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ORIGINAL ARTICLE

Effect of dronabinol therapy on physical activity in anorexia nervosa: a randomised, controlled trial

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Abstract
Purpose 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. The purposes of this paper were to (1) assess the effect of dronabinol—a synthetic cannabinoid agonist—on physical activity in patients with chronic and stable AN, and to (2) unravel the role of leptin and cortisol in this process.
Methods This prospective, randomised, double-blind, crossover study was conducted at a specialised care centre for eating disorders. Twenty-four adult women with AN of at least 5-year 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 behavioural dimensions related to AN were assessed by Eating Disorder Inventory-2.
Results 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.
Conclusions This randomised, 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, we detected a strong relationship between the circulating levels of leptin and physical activity in these chronically undernourished patients.

Keywords Anorexia nervosa · Physical activity · Urinary free cortisol · Leptin · Dronabinol

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Up to 80 % of patients suffering from anorexia nervosa (AN) [1] have inappropriately high levels of physical activity; the phenotype varying from constant agitated restlessness to excessive exercising that is undertaken deliberately to induce weight loss [2]. Its implications for the outcome of AN are still unclear, the evidence on this matter being somehow divergent; while some authors described increasing levels of physical activity parallel to weight restoration during inpatient treatment [3–5], others identified these as significant predictors of relapse in patients with long-standing AN [6, 7].

In contrast with the loss of energy and fatigue associated with other states of severe emaciation, the high amount of physical activity is a pivotal and challenging feature of AN, being the result of the conscious efforts to increase energy

consumption and to enhance weight loss, an affect regulation strategy [8] and an expression of the neuroendocrine adaptive changes to chronic starvation [9].

As central behavioural responses to starvation are mediated by the hypothalamic–pituitary–adrenal (HPA) axis, the hyper-secretion of corticotropin releasing hormone and hypercortisolism is well documented in AN and in other causes of prolonged starvation [10]. Additionally, both animal studies observing rodents with "semi-starvation-induced hyperactivity" (often labelled as "activity anorexia") and human data [11] suggest that exercise behaviour is related to an increased HPA-axis activity independent of an eating disorder.

Leptin—a fat tissue hormone synthesised in adipocytes—is essentially involved in the hypothalamic regulation of the metabolic processes triggered by food restriction. Hypoleptinemia has been proposed as a diagnostic marker of AN [12, 13] and co-occurs with high levels of physical activity [14]. Conversely, in animal models of "activity anorexia", administration of leptin led to a marked decrease in semi-starvation-induced physical activity [15], suggesting a direct relationship between the levels of leptin and the amount of physical activity.

Increasing evidence promotes the cannabinoid system as a novel therapeutic target in extreme nutritional states. Specific CB1 antagonists—such as rimonabant—were proved to induce weight loss in the morbidly obese [16], and conversely, agonists have been reported to exert appetitive effects in cachectic subjects [17]. In a previous report [18], we found that dronabinol, a synthetic cannabinoid agonist, safely induced a minor weight gain in patients with severe and longstanding AN, without interfering with the eating disorder-related behaviour and symptomatology. Unfortunately, the potential psychological effects of cannabinoid agonists have limited the human evidence regarding the mechanisms behind their orexigenic effects.

To our knowledge, the effect of cannabinoid agonist stimulation on physical activity has not been tested in humans. A biphasic, excitatory/inhibitory effect of cannabinoids has been repeatedly acknowledged in animal models, but the evidence on this matter is somehow divergent. While some authors found that low doses of cannabinoid agonist decreased locomotor activity, while higher doses increased it in a dose-dependent manner [19], other authors described quite opposite effects.

The HPA-axis activity is suppressed by the endocannabinoid signalling at several cortical and hypothalamic regions, both during basal conditions and in response to acute stress [20]. As excessive physical activity seems to mutually reinforce the HPA-axis over-activation in a vicious circle in some patients with AN [21], cannabinoid stimulation may hypothetically exert a moderating effect on physical activity inducing a decrease in energy expenditure, and thus explaining at least one of the mechanisms involved in the moderate increase in body weight reported during synthetic cannabinoid agonist therapy [18].

Furthermore, exogenous stimulation of the cannabinoid system was both reported to increase the circulating levels of leptin [22] and to induce locomotor suppression in rodent models [23, 24], suggesting another pathway through which cannabinoid agonists may mediate physical activity.

The purposes of this paper were twofold. First: to determine the effect of dronabinol—a synthetic cannabinoid agonist—on physical activity in patients with severe and chronic AN. Secondly: to assess the hypothesised role of HPA-axis activity and leptin secretion in this process.

Methods

Participants

Twenty-four adult women with chronic AN participated in the study. All the participants fulfilled the diagnostic criteria for AN according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision for at least 5 years and attended voluntary both psychiatric therapy and somatic therapy as in- or outpatient at our centre. Patients with previous or current alcohol or drug abuse, and primary diagnosis of mania, schizophrenia or depression were not eligible to participate in the study. Women with unstable heart disease (not comfortable with more than moderate exertion or at rest) were not eligible to participate in the study, nor were women with known allergy to dronabinol or sesame oil.

In addition to the baseline therapeutic regime, the participants received dronabinol, 2.5 mg twice daily for 4 weeks and matching placebo for 4 weeks, separated by a 4-week washout period. The individual therapeutic regimes—including the in- or outpatient status—were identical during both interventions of the study. Participants were randomly allocated to one of the two treatment sequences (placebo-dronabinol and dronabinol-placebo) following a simple, computer-generated randomisation list. The dronabinol and placebo capsules were produced by independent pharmacists [18]. Both the participants but also the staff involved in the trial were kept blind to the treatment sequence and urinary THC analyses during the study.

The effect of dronabinol therapy, primarily assessed by monitoring the changes in body weight, has been reported elsewhere [18]. The changes in physical activity and the hormonal, attitudinal, and behavioural dimensions relevant to AN were assessed as secondary outcome measures.

Setting

This add-on, double-blind, randomised, controlled, cross-over study was conducted from December 2008 to December 2011 at the Odense University Hospital in Denmark. The centre applies a well-documented multi-disciplinary treatment programme [25] comprising psychotherapy, somatic control and nutritional rehabilitation. Approximately 30 % of the referred patients have AN [26]. The study was approved by The Danish Medical Agency (Journal Number: 2612-3699), The Regional Scientific Ethical Committee for Southern Denmark (Project ID: S-20080016) and The Danish Data Protection Agency. It was registered at the European Union Drug Regulating Authorities Clinical Trials (EudraCT number 2007-005631-29) and listed at ClininalTrials.gov (Identifier: NCT00760695). The Regional Unit for Good Clinical Practice monitored the trial.

Data regarding both the duration and the continuity of AN were obtained through a retrospective review of our patient database [25]. Nineteen percentage ($n = 27$) of the 140 consecutively screened patients matched our criteria of eligibility. The results presented in this paper are based on the 24 participants who completed the study [18].

Thirty-eight percentage ($n = 9$) of the participants chose to be monitored in an outpatient setting throughout the study, while 62 % ($n = 15$) were monitored during hospitalisation. All participants (both in- and outpatients) were prescribed individual, nutritionally balanced diets which they followed during the trial. According to the therapeutic regimen, formal exercise groups were not available during the hospitalisation. However, physical activities were not restricted, inpatients having unrestricted access to open-air breaks or home-visits during the weekends. Compliance to treatment was assessed by a count of the capsules returned at each visit and qualitative urinary THC analysis in both in- and outpatients.

Outcomes

Clinical assessments

The participants were clinically evaluated at baseline and during each intervention on a weekly basis, together with a qualitative assessment of urinary 9-tetrahydrocannabinol (THC) by a Roche Integra 400 kit. Body weight was assessed in the morning, at the same time of the day, with the subjects in underwear and barefooted. The measurements were approximated to the nearest 0.1 kg on a calibrated electronic scale.

Accelerometry

The accelerometer (MTI ActiGraph model GT1M) was worn for seven full, consecutive days during the last week of each intervention. The device was initialised before each measurement according to the manufacturer's specifications. The participants were instructed to wear it over the hip from the time they woke up in the morning until bedtime, excepting showering or swimming.

We assessed the average physical activity intensity expressed in counts/minute (CPM) and the duration of PA expressed in minutes/day. The ranges (in CPM) for activity intensities were 0–1,951 for light, and above 1,952 for moderate to hard intensity, as validated by Freedson et al. [27]. for hip worn devices.

Data were compiled using the computer software Propero, recently developed by researchers at the University of Southern Denmark. The epoch length was set to 60 s, and sequences of at least 60 min of consecutive zero counts, indicating that the accelerometer was not in use, were excluded from the recordings. Only data from participants accumulating at least 10 h of activity per day for at least 4 days were analysed.

Energy expenditure was estimated by the Freedson Combination ('98) method,[1] which automatically uses the Work-Energy Theorem to calculate energy expenditure below 1,952 CPM and the Freedson'98 equation to calculate energy expenditure above 1,952 CPM.

Hormone analysis

Plasma leptin was measured in blood samples collected on weekly basis, at the same time of the day, under fasting conditions. Leptin concentrations were determined in duplicates in EDTA plasma using an in-house time-resolved immunofluorometric assay based on commercial reagents as previously described [28]. The intra-assay and inter-assay coefficients of variation were less than 5 and 10 %, respectively.

The secretion of cortisol was assessed during the last day of each intervention, contemporaneously with activity monitoring. Patients were responsible for collecting their own urine, being assisted by our nursing staff in order to assure the integrity of the sample. Twenty-four-hour urine samples were collected, and the urinary free cortisol (UFC) excretion was determined by liquid chromatography–tandem mass spectrometry analysis, with a reported coefficient of variation of 10 %.

[1] as recommended by the manufacturer: http://www.actigraphcorp.com/research-database/kcal-estimates-from-activity-counts-using-the-potential-energy-method/.

Table 1 Baseline data for 24 women with anorexia nervosa participating in a randomised crossover trial of dronabinol and placebo therapy

	Overall ($n = 24$)	Outpatients 38 % ($n = 9$)	Inpatients 62 % ($n = 15$)	*P*
Mean age (years)	33.3 ± 12.7	36.2 ± 15.5	31.6 ± 10.9	N.S.
Disease burden (mean years)	15 ± 11.5	20.8 ± 14.9	11.5 ± 7.6	0.05
Body mass index				
kg/m^2	15.7 ± 1.7	16.4 ± 0.9	15.3 ± 2	N.S.
% of IBW[a]	74.7 ± 8.1	78 ± 4.3	72.7 ± 9.3	N.S.
P-Leptin (μg/l)	2.8 ± 2.7	2.3 ± 1.5	3.2 ± 3.2	N.S.
Urinary free cortisol (nmol/day)	101 ± 75.1	139.2 ± 97.2	78.1 ± 48.7	N.S.
Binge purging behaviour	50 % ($n = 12$)	33.3 % ($n = 3$)	60 % ($n = 9$)	N.S.
Eating disorder inventory-2 total score	104.6 ± 53.8	112.9 ± 53.8	99.7 ± 53.7	N.S.

Data are mean and standard deviation. *P* values greater than 0.05 were noted as nonsignificant (N.S.)

[a] Based on reference values from Nysom et al. [43]

Psychological measures

The attitudinal and behavioural dimensions relevant to AN were assessed during the first and the last week of each intervention, by applying the self-reported Eating Disorder Inventory-2 (EDI-2) [29]. The EDI-2 consists of 91 items and 11 sub-scales measuring the drive for thinness, bulimia, body dissatisfaction, ineffectiveness, perfectionism, interpersonal distrust, interoceptive awareness, maturity fears, asceticism, impulse regulation and social insecurity. EDI-2 has previously been validated in Danish patients [30]; it has good test–retest reliability [31]; and it is recommended by the Practice Guideline for the Treatment of Patients with Eating Disorders [American Psychiatric 32] as a representative instrument for the assessment of patients with eating disorders.

Statistical methods

Continuous variables were described by means and standard deviations. Categorical variables were described by frequencies and percentages. A two-sided test approach was used. *P* values of 0.05 or less were considered statistically significant. Statistical analyses were performed in Stata (version IC 12.1).

Due to technical errors, we failed to obtain valid accelerometry data covering at least 10 h of activity per day for at least 4 days during both interventions in three participants. With respect to the intention to treat principle, the missing data were replaced with the available measurements after the "last observation carried forward" principle. The differences in physical activity between each medication and between in- and outpatients were assessed by paired and nonpaired student's *t* tests, respectively. Nonparametric variables were naturally transformed. Variables describing both primary and secondary outcomes were tested for period, treatment sequence and carryover effects [33]. The predictors of physical activity were assessed in a multiple linear regression model with fixed and random coefficients. Effect sizes for significant predictors were estimated by Cohen's f^2.

Results

Twenty-four women with chronic and severe AN completed the study. Their age ranged from 19 to 62 years, with a mean of 33.3 ± 12.7 years. The average duration of the disease was of 15 ± 11.6 years, ranging from 5 to 50 years (Table 1).

The mean increase in body weight after the 4 weeks of dronabinol intervention was of 1 ± 1.4 kg, with 0.7 ± 1.4 kg ($P = 0.03$) above placebo [18]. The cumulated rate of weight gain during the study was of 0.7 ± 1.3 kg/month. As expected, inpatients had a higher rate of weight change throughout the study (1 ± 1.5 kg/month vs. 0.1 ± 0.8 kg/month in outpatients; $P = 0.02$). However, the difference in weight gain between the two interventions was similar in both in- and outpatients (0.7 ± 1.8 kg vs. 0.6 ± 0.7 kg; $P = 0.9$) (Table 2).

The circulating levels of plasma leptin and UFC excretion were also comparable between in- and outpatients, regardless the intervention. Also the EDI-2 scores were comparable, with minimal changes during both interventions (Table 3). No serious adverse events were recorded during the study [18].

Apart from a steeper weight gain during the first medication period (regardless the drug received), we did not detect any carryover or treatment sequence effects, neither for changes in body weight [18] nor for variables describing physical activity. We found no difference in mean days of the valid activity recordings (6.3 ± 0.1) between the two interventions.

The average daily physical activity duration during dronabinol was similar to placebo, in spite of a modest increase in the duration of moderate to hard physical activity (Table 4).

The duration of physical activity throughout the study was similar in both in- and outpatients (14.3 ± 1.2 vs.

Table 2 Changes in body weight for ambulant and hospitalised women with anorexia nervosa participating in a randomised crossover trial of dronabinol and placebo therapy

	Overall	Placebo	Dronabinol	Δ	*P*
Change in body weight (kg)	0.7 ± 1.3	0.3 ± 1.1	1 ± 1.4	0.7 ± 1.4	0.03
Outpatients ($n = 9$)	0.1 ± 0.8	−0.2 ± 0.7	0.4 ± 0.7	0.6 ± 0.7	0.03
Inpatients ($n = 15$)	1 ± 1.5	0.7 ± 1.2	1.4 ± 1.7	0.7 ± 1.8	N.S.
P	0.02	N.S.	N.S.	N.S	

Data are mean and standard deviation. *P* values greater than 0.05 were noted as nonsignificant (N.S.)

15 ± 1.7 h/day; $P = 0.11$). Outpatients were, however, more active in the range of moderate to hard activities during dronabinol intervention than during placebo (Table 5).

The physical activity intensity was modestly but significantly increased during dronabinol, exceeding the placebo level by approximately 20 % (Table 4). This increase occurred exclusively in the range of moderate to hard activities. While both in- and outpatients had similar activity levels during the study (504.1 ± 303 vs. 371.4 ± 256.8 CPM; $P = 0.13$), only inpatients showed a significant difference in physical activity intensity between the two interventions (Table 5).

The estimated energy expenditure during the trial averaged 668.9 ± 304.3 kcal/day, ranging from 187.2 to 1,430.1 kcal/day. The amount of energy expended through physical activity during dronabinol therapy was with 68.2 ± 126.6 kcal/day higher than during placebo ($P = 0.01$).

Neither the participant's age nor their body weight w correlated to the levels of physical activity. Among the measured clinical and biological parameters, only the UFC excretion was moderately associated with the duration of physical activity ($r = 0.39$, $P = 0.04$). The effect of dronabinol, and the impact of the individual UFC excretion and leptin levels on physical activity were estimated by multiple regression. Each model was adjusted for the random effect of the hospitalisation status and accounted for a large part of the individual variation in both the overall duration and the intensity of moderate to hard physical activity during the study (90 and 98 %, respectively). The estimated change in the duration of physical activity due to dronabinol was under the chosen level of significance. However, dronabinol intervention was significantly related to a modest increase in the intensity of moderate to hard physical activity (Table 6).

Table 3 Absolute changes in EDI-2 score in 24 women with anorexia nervosa participating in a randomised crossover trial of dronabinol and placebo therapy

EDI-2	Placebo	Dronabinol	Difference	*P*
Drive for thinness	−0.3 ± 2.8	−1 ± 2.8	−0.7 ± 5	N.S.
Bulimia	−0.5 ± 2.4	−0.1 ± 3.4	0.3 ± 4.3	N.S.
Body dissatisfaction	0.6 ± 3.3	0.33 ± 3.1	−0.3 ± 4.6	N.S.
Ineffectiveness	0.2 ± 3.1	−0.3 ± 4	−0.5 ± 5.1	N.S.
Perfectionism	0.6 ± 2	−0.5 ± 2.6	−1.1 ± 3	N.S.
Interpersonal distrust	−1.2 ± 2.9	−1 ± 3.7	0.2 ± 5	N.S.
Interoceptive awareness	0.1 ± 4.3	0.2 ± 6.3	0.1 ± 8.8	N.S.
Maturity fears	0 ± 2.16	−1 ± 2.3	−1 ± 3.7	N.S.
Asceticism	0.9 ± 2.6	−1 ± 4.4	−1.8 ± 5.5	N.S.
Impulse regulation	0.3 ± 3.1	−0.3 ± 4.6	−0.6 ± 7	N.S.
Social insecurity	0.4 ± 2.7	−0.5 ± 2.9	0.9 ± 4.7	N.S.
Total score	1 ± 16.4	−5.3 ± 22.3	−6.3 ± 32.1	N.S.

Data are mean and standard deviation. *P* values greater than 0.05 were noted as nonsignificant (N.S.)

Table 4 The duration and the intensity of physical activity in 24 women with anorexia nervosa participating in a randomised crossover trial of dronabinol and placebo therapy

Physical activities	Overall	Placebo	Dronabinol	*P*
Duration (h/day)	14.5 ± 1.4	14.6 ± 1.4	14.5 ± 1.5	N.S.
Light (0–1,951 CPM)	13.5 ± 1.7	13.6 ± 1.8	13.4 ± 1.6	N.S.
Moderate to hard (>1,952 CPM)	1.1 ± 0.8	1.0 ± 0.7	1.1 ± 0.9	0.04
Intensity (CPM)	454.3 ± 291.1	428 ± 285.4	480.6 ± 300.4	0.02
Light (0–1,951 CPM)	154.5 ± 62.9	152.9 ± 63.4	156 ± 63.6	N.S.
Moderate to hard (>1,952 CPM)	3,787.9 ± 887.1	3,686.7 ± 888.3	3,889.1 ± 893.2	0.02

Data are mean and standard deviation. *P* values greater than 0.05 were noted as nonsignificant (N.S.)

Table 5 A comparison of the levels of light and moderate to hard physical activity between ambulant ($n = 9$) and hospitalised ($n = 15$) women with anorexia nervosa participating in a randomised crossover trial of dronabinol and placebo therapy

	Light		*P*	Moderate to hard		*P*
	Placebo	Dronabinol		Placebo	Dronabinol	
Duration (h/day)						
Outpatients	14.4 ± 2.3	13.9 ± 1.8	N.S.	0.8 ± 0.6	0.9 ± 0.6	0.02
Inpatients	13.1 ± 1.3	13.1 ± 1.4	N.S.	1.1 ± 0.8	1.3 ± 1	N.S.
P	N.S.	N.S.		N.S.	N.S.	
Intensity (CPM)						
Outpatients	134.6 ± 28.1	137.4 ± 35.1	N.S.	3,610.2 ± 851.1	3,773.7 ± 1,086.3	N.S.
Inpatients	163.9 ± 76.2	167.1 ± 74.8	N.S.	3,732.6 ± 936.1	3,958.3 ± 789.2	0.04
P	N.S.	N.S.		N.S.	N.S.	

Data are mean and standard deviation. *P* values greater than 0.05 were noted as nonsignificant (N.S.)

Table 6 Mixed effects regression models estimating the predictors of the overall duration and the intensity of moderate to hard physical activity in 24 women with anorexia nervosa participating in a randomised crossover trial of dronabinol and placebo therapy

	Coefficient	*P*
Duration of physical activity (h/day)		
Dronabinol	$15 \times 10^{-3} \pm 0.2 \times 10^{-3}$	N.S.
UFC (nmol/day)	$8.4 \times 10^{-3} \pm 2.9 \times 10^{-3}$	<0.01
Leptin (μg/l)	0.09 ± 0.09	N.S.
Constant	13.49 ± 0.49	<0.01
Intensity of moderate to hard physical activity (CPM)		
Dronabinol	208.9 ± 59.4	<0.01
UFC (nmol/day)	0.5 ± 1.3	N.S.
Leptin (μg/l)	316 ± 71	<0.01
Leptin^2	−19.1 ± 5.3	<0.01
Constant	3,023 ± 310.5	<0.01

Both models were adjusted for the random effect of the hospitalisation status (in-/outpatient). Correlation coefficients are presented in means and standard errors. *P* values greater than 0.05 were noted as nonsignificant (N.S.)

Regardless the intervention, the UFC excretion emerged as a moderate predictor (Cohen's $f^2 = 0.35$) for the duration of physical activity (Table 6), but was not associated with a significant variation in the physical activity intensity. Conversely, the levels of leptin were strongly related to the intensity of moderate to hard physical activity (Cohen's $f^2 = 0.90$), this relationship being best described by a nonlinear equation (Table 6).

Discussion

The level of physical activity in AN reflects a complex interaction between the neurohormonal response to starvation and the attitudinal and behavioural dimensions of the disease, carrying meaningful information on both the patient's clinical profile and the outcome of the disease [6, 7]. This is the first report—to our knowledge—of the effect of a synthetic cannabinoid agonist on the levels of physical activity in adult women with severe and longstanding AN. By comparing the levels of physical activity during dronabinol intervention to placebo, we found a modest increase in the level of physical activity in these patients.

The evidence regarding the effect of cannabinoid agonist therapy on physical activity is sparse and based exclusively on results from animal studies. A biphasic, dose-dependent effect was repeatedly acknowledged [19, 34], anxiolytic- and anxiogenic-like effects being reported in rodents at low and high doses, respectively [34, 35]. Our results indicate that a relatively low dose of dronabinol was associated with a modest, but significant increase in the intensity of physical activity, suggesting a similar effect of low-dose cannabinoid agonist therapy in women with AN. However, the moderate increase in physical activity did not have a negative impact on body weight, nor did it on the attitudinal and behavioural dimensions relevant to AN [18].

Both animal [36–38] and human [21] reports suggest HPA-axis over-activation and the amount of physical activity are mutually reinforcing in AN. The most compelling evidence is provided by animal studies, in which administration of corticotropin releasing factor (CRF) leads to increased physical activity [37], and conversely, CRF antagonists attenuate the development of exercise-induced anorexia [36, 38], suggesting that the HPA-axis activity in particular mediates the link between food restriction-induced weight loss and increased exercise in animal models of activity based anorexia. Parallel with these reports, the UFC was linearly associated with the duration of physical activity in our group of women with severe and chronic AN. However, neither the intensity nor the amount of energy expenditure through physical activity was related to UFC, suggesting that HPA-axis activity was not directly

related to the level of physical activity in these chronically undernourished patients.

Conversely, we found that dronabinol intervention and the levels of plasma leptin were significantly associated with the amount of moderate to hard physical activity in a regression model explaining approximately 98 % of its total variance. In accordance with Holtkamp et al. [39] in adolescents with AN, we identified the circulating level of plasma leptin among the study group as being the strongest predictor for moderate to hard physical activities. The U shape of this relationship confirms the inverse correlation between the level of leptin and the amount of physical activity described by Holtkamp et al. [39] in severely undernourished participants, but at the same time indicates that this relationship might change in less affected participants with over-average leptin levels. Less than 10 % of the variance in moderate to hard physical activity intensity was due to dronabinol intervention, suggesting that the level of physical activity during the study was primarily related to the metabolic activity of fat tissue, and to a lesser extent a direct consequence of dronabinol therapy. Excessive physical activity in AN is a significant predictor of disease duration [6, 7]. Our inclusion criterion regarding the duration of AN, i.e. minimum 5 years, might have induced a selection bias, so that participants with long-standing AN have higher habitual levels of physical activity than in the general population of women with chronic AN. Nevertheless, the levels of physical activity were homogenous in our group, in spite of the nearly significant age difference between in- and outpatients. "Excessive exercisers" have been defined [1, 5] as exercise dependent and performing more than 6 h moderate to hard physical activity per week for at least 1 month. Amongst our participants, the overall duration of moderate to hard physical activity during the trial was fairly long, averaging over 7 h per week. However, the lack of data on the patients' habitual level of physical activity prevented us from investigating the effects of dronabinol in excessive exercisers versus nonexcessive exercisers.

The prospective design and the repeated measurements improved the accuracy of detecting changes that occurred during dronabinol medication. Potentially biasing factors were minimised by keeping the baseline therapeutic regime unchanged during the trial, each participant being monitored in the same setup (in- or outpatient) during both medications. The 4-week interval between the two medication periods seemed to prevent an ordering effect, as we were not able to detect a statistical carryover effect, neither for the main outcome, nor for variables describing physical activity.

The accelerometer produces quantitative data that reflect physical activity ranging from stationary movements (i.e. jogging in place) to the patient's actual walking and running, but it does not provide qualitative data describing the exact nature of the physical activity. However, other alternative techniques such self-report or video-monitoring could have a suppressive effect on the measured physical activity.

The amount of physical activity recorded by accelerometer was assessed by two independent variables, namely duration and intensity. Bothe could have been influenced by the participants, for instance by removing the device during day time. The hospitalisation's behavioural disincentive effect might also have influenced the pattern of physical activity during the two interventions. Outpatients spent more time performing moderate to hard physical activities during dronabinol intervention, while inpatients merely increased the intensity of these activities. However, the levels of physical activity were comparable between in- and outpatients, regardless the intervention, and the crossover design assured that the study environment remained unchanged during both interventions. Thus, we assumed that eventual behavioural reactions induced by the study setup (including intentional removal of the device) did not affect the validity of the observed differences in physical activity between the two interventions.

Apart from eating disorder-related attitudinal and behavioural traits, dronabinol might also influence other psychological dimensions associated with exercise behaviour and AN such as anxiety and depression and thus activate psychological mechanisms aiming at decreasing energy expenditure. The modest increase in the estimated energy expenditure as a result of 4 weeks of treatment with a cannabinoid agonist drug may therefore seem intriguing, also given the fact that cannabinoid antagonists—such as rimonabant—have been reported to increase energy expenditure in animal studies [40]. Therefore, measurement of real energy expenditure by calorimetric methods would have been a more reliable method to assess dronabinol-induced changes in energy expenditure.

The potential psychogenic effects of dronabinol, the low prevalence of patients with severe and longstanding AN (only 19 % of the 140 screened patients matched our inclusion criterion of having AN for at least five years) and the expected high drop-out rate [41] were factors influencing the small sample size in this study and on the short medication periods. Unexpectedly, and in contrast with reports from other studies [42], nearly 90 % of the potentially eligible patients consented to participate and also completed the study. This led to a highly selected and homogenous study population and thus prevents us to draw firm conclusions regarding the effects of dronabinol in a broader category of AN patients. Larger clinical studies are needed in order to gain more insight into the physiological mechanisms and the effects of dronabinol and to assess the safety of cannabinoid-based therapy in patients with AN.

This trial was the first prospective, randomised and controlled study to objectively assess changes in physical activity in patients with severe and longstanding AN, showing that dronabinol—a synthetic cannabinoid agonist—was associated with a modest increase in physical activity. In concordance with other studies, our data confirm the strong relationship between the circulating levels of leptin and physical activity in women with stable and severe AN.

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Conflict of interest None.

References

1. Davis C, Katzman DK, Kaptein S, Kirsh C, Brewer H, Kalmbach K, Olmsted MP, Woodside DB, Kaplan AS (1997) The prevalence of high-level exercise in the eating disorders: etiological implications. Compr Psychiatry 38(6):321–326
2. Beumont PJ, Arthur B, Russell JD, Touyz SW (1994) Excessive physical activity in dieting disorder patients: proposals for a supervised exercise program. Int J Eat Disord 15(1):21–36
3. Blinder BJ, Freeman DM, Stunkard AJ (1970) Behavior therapy of anorexia nervosa: effectiveness of activity as a reinforcer of weight gain. Am J Psychiatry 126(8):1093–1098
4. Falk JR, Halmi KA, Tryon WW (1985) Activity measures in anorexia nervosa. Arch Gen Psychiatry 42(8):811–814
5. Bratland-Sanda S, Sundgot-Borgen J, Ro O, Rosenvinge JH, Hoffart A, Martinsen EW (2010) Physical activity and exercise dependence during inpatient treatment of longstanding eating disorders: an exploratory study of excessive and non-excessive exercisers. Int J Eat Disord 43(3):266–273. doi:10.1002/eat.20769
6. Carter JC, Blackmore E, Sutandar-Pinnock K, Woodside DB (2004) Relapse in anorexia nervosa: a survival analysis. Psychol Med 34(4):671–679. doi:10.1017/S0033291703001168
7. Strober M, Freeman R, Morrell W (1997) The long-term course of severe anorexia nervosa in adolescents: survival analysis of recovery, relapse, and outcome predictors over 10–15 years in a prospective study. Int J Eat Disord 22(4):339–360
8. Penas-Lledo E, Vaz Leal FJ, Waller G (2002) Excessive exercise in anorexia nervosa and bulimia nervosa: relation to eating characteristics and general psychopathology. Int J Eat Disord 31(4):370–375. doi:10.1002/eat.10042
9. Casper RC (2006) The 'drive for activity' and "restlessness" in anorexia nervosa: potential pathways. J Affect Disord 92(1):99–107. doi:10.1016/j.jad.2005.12.039
10. Stoving RK, Hangaard J, Hagen C (2001) Update on endocrine disturbances in anorexia nervosa. J Pediatr Endocrinol Metab 14(5):459–480
11. Mastorakos G, Pavlatou M, Diamanti-Kandarakis E, Chrousos GP (2005) Exercise and the stress system. Hormones 4(2):73–89
12. Focker M, Timmesfeld N, Scherag S, Buhren K, Langkamp M, Dempfle A, Sheridan EM, de Zwaan M, Fleischhaker C, Herzog W, Egberts K, Zipfel S, Herpertz-Dahlmann B, Hebebrand J (2011) Screening for anorexia nervosa via measurement of serum leptin levels. J Neural Transm 118(4):571–578. doi:10.1007/s00702-010-0551-z
13. Hebebrand J, Bulik CM (2011) Critical appraisal of the provisional DSM-5 criteria for anorexia nervosa and an alternative proposal. Int J Eat Disord 44(8):665–678. doi:10.1002/eat.20875
14. Holtkamp K, Herpertz-Dahlmann B, Mika C, Heer M, Heussen N, Fichter M, Herpertz S, Senf W, Blum WF, Schweiger U, Warnke A, Ballauff A, Remschmidt H, Hebebrand J (2003) Elevated physical activity and low leptin levels co-occur in patients with anorexia nervosa. J Clin Endocrinol Metab 88(11):5169–5174
15. Exner C, Hebebrand J, Remschmidt H, Wewetzer C, Ziegler A, Herpertz S, Schweiger U, Blum WF, Preibisch G, Heldmaier G, Klingenspor M (2000) Leptin suppresses semi-starvation induced hyperactivity in rats: implications for anorexia nervosa. Mol Psychiatry 5(5):476–481
16. Pi-Sunyer FX, Aronne LJ, Heshmati HM, Devin J, Rosenstock J (2006) Effect of rimonabant, a cannabinoid-1 receptor blocker, on weight and cardiometabolic risk factors in overweight or obese patients: RIO-North America: a randomized controlled trial. JAMA J Am Med Assoc 295(7):761–775
17. Beal JE, Olson R, Laubenstein L, Morales JO, Bellman P, Yangco B, Lefkowitz L, Plasse TF, Shepard KV (1995) Dronabinol as a treatment for anorexia associated with weight loss in patients with AIDS. J Pain Symptom Manage 10(2):89–97
18. Andries A, Frystyk J, Flyvbjerg A, Stoving RK (2014) Dronabinol in severe, enduring anorexia nervosa: a randomized controlled trial. Int J Eat Disord 47(1):18–23. doi:10.1002/eat.22173
19. Sanudo-Pena MC, Romero J, Seale GE, Fernandez-Ruiz JJ, Walker JM (2000) Activational role of cannabinoids on movement. Eur J Pharmacol 391(3):269–274
20. Hill MN, Tasker JG (2012) Endocannabinoid signaling, glucocorticoid-mediated negative feedback, and regulation of the hypothalamic–pituitary–adrenal axis. Neuroscience 204:5–16. doi:10.1016/j.neuroscience.2011.12.030
21. Klein DA, Mayer LE, Schebendach JE, Walsh BT (2007) Physical activity and cortisol in anorexia nervosa. Psychoneuroendocrinology 32(5):539–547. doi:10.1016/j.psyneuen.2007.03.007
22. Aguirre CA, Castillo VA, Llanos MN (2012) Excess of the endocannabinoid anandamide during lactation induces overweight, fat accumulation and insulin resistance in adult mice. Diabetol Metab Syndr 4(1):35. doi:10.1186/1758-5996-4-35
23. McLaughlin PJ, Thakur GA, Vemuri VK, McClure ED, Brown CM, Winston KM, Wood JT, Makriyannis A, Salamone JD (2013) Behavioral effects of the novel potent cannabinoid CB1 agonist AM 4054. Pharmacol Biochem Behav 109:16–22. doi:10.1016/j.pbb.2013.04.011
24. Verty AN, Evetts MJ, Crouch GJ, McGregor IS, Stefanidis A, Oldfield BJ (2011) The cannabinoid receptor agonist THC attenuates weight loss in a rodent model of activity-based anorexia. Neuropsychopharmacology 36(7):1349–1358. doi:10.1038/npp.2011.19
25. Stoving RK, Andries A, Brixen K, Bilenberg N, Horder K (2011) Gender differences in outcome of eating disorders: a retrospective cohort study. Psychiatry Res 186(2–3):362–366. doi:10.1016/j.psychres.2010.08.005
26. Stoving RK, Andries A, Brixen KT, Bilenberg N, Lichtenstein MB, Horder K (2012) Purging behavior in anorexia nervosa and eating disorder not otherwise specified: a retrospective cohort study. Psychiatry Res. doi:10.1016/j.psychres.2011.10.009
27. Freedson PS, Melanson E, Sirard J (1998) Calibration of the computer science and applications, Inc. accelerometer. Med Sci Sports Exerc 30(5):777–781
28. Asferg C, Mogelvang R, Flyvbjerg A, Frystyk J, Jensen JS, Marott JL, Appleyard M, Jensen GB, Jeppesen J (2010) Leptin,

not adiponectin, predicts hypertension in the Copenhagen City Heart Study. Am J Hypertens 23(3):327–333. doi:10.1038/ajh.2009.244
29. Garner DM (1991) Eating Disorder Inventory-2: professional manual. Psychological Assessment Resources, Inc., Odessa, FL
30. Clausen L, Rokkedal K, Rosenvinge JH (2009) Validating the eating disorder inventory (EDI-2) in two Danish samples: a comparison between female eating disorder patients and females from the general population. Eur Eat Disord Rev 17(6):462–467. doi:10.1002/erv.945
31. Thiel A, Paul T (2006) Test–retest reliability of the Eating Disorder Inventory 2. J Psychosom Res 61(4):567–569. doi:10.1016/j.jpsychores.2006.02.015
32. Practice guideline for the treatment of patients with eating disorders (revision). American Psychiatric Association Work Group on Eating Disorders. Am J Psychiatry 157(1 Suppl):1–39
33. Senn S (2002) Cross-over trials in clinical research. Wiley, New York
34. Rey AA, Purrio M, Viveros MP, Lutz B (2012) Biphasic effects of cannabinoids in anxiety responses: CB1 and GABA(B) receptors in the balance of GABAergic and glutamatergic neurotransmission. Neuropsychopharmacology 37(12):2624–2634. doi:10.1038/npp.2012.123
35. Viveros MP, Marco EM, File SE (2005) Endocannabinoid system and stress and anxiety responses. Pharmacol Biochem Behav 81(2):331–342. doi:10.1016/j.pbb.2005.01.029
36. Kawaguchi M, Scott KA, Moran TH, Bi S (2005) Dorsomedial hypothalamic corticotropin-releasing factor mediation of exercise-induced anorexia. Am J Physiol Regul Integr Comp Physiol 288(6):R1800–R1805. doi:10.1152/ajpregu.00805.2004
37. Sutton RE, Koob GF, Le Moal M, Rivier J, Vale W (1982) Corticotropin releasing factor produces behavioural activation in rats. Nature 297(5864):331–333
38. Rivest S, Richard D (1990) Involvement of corticotropin-releasing factor in the anorexia induced by exercise. Brain Res Bull 25(1):169–172
39. Holtkamp K, Herpertz-Dahlmann B, Hebebrand K, Mika C, Kratzsch J, Hebebrand J (2006) Physical activity and restlessness correlate with leptin levels in patients with adolescent anorexia nervosa. Biol Psychiatry 60(3):311–313. doi:10.1016/j.biopsych.2005.11.001
40. Zhang LN, Gamo Y, Sinclair R, Mitchell SE, Morgan DG, Clapham JC, Speakman JR (2012) Effects of chronic oral rimonabant administration on energy budgets of diet-induced obese C57BL/6 mice. Obesity 20(5):954–962. doi:10.1038/oby.2011.357
41. Zeeck A, Hartmann A, Buchholz C, Herzog T (2005) Drop outs from in-patient treatment of anorexia nervosa. Acta Psychiatr Scand 111(1):29–37
42. Bissada H, Tasca GA, Barber AM, Bradwejn J (2008) Olanzapine in the treatment of low body weight and obsessive thinking in women with anorexia nervosa: a randomized, double-blind, placebo-controlled trial. Am J Psychiatry 165(10):1281–1288. doi:10.1176/appi.ajp.2008.07121900
43. Nysom K, Molgaard C, Hutchings B, Michaelsen KF (2001) Body mass index of 0 to 45-y-old Danes: reference values and comparison with published European reference values. Int J Obes Relat Metab Disord 25(2):177–184. doi:10.1038/sj.ijo.0801515