested their effects on appetite in these mice models (10, 11). A small dose of anandamide (0.001 mg/kg) improved food consumption and cognitive function and normalized neurochemical changes caused by diet restriction in both the hypothalamus and hippocampus, responsible for appetite regulation and learning, respectively. Diet-restricted mice treated with anandamide for one week consumed 44% more food than controls and performed better in the eight arm maze test testing spatial memory (11). This was accompanied by higher norepinephrine (NE) and dopamine levels in the hypothalamus and hippocampus, serotonin (5-HT) in the hypothalamus and lower 5-HT in the hippocampus. NE turnover in the brain increased following anandamide administration and corticosterone concentrations in the plasma were normalized (11). Administration to mice of SR 141716A, an antagonist of the CB1 cannabinoid receptor, led to significant weight loss (11). These results suggested the therapeutic potential of manipulating the endocannabinoid system. Furthermore, 0.001 mg/kg Δ^9-THC given to Sabra mice increased food consumption by 22%, with some improvement of cognitive function. A decrease in dopamine and 5-HT and increase in NE were observed without any addictive effects. SR 141716A reversed these effects (8). AN is also characterized by anhedonia whereby patients experience little pleasure or reward. Reward pathways and the endocannabinoid system have been implicated in mediating food intake. The effect of sub-chronic (6 days) Δ^9-THC (0.1, 0.5, or 2.0 mg/kg/day) has been assessed on normal and high-fat diet (HFD) intake, body weight, running wheel activity (RWA), thermogenesis in brown adipose tissue (BAT) and lipid metabolism in white adipose tissue (WAT). Limited time availability of food and continuous access to running wheels led to anorexia and significantly reduced body weight. Δ^9-THC (0.5 and 2.0 mg/kg/day) stimulated food intake with moderate effect on RWA. Δ^9-THC (2.0 mg/kg/day) combined with HFD produced increased food intake, reduction in RWA, attenuation of body weight loss and changes in markers of thermogenesis in BAT and lipolysis in the WAT. The results have shown the effectiveness of the endocannabinoid system in attenuating the weight loss associated with the development of ABA by both increased food intake and reduced energy expenditure (12).

The activity-based anorexia (ABA) paradigm was optimized so that food-restricted wheel-running mice displayed anorexia, reduced body weight and disrupted activity and circadian cycles (13). The effects of Δ^9-THC and the endocannabinoid uptake inhibitor OMDM-2 were investigated in C57BL/6 mice. Daily Δ^9-THC (0.5 mg/kg) decreased survival in the ABA animals but increased feeding in the survivors, OMDM-2 (3 mg/kg) increased food intake, but not sufficiently to reverse weight loss (13).

In human subjects, studies assessing the acute appetitive effects of Δ^9-THC showed an increased intake, elevated hunger ratings and enhanced food appreciation (14-17). Gross et al. (14) compared the effects of high doses of THC (from 7.5 mg/day to 30 mg/day) and diazepam in 11 patients with primary AN after a weight loss of 25%, even though benzodiazepines may also increase food intake. The medication was discontinued over the weekend to avoid addiction, and THC-induced weight gain was slightly higher (1 kg) than observed during diazepam treatment. Three patients (27%) withdrew after experiencing severe dysphoric reactions during active treatment, suggesting that high-dose THC was not tolerated in the treatment of primary AN. Hollister et al. (15) gave Δ^9-THC to a group of patients after fasting and to a group that ate normally. Each group received 32 mg/day of Δ^9-THC that was taken in a low caloric soft drink. The study showed that Δ^9-THC significantly increased food intake.

Nelson et al. (16) showed a median weight gain of 1.3 kg over 28 days on relatively small daily doses of THC (2.5 mg) in an interventional phase II study in patients with cancer-associated anorexia. Strasser et al. (17) compared the effects of cannabis extract, delta-9-tetrahydrocannabinol, and placebo on appetite and quality of life in Adult patients with advanced cancer with cancer-related anorexia-cachexia syndrome. Cannabis extract standardized for 2.5 mg THC and 1 mg cannabidiol) or THC (2.5 mg) or placebo orally, twice daily for 6 weeks. Cannabis extract at the oral dose administered was well tolerated by these patients with cancer-related anorexia-cachexia syndrome. No differences in patients' appetite or quality of life were found either between cannabis extract, THC, and placebo or between cannabis extract and THC at the dosages investigated. Beal et al. (18) had shown long-term, safe use of dronabinol for anorexia associated with weight loss in patients with AIDS (19). Haney et al. (19) showed in a multicenter, double-blind, placebo-controlled parallel-group

trial in participants with AIDS-induced anorexia a minor weight gain in the THC group of 0.5 kg above placebo after receiving 5 mg THC daily over 6 weeks.

Bedi et al. (20) showed in HIV-positive marijuana smokers, that high dronabinol(a synthetic cannabinoid) doses safely and effectively increased caloric intake. However, repeated high-dose dronabinol appeared to result in selective tolerance to these effects. These findings indicate that HIV-positive individuals who smoke marijuana may require higher dronabinol doses than are recommended by the FDA. Andries et al. (21) investigated the orexigenic and anabolic effects of dronabinol in 25 women over 18 years with AN of at least 5 years duration. A prospective, randomized, double-blind, controlled crossover study was conducted between 2008 and 2011 at a specialized care center for eating disorders. The patients were randomized to treatment with either dronabinol-placebo or placebo-dronabinol. In addition to the standardized baseline therapeutic regimen, the participants received dronabinol, 2.5 mg twice daily for 4 weeks and matching placebo for 4 weeks, separated by a 4-week wash-out period. Primary outcome was the mean change in body weight. Secondary outcome was score changes on the Eating Disorder Inventory-2 (EDI-2). Data were analyzed for the 24 patients who completed the trial. During dronabinol treatment, participants gained 0.73 kg ($p < 0.01$) above placebo without significant psychotropic adverse events. Dronabinol significantly predicted weight gain in a multiple linear regression including EDI-2 body dissatisfaction score and leptin. EDI-2 subscale scores showed no significant changes over time. The dronabinol therapy was well tolerated. The effect of dronabinol therapy on physical activity in AN was tested by Andries et al. (22) in a randomized, controlled double-blind study. The cannabinoid agonist treatment was associated with a modest increase in physical activity in adult women with severe and longstanding AN. Additionally, there was a strong relationship between the circulating levels of leptin and physical activity in these chronically undernourished patients. Low dose dronabinol did not affect the concentration or the activity of the circulating IGF-system in women with severe and chronic AN. However, the results suggest that such treatment may alleviate the increased hypothalamic-pituitary-adrenal axis activity seen in these patients (23). The majority of trials investigating the orexigenic effects of cannabinoids (8-23) have reported increased appetite and body weight, providing evidence of the effects of CB1 agonist treatment in humans and the safety of using it in underweight individuals.

In view of the above considerations, we decided to perform a small pilot study to treat AN patients for a 4-week period of time with low doses of THC, in order to determine effects on appetite and cognition and avoid any psychotropic effects of the drug. This study is one of only three that has tried to assess the effect of THC in the treatment of AN. Taking into account the limited treatment options for severe AN and the high morbidity and mortality rate for this psychiatric disorder, and their poor cooperation in treatment, we justify this preliminary trial with a small sample size since any progress is of clinical importance.

METHODS

This research is a preliminary open-label trial with no placebo control group due to the difficulties to recruit patients with AN to cooperate in research protocols in general, and in placebo trials in particular.

Participants. Ten female volunteers aged ≥18 y diagnosed with AN according to DSM-IV criteria (1, 2) were recruited from the outpatient eating disorder treatment facility at the Rambam Medical Center, Haifa, Israel. The patients, with a mean age was 45.0±3.2 years, were suffering from chronic AN (average duration seven years). Mean body mass index (BMI) (weight and height were measured at the clinic) was 16.1±1.6 kg/m^2. The participants were examined for comorbidities including personality disorders using a structured clinical interview for DSM-IV that was reached by experienced psychiatrists via standard clinical interview procedures (MINI-SCID)(24).

Exclusion criteria included: physical and mental illnesses which might cause weight loss not related to AN, drug treatment which might increase weight, affective or psychotic mental illnesses and a history of drug/alcohol abuse during the year preceding the treatment. Ten female volunteers aged ≥18 met the entry requirements and were enrolled, six had AN restrictive type and four had AN binge purge type. Nine of the participants completed the study, with one dropout (patient 2). This participant was withdrawn after one week due to deterioration in mental state and the need for psychotropic medication.

No adverse or side effects were observed and the remaining participants showed willingness and full compliance during the course of the study. Of interest to note that during recruitment, some AN patients refused to participate because of fear of gaining weight from the minute amounts of olive oil used as a solvent for the drug. It was very difficult to recruit 10 women to participate.

All the patients were at a severe chronic state of the illness, thus the changes in psychological symptoms may count as relatively significant.

All women were receiving weekly supportive psychotherapy, biweekly nutritional therapy, and medical and psychiatric follow-up about every three months. They were in moderate to severe medical and psychiatric condition, and they had nutrition and medical supervision about once in two weeks, and psychiatric treatment as needed. They had no other treatment.

INSTRUMENTS

Participants were requested to complete the following surveys:

Eating Disorder Inventory (EDI-2) (25). The EDI-2 is a widely used 91-item questionnaire designed to provide a broad assessment of the prevalence and intensity of psychological traits known to be associated with eating disorders. The EDI-2 is organized into 12 primary scales, three of which are specific to eating disorders and nine are general psychological scales that are highly relevant to eating disorders. It also provides six composites that measure eating disorder risk, ineffectiveness, interpersonal problems, affective problems, over-control, and general psychological maladjustment. The overall Summary Score was used as a primary outcome measure. The Hebrew translation of this inventory was found valid and reliable (26).

Eating Attitude Test (EAT-26) is a widely used standardized self-report measure of symptoms and concerns characteristic of eating disorders (27). The EAT-26 has been particularly useful as a *screening* tool to assess "eating disorder risk." The tests are rated on a six-point scale in response to how often the individual engages in specific behaviors. The EAT-26 includes three subscales, oral control, dieting and bulimia, and can be scored according to subscales and total score (27).

The Beck Depression Inventory (BDI–II) is one of the most useful tools for assessing depressive symptoms in both clinical and non-clinical settings (28). It is a 21-item scale that asks responders to choose one out of four statements that best describe their feelings over the last two weeks. Responses are scored from 0-3, and total scores range from 0-63, with higher scores indicating greater levels of depressive symptomology. A score of 0-9 indicates no depression, 10-18 indicates mild depression, 19-29 indicates moderate depression and 30+ indicates severe depression (28).

The Body Shape Questionnaire (BSQ) is a 34-item instrument designed to measure concerns about body shape among young women. The BSQ is based on the notion that disturbance of body image is a central feature of both anorexia nervosa and bulimia. Although a number of assessment procedures have been developed that deal with various aspects of body image, the BSQ is one of the few measures that focus on concerns about body shape. This is especially important because concern about body shape is one of the key dimensions distinguishing the disorder of anorexia. In particular, the BSQ focuses on the phenomenological experience of "feeling fat." The BSQ can be used for both assessment purposes and to evaluate response to treatment. Responses are scored in a 6-point Likert type scale with responses ranging from "always" = 6 to "never" = 1. Scores on the BSQ can range from 34-204, with a higher score indicating more body dissatisfaction. The BSQ has demonstrated high internal consistency (29).

Spilberger State and Trait Anxiety Inventory (STAI) is a commonly used measure of trait and state anxiety (30, 31). It is used in clinical settings to diagnose anxiety and to distinguish it from depressive syndromes. It also is often used in research as an indicator of caregiver distress. Participants were instructed to avoid driving, alcohol use, psychotropic drugs and drug abuse during the course of the experiment. They were requested to report any other drug used during the four weeks of experiment. A one-hour visit at the beginning of each week included score of weight gain, caloric consumption and psychiatric evaluation.

Diagnosis and symptoms: DSM-IV diagnosis was made using the Mini International Neuropsychiatric Interview for DSM-IV Axis I Disorders (MINI) (24)**.**

PROCEDURE

The participants were initially screened for eligibility upon signing a consent form. Study assessment took place at baseline (week 0) and at the end of week 4 and included survey filling. Δ^9-THC was prepared from crystalline cannabidiol, CBD (99% purity) according to Gaoni and Mechoulam (32).

Δ^9-THC was dissolved in olive oil. The THC container was slightly heated by touching prior to administration to the patients. Each push of the bottle released one drop. In the first week of the experiment, 3 drops were administered to the patients by placing them under the tongue, each day at 16:00pm, a total of 1 mg/day. In the following three weeks, three drops were taken in the morning and three at 16:00pm each day, a total of 2 mg/day. The patients were shown how to administer it by a staff member who provide the participants an explanation about the study, possible side effects, not to drive or to take more than the dosage suggested.

Diaries were provided along with the study medication to record daily administration of the drug and feelings concerning appetite and anxiety. The medication was given for a 4-week period. Questionnaires were administered at

baseline T1 as well as at the end of intervention period, T2. The experimental protocol was approved by the Helsinki Committee of the Ministry of Health no. 1960. The procedures followed were in accordance with the Helsinki Declaration of 1975 as revised in 1983. Written consent was provided by each patient at the beginning of the study.

STATISTICAL ANALYSIS

For each survey, sub-scales concerning certain parameters were analyzed: in EDI-2 – drive for thinness (DT), bulimia (B), body dissatisfaction (BD), ineffectiveness (I), impulse regulation (IR) and social insecurity (SI), in BDI – depression rank, in BSQ – feeling and positions regarding body image, feeling of comfort as a result of touch, body care, and body protection, in Spielberger test – anxiety rank, in EAT-26 – diet, bulimia and anorexia sub-scales. Each survey was scored at week 0 and at week 4 for the same participant, in order to reveal within-subject differences as a result of the treatment with Δ9-THC. Results were analyzed by paired Student t-tests. P value<0.05 was considered significant. Data are presented as mean ± standard error of the mean (SEM).

RESULTS

BODY WEIGHT CHANGES

The average weight gain over four weeks was 0.95kg (p= 0.24). From Table 1, it seems that the weight of most of the participants (except no. 4 whose diagnosis was EDNOS-AN and patient no. 10) actually gained weight.

EDI-2 TEST

A significant decrease in the asceticism sub-scale was observed in this test (p=0.049). The decrease in ineffectiveness sub-scale nearly reached statistical significance (p=0.08). No significant differences were found in other sub-scales (Table 2). There were no other significant differences in the total EDI-2 test between baseline and post-treatment scores.

BDI TEST

There was a significant decrease in depression rank in the Beck depression inventory test (3.12 vs 2.50, p<0.049).

BSQ TEST

A significant increase was found in body care sub-scale (p=0.02). No significant differences were observed in other sub-scales (Table 3).

EAT-26

No significant differences were found in any of the sub-scales or in the total score of this test .

Table 2. *Baseline and post-treatment scores of the EDI-2 test, including sub-scales, presented as mean ± SEM*

	baseline (week 0)	end of experiment (week 4)	p-value (2-tailed)
Drive for thinness	13.22±1.95	13.44±2.06	0.86
Bulimia	2.44 ± 1.31	3.11 ± 1.36	0.19
Body dissatisfaction	11.11 ± 2.41	11.33 ± 2.86	0.89
Ineffectiveness	15.22 ± 3.82	11.22 ± 3.37	0.08
Perfectionism	7.89 ± 1.24	7.89 ± 1.94	1.00
Interpersonal distrust	5.78 ± 1.52	7 00 ± 2.01	0.36
Internal awareness	9.22 ± 2.27	11.44 ± 3.35	0.45
Maturation fear	10.22 ± 2.36	8.22 ± 2.40	0.21
Asceticism	10.00 ± 2.46	7.06 ± 1.61	0.049
Impulse regulation	10.33 ± 2.84	12.44 ± 4.03	0.57
Social insecurity	6.89 ± 1.56	6.67 ± 0.90	0.9

Table 3. *Baseline and post-treatment scores of the BSQ test, including sub-scales, presented as mean ± SEM.*

	baseline (week 0)	end of experiment (week 4)	p-value (2-tailed)
Body image	14.22±2.53	14.67±2.53	0.76
Touch	18.33±2.6	18±2.78	0.77
Body protection	17.56±2.1	18.44±2.79	0.44
Body care	19.22±1.87	20.22±1.79	0.02

Table 1. *Baseline and post-treatment characteristics of the participants in the study*

Subject	Age (yr)	AN subtype'	Weight (kg) at week 0 (baseline)	Weight at week 4	Weight change	Height (m)
1	42	restrictive AN	40.70	40.85	+1.50	1.55
3	21	restrictive AN	28.00	32.50	+ 4.50	1.77
4	25	binge purge AN-EDNOS	57.50	56.10	-1.40	1.69
5	38	restrictive AN	38.50	38.70	+ 0.20	1.50
6	19	restrictive AN	38.10	41.50	+ 3.40	1.57
7	24	binge purge AN	50.00	52.50	+ 2.50	1.64
8	34	restrictive AN	46.40	47.60	+1.20	1.55
9	48	binge purge AN-EDNOS	57.00	57.50	+ 0.50	1.71
10	25	binge purge AN	39.50	37.00	- 2.50	1.58

SPIELBERGER STATE AND TRAIT

There were no significant changes in the anxiety rank scored in this test.

DISCUSSION

Low dose Δ^9-THC significantly improved depression rank and asceticism and body care sub-scales, with a positive effect on ineffectiveness and body weight (1.9 kg /4 weeks, $p<0.098$), but might affect also the patient's psychological traits. From the information provided in Table 1, it seems that the body weight of most of the participant (except no. 4 whose diagnosis was EDNOS-AN and patient 10), gained weight in absolute terms. This supports the hypothesis that the intervention seems to have been helpful also in terms of weight gain, but that the strength of the study was not adequate to show this. The weight changes implied that participants adopted a less restricted attitude towards body feeling and self-esteem in general, which may have caused an improved mood. This hypothesis should be examined in future research.

No side effects for Δ^9-THC were observed in the low doses used in this study in contrast to the findings for higher dosages (14). Cannabinoids may stimulate appetite and increase body weight in AIDS and cancer patients (16-23) as well as food craving (33). Nelson et al. (16) reported that 2.5mg Δ^9-THC, given orally two or three times a day to cancer patients with anorexia, resulted in an increase in food intake, in the low dosage group (two times a day). In the high dosage group (three times a day), the patients experienced severe side effects, especially dizziness and nausea. In addition, a biphasic effect was noticed in animal models, following cannabinoids agonist treatment where low doses are anxiolytic but anxiogenic in higher ones together these results support the use of lower doses as in the current pilot study.

Plasse et al. (34) reported the effect of dronabinol as an appetite stimulant in cancer patients. Results were inconsistent although some patients did actually gain weight. However, there was a reduction in the rate of weight loss in all groups, which was significant at doses of 2.5 or 5mg administered four times a day. AIDS patients, who were losing 0.93kg/month, showed a weight gain of 0.54 kg/month after receiving 2.5 mg dronabinol three times a day.

Hollister (15) gave Δ^9-THC to a group of patients after fasting and to a group that ate normally. Each group received 32 mg/day of Δ^9-THC that was taken in a low caloric soft drink. The study showed that Δ^9-THC significantly increased food intake.

The effect of Δ^9-THC on patients with AN has been evaluated using Δ^9-THC in much higher doses. In Gross et al. (14) Δ^9-THC was given three times a day to subjects with AN, and the dosage was increased over a two-week period from 7.5 mg to 30 mg (about 0.22-0.88 mg/kg). No weight increase was found in the Δ^9-THC-receiving patients in comparison with the placebo treated patients. However, Gross et al. (14) pointed out that the placebo used – diazepam - was known to cause an increase in food intake when taken in certain doses. Furthermore, at higher doses there were no significant effects on food intake, and there was a possibility of developing tolerance to the drug with cannabinomimetic side effects (14).

Andries et al. (21) investigated the effects of treatment with a synthetic cannabinoid agonist on body weight and eating disorder-related psychopathological personality traits in women with severe, enduring AN. This add-on, prospective, randomized, double-blind, controlled cross-over study was conducted between 2008 and 2011 at a specialized care center for eating disorders. Twenty-five women over 18 years with AN of at least five years duration were randomized to treatment with either dronabinol-placebo or placebo-dronabinol. In addition to the standardized baseline therapeutic regime, the participants received dronabinol, 2.5 mg twice daily for four weeks and matching placebo for four weeks, separated by a four-week wash-out period. Primary outcome was the mean change in body weight. Secondary outcome was score changes on the Eating Disorder Inventory-2 (EDI-2). Data were analyzed for the 24 patients who completed the trial. It was shown that dronabinol therapy to severe enduring patients with AN during four weeks of exposure induced a small but significant weight gain in the absence of severe adverse events. The 25 participants received dronabinol 2.5mg twice daily for four weeks, the participants gained 0.73kg above placebo without side effects. Dronabinol significantly predicted weight gain in a multiple linear regression including EDI-2 body dissatisfaction score and leptin, EDI subscale scores showed no significant changes over time. Dronabinol therapy was well tolerated. During four weeks of exposure it induced a small but significant weight gain in the absence of severe adverse events (21).

The level of physical activity is inappropriately high in up to 80% of the patients suffering of anorexia nervosa (AN), as a result of conscious efforts to lose weight, affect regulation and biological adaptive changes to starvation induced by hypothermia and neuroendocrine mechanisms. Andries et al. (22) detected the effect of dronabinol on physical activity in patients with chronic and stable

AN, and the role of leptin and cortisol in this process.

This prospective, randomized, double-blind, crossover study was conducted at a specialized care center for eating disorders. Twenty-four adult women with AN of at least five years duration received either the dronabinol-placebo or placebo-dronabinol sequence. Physical activity was monitored during the fourth week of each intervention. Body weight, leptin and urinary free cortisol excretion were measured repeatedly during the trial. Changes in behavioral dimensions related to AN were assessed by Eating Disorder Inventory-2.

The total duration of physical activity did not change, while its average intensity increased by 20% (P = 0.01) during dronabinol therapy, resulting in an increased energy expenditure with 68.2 kcal/day (P = 0.01) above placebo.

This randomized, double-blind study revealed that cannabinoid agonist treatment was associated with a modest increase in physical activity in adult women with severe and longstanding AN. Additionally, they detected a strong relationship between the circulating levels of leptin and physical activity in these chronically undernourished patients.

Andries et al. (23) detected changes in IGF-I, urinary free cortisol and adipokines during dronabinol therapy in AN: results from a randomized, controlled trial.

Cannabinoid agonists are used to treat cachexia of various causes, but their interactions with the hormonal systems that are involved in energy metabolism have not been previously described in humans. Therefore they found it of interest to assess interactions between the synthetic cannabinoid agonist dronabinol and insulin-like growth factor I (IGF-I), urinary free cortisol (UFC) and adipokines in patients with chronic AN. This was a prospective, double-blind randomized crossover study, conducted at a specialized care center for eating disorders. The results are based on 24 adult women with chronic AN who completed the study. The participants received dronabinol (oral capsules, 5mg daily) and matching placebo over four weeks, separated by a four-week washout period. Bioactive IGF was determined by a cell-based bioassay, whereas total IGF-I, IGFBP-2 and -3 and the two adipocines leptin and adiponectin were measured by immunoassays. Dronabinol treatment caused a small, yet significant increase in BMI as compared to placebo (+0.23 kg/m(2); P = 0.04). This modest weight gain predicted a corresponding increase in bioactive IGF-I, while the amount of daily energy expenditure due to physical activity had a comparable but opposite effect. Nevertheless, neither IGF-I, bioactive IGF nor the IGFBPs levels changed significantly during dronabinol intervention as compared to placebo. Adiponectin also remained unaffected by the weight gain, whereas plasma leptin showed a transient increase at three weeks ($P < 0.05$). Their results showed that low-dosage therapy with dronabinol affected neither the concentration nor the activity of the circulating IGF-system in women with severe and chronic AN. However, their results suggest that such treatment may alleviate the increased hypothalamic-pituitary-adrenal axis activity seen in these patients.

Montelone et al. (35) suggested that endocannabinoids are involved in food-related reward and suggest a dysregulation of their physiology in AN. Low dose Δ9-THC might normalize these systems and improve psychological symptoms before weight gain.

Following the promising results of Andries et al. (21) with dronabinol 2.5mg twice daily for four weeks, the small impact on body weight might be due to the low dose of THC administered (2.0 mg/daily), another possibility is that the THC administered contained traces of cannabidiol. Morgan et al. (36) showed that cannabidiol attenuates the appetitive effects of Delta 9-tetrahydrocannabinol in humans smoking their chosen cannabis. The ratio of THC: Cannabidiol might affect appetite. Thus, if the extract contained relatively high dose of cannabidiol it might be less effective.

Therefore, higher sample size and THC dose might result in increased body weight.

STUDY LIMITATIONS AND STRENGTHS

This study is one of only three that have evaluated the effectiveness of THC in the treatment of AN and is therefore very timely and important taking into account the limited treatment options for AN and the high morbidity and mortality rate. However this study was an open-label pilot trial with no placebo control group and with a small sample size. An additional limitation was the lack of measure of compliance with the medication regimen.

All women were receiving weekly psychotherapy, biweekly nutritional therapy, and medical and psychiatric follow-up every three months. This treatment they were receiving at the time of the intervention. It is not possible to rule out that the improvement was due to their ongoing therapy although we think that this is unlikely.

However, the present study is the first to show improvement in the psychological symptoms of patient with AN when treated with Δ^9-THC , without side effects, such as: depression rank, asceticism, ineffectiveness and body care. All the patients were at a severe chronic state of the

illness, thus the changes in psychological symptoms may count as clinically important. These encouraging results on a group of chronic AN patients suggest that low doses of Δ^9-THC should be further studied as an adjunct to the treatment of patients with AN.

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