



BRIEF OBSERVATION

Does Methylphenidate Reduce the Symptoms of Chronic Fatigue Syndrome?

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ABSTRACT

PURPOSE: Chronic fatigue syndrome is a clinical entity consisting of prolonged and debilitating fatigue in which concentration disturbances are very frequent. Until now, no medical treatment has shown any efficacy. The objectives of this study were to investigate the short-term effects of methylphenidate, an amphetamine derivative, on fatigue, concentration disturbances, and quality of life.

SUBJECTS AND METHODS: A double-blind randomized placebo-controlled crossover study was conducted in 60 patients who fulfilled the 1994 Centers for Disease Control criteria for chronic fatigue syndrome and had concentration difficulties. Patients were enrolled between March 2003 and March 2004 at the outpatient department of a university hospital referral center for chronic fatigue syndrome patients. Random assignment to 4 weeks treatment with methylphenidate 2 × 10 mg/day, followed by 4 weeks of placebo treatment, or 4 weeks of placebo treatment, followed by methylphenidate treatment. Fatigue and concentration were measured with a Checklist Individual Strength (CIS) and a Visual Analogue Scale (VAS).

RESULTS: Fatigue scores fell significantly during methylphenidate intake in comparison with baseline (mean difference: -0.7, $P = .010$ for VAS; mean difference: -11.8, $P < .0001$ for CIS) and in comparison with placebo (mean difference: -1.0, $P = .001$ for VAS; mean difference: -9.7, $P < .0001$ for CIS). Concentration disturbances, measured with a VAS improved significantly under methylphenidate treatment compared with baseline (mean difference: -1.3, $P < .0001$) and compared with placebo (mean difference: -1.1, $P < .0001$). A clinical significant effect ($\geq 33\%$ improvement or CIS ≤ 76) on fatigue was achieved in 17% of patients, who were considered responders; on concentration in 22% of patients.

CONCLUSIONS: Methylphenidate at a dose of 2 × 10 mg/day is significantly better than placebo in relieving fatigue and concentration disturbances in a minority of chronic fatigue syndrome patients. Further studies are needed to investigate the long-term effects of this treatment. © 2006 Elsevier Inc. All rights reserved.

KEYWORDS: Chronic fatigue syndrome; Fatigue; Methylphenidate; Concentration difficulties

Over the last 2 decades, there seems to be a marked increase of patients in the Western world complaining of chronic and debilitating fatigue, in combination with other nonspecific somatic and neuropsychological symptoms. Very often, these patients also suffer from severe concentration and memory disturbances. Full clinical, biochemical and tech-

nical explorations are normal. In 1994, the Centers for Disease Control and Prevention (CDC) published widely accepted criteria for a syndrome called 'chronic fatigue syndrome', which requires a minimal symptomatic period of 6 months and the exclusion of any underlying organic or psychiatric disorder, which can cause chronic fatigue.¹

Although several etiologic and pathophysiological explanations for this disorder have been proposed, such as a new or prolonged viral infection,² Mycoplasma infections,³ impaired activation of the hypothalamic-pituitary-adrenal axis,⁴ immunological disturbances,⁵ autonomic dysfunc-

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tion,⁶ and abnormalities in the ribonuclease L pathway,⁷ chronic fatigue syndrome remains a syndrome of unknown cause, without a test of adequate sensitivity and specificity to constitute a diagnostic assay. Moreover, treatment strategies based on these hypotheses, such as antiviral, hormonal, immunological, or antibiotic therapy have not proven to be very successful.^{8,9}

Other investigators regard chronic fatigue syndrome as a functional somatic syndrome,¹⁰ most probably stress-related.¹¹ Cognitive behavioral therapy and graded exercises have been shown in many (but not all) studies to improve the ability of patients to function and cope and are now considered as evidence-based treatments.^{8,12} However, these treatment strategies are laborious, time-consuming, and not curative. Whatever the exact nature of chronic fatigue syndrome may be, a symptom-relieving, inexpensive drug that is free of severe side effects would be most welcome.

Methylphenidate, an amphetamine derivative and stimulatory drug, has been used recently to relieve fatigue in cancer patients¹³⁻¹⁵ and in human immunodeficiency virus (HIV) patients.¹⁶ Methylphenidate used to be one of the commonest forms of therapy for excessive daytime sleepiness, such as in idiopathic hypersomnia or narcolepsy, but it is now largely replaced by modafinil for this latter indication.¹⁷ Moreover, it is widely used in patients with attention deficit and hyperactivity disorder who share severe concentration disturbances with chronic fatigue syndrome patients.¹⁸ The primary aim of the present study was to investigate the effect of methylphenidate on fatigue and on concentration disturbances in chronic fatigue syndrome.

METHODS

Participants

The study was carried out at the general internal medicine outpatient clinic of the University Hospital Gasthuisberg, which is recognized by the Flemish Government as a reference center for chronic fatigue syndrome (ie, primary and secondary care, and not tertiary care). Most patients were referred by their general practitioner; some came without any referral.

Consecutive ambulant patients complaining of fatigue of at least 6 months' duration were checked for underlying organic or psychiatric disorders and for CDC minor criteria, of which at least 4 had to be present; moreover, concentration problems was a mandatory criterion for inclusion. We

performed routine screening investigations, including biochemical investigation (full blood count, sedimentation rate and C-reactive protein, protein electrophoresis [if >40 years old] ionogram, calcium and phosphorus, renal function, liver function, glycemia, muscle enzymes, antinuclear factor, cortisol, thyroid function, hepatitis B and C serology, Borrelia and HIV serology), urine microscopy, chest radiograph, and abdominal ultrasound. Any abnormality was further checked and the patient was excluded if this screening was not completely normal.

Patients were assessed by a psychiatrist to exclude primary psychiatric disorders (eg, major depressive disorder) by using the semi-structured diagnostic Schedules for Clinical Assessment in Neuropsychiatry, version 2.0.¹⁹ Patients prone to addiction were not eligible.

We excluded patients younger than 18 years or with a history of stomach or duodenal ulcer, arterial hypertension, glaucoma, diabetes mellitus, cardiac arrhythmia or cardiac ischemia, syndrome of Gilles

de la Tourette, substance abuse, current use of a beta-blocker, an antidepressant or antipsychotic medication, or ongoing pregnancy. Patients receiving other therapy aimed to improve their fatigue were excluded as well. All patients gave informed consent.

Study Design, Interventions and Objectives

The design of the study was a double-blind randomized crossover study in which treatment with methylphenidate 10 mg taken twice daily (at 8 AM and 2 PM) was compared with placebo. Both compounds were taken for 1 month each, by every participating patient, with a washout period of 1 week at crossover ($t_{1/2}$ of methylphenidate = 2 hours). Patients who stopped the treatment during the first period but who returned after 4 weeks were allowed to start therapy with the second compound. At baseline, after the first (4 weeks) and the second (9 weeks) treatment episodes, all patients were clinically evaluated, questionnaires were completed, and side effects were checked. Blood tests (hemoglobin, CBC, platelets and liver tests) were done at every visit to exclude drug-related adverse events.

The primary objective of the study was to assess if fatigue and concentration improved significantly after methylphenidate and if this compound was superior over treatment with placebo. As secondary objectives, the effects of methylphenidate on overall emotional well-being, quality of life, depressed and anxious mood, and symptoms included in the CDC minor criteria (sore throat, painful lymphaden

CLINICAL SIGNIFICANCE

- Significant improvement of fatigue and concentration disturbances in 60 chronic fatigue syndrome patients was observed when they were taking methylphenidate 2×10 mg/day compared to placebo.
- One patient out of 6 reported clinically significant improvement or cure.
- Given the absence of other efficacious medications for this indication, and the lack of severe side effects and low cost of methylphenidate, we think that this drug is worth a try in chronic fatigue syndrome patients with concentration difficulties.

nopathies, muscle pain, arthralgias, headache, postexertional malaise, and sleep disturbances) were assessed, in comparison with baseline and placebo.

The Ethical Committee of our university hospital approved the study protocol.

OUTCOME MEASURES

Primary Outcome Measure: Fatigue and Concentration Disturbances

Two instruments were used to assess fatigue: (1) The Checklist Individual Strength (CIS)^{20,21} is a self-report questionnaire that assesses the severity of fatigue over the previous 2 weeks, ranking from 20 to 140. We defined a clinically significant response as a $\geq 33\%$ fall in fatigue scores or a score on the CIS ≤ 76 , which has been defined previously as the cut-off point for probable fatigue in employees.²² Patients fulfilling these criteria were considered responders. (2) A Visual Analogue Scale (VAS) measuring subjective fatigue was used as a second instrument (range 0 to 10).

Concentration disturbances were assessed with the concentration subscale of the CIS (5 items, range 5-35) on the one hand, and with a VAS (range 0-10) measuring subjective concentration on the other hand. Analogous to the CIS total score, significant clinical improvement was defined as a 33% fall of the concentration disturbance score on the CIS subscale.

Secondary Outcome Measures: Emotional Well-Being, Quality of Life, Depressed and Anxious Mood and Minor CDC Criteria

Patients indicated the degree of general emotional well-being on a single VAS (range 0-10). Health-related quality of life (QOL) was measured with a validated Dutch translation of the Medical Outcome Study Short-Form 36 items (SF-36), subdivided in: (a) a Physical Factor (physical functioning, bodily pain, general health and role-physical) and (b) a Mental Factor (mental health, social functioning, energy/vitality and role-emotional).²³ The severity of depressed and anxious mood was assessed with the Hospital Anxiety and Depression Scale (HADS) with a range from 0 to 21.^{24,25} The severity of the CDC minor criteria were measured with a VAS (sore throat, adenopathy, muscle pain, joint pain, headache, post-exertional malaise and sleep disturbance).

SAMPLE SIZE, RANDOMIZATION AND BLINDING

Before the start of the study, a power analysis was done to estimate the number of patients minimally required to detect a difference of at least 10% on any of the primary outcome measures. The participation of 54 patients was required to detect such a difference with 90% certainty, using a double-sided significance level of 5%. Anticipating a dropout rate of 10% during the study, 60 patients were randomized by computer software, designed by the hospital pharmacy, which generated the randomization sequence to allocate

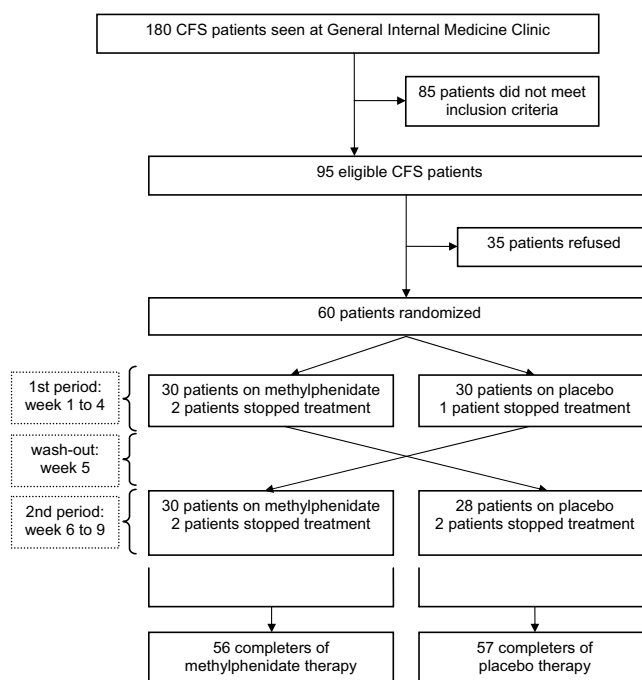


Figure 1 Flow-chart of the study.

participants to start in the placebo group or in the methylphenidate group. Consecutive patients received a numbered container at the start of each treatment period. The active compound and the placebo were indistinguishable in color, odor, size and taste. The allocation sequence was generated by and only known to the pharmacist. The investigators who enrolled the patients were blinded until the end of the study.

STATISTICAL ANALYSIS

Statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS 12.0 for Windows, Chicago, Ill). Descriptive statistics were calculated for all patient characteristics and variables at baseline. The Missing Value Analysis (MVA) procedure describes the pattern of missing data, estimates means, standard deviations, covariances, and correlations (SPSS Missing Value Analysis 12.0 for Windows, Chicago, Ill). MVA with an expectation-maximization (EM) method was used to estimate continuous missing values. EM estimates the means, the covariance matrix, and the correlation of quantitative variables with missing values using an iterative process, and the missing values were imputed with estimated values using this method. For missing categorical data, the last observation was carried forward. Repeated measures analysis was used to compare the change in scores of the patient's self-ratings from baseline, after placebo treatment and after active treatment. The proportions of patients who responded or who achieved clinical remission to active treatment or placebo, and proportions of side effects were compared by McNemar tests. A double-sided significance level of 5% was used. The data of all 60 patients who started the study were analyzed on an intention-to-treat basis.

RESULTS

Figure 1 shows the flow of the participants through the trial. Between March 24, 2003 and March 15, 2004, 180 patients with a diagnosis of chronic fatigue syndrome were seen at the Internal Medicine Outpatient Department. Inclusion criteria were not met in 85 patients because of the following reasons: antidepressant therapy in 75 patients, other therapy aimed to improve fatigue in 6 patients, no concentration difficulties in 2 patients, pregnancy in 1, and 1 patient was under 18 years of age. Consequently, 95 chronic fatigue syndrome patients were eligible as possible candidates for enrollment. Thirty-five patients refused to participate, and the remaining 60 patients were randomized. Four patients did not complete treatment with methylphenidate (3 patients due to side effects and 1 patient due to a severe aggravation of chronic fatigue syndrome after 2 days); 3 patients did not complete treatment with placebo (2 patients due to side effects and 1 patient due to acute suicidal tendency).

The mean age of the included patients was 40 years \pm 8 years; 45 women (75%) and 15 men (25%) participated. The median duration of fatigue was 36 months (inter-quartile range = 22-74).

Primary Outcome: Effects on Fatigue and Concentration

The scores of the outcome variables at baseline and after intervention with, respectively, placebo or methylphenidate and the mean differences between these 3 conditions are shown in Table 1. Fatigue scores, measured with a VAS and the CIS total score, decreased significantly in the methylphenidate group in comparison with baseline. This was also observed for all subscales of the CIS, except for the activity subscale. In the placebo group, the total fatigue score, measured with the CIS, also improved slightly, yet not significantly compared with baseline, and no improvement was observed on the VAS. The paired comparison of methylphenidate versus placebo for fatigue scores yielded a significant mean benefit in favor of the active compound. The results were not affected by which treatment was received first (Figure 2).

In 10 patients (17%) there was a clinically significant response after treatment with the active compound, whereas no patient responded in this way on placebo. The number needed to treat to achieve a clinically significant response was 6 (95% confidence interval [CI]: 3.8 to 14.4).

Concentration disturbances, measured as a subscale of the CIS and with a VAS, improved significantly in comparison with the baseline scores (Table 1). After treatment with methylphenidate, the mean scores of concentration disturbances had decreased significantly more than after treatment with placebo. A statistically significant placebo effect was observed for the concentration subscale of the CIS compared with baseline, but not for the VAS concentration disturbances. Clinically significant improvement of the score of the CIS concentration subscale was achieved in 13 patients (22%) after treatment with methylphenidate,

whereas this occurred in only 3 patients (5%) after placebo ($P = .013$). The number needed to treat to achieve clinically significant improvement of concentration disturbances on the CIS was 6 (95% CI, 4.6 to 8.6).

Effects on Secondary Endpoints

Overall emotional well-being of patients did not change from baseline after treatment with the active compound or after placebo (Table 1).

Global physical disability, reflected by the mean scores of the SF-36 physical factor, improved significantly after both treatment conditions (Table 1). However, a significant mean benefit for methylphenidate treatment in comparison with placebo treatment was observed. Bodily pain was the only subscale where no effect was seen, in any treatment period. Of note were the significant placebo effects on the physical factor and the general health subscale. The SF-36 mental factor was globally not affected by the interventions. During treatment with methylphenidate, only the score of the subscale vitality, which reflects the impact of fatigue on quality of life in the SF-36, improved significantly compared with baseline and with placebo.

Globally, depression and anxiety scores were not significantly affected by any intervention (Table 1).

The severity of a number of accompanying complaints was affected by the intervention (Table 1). The degree of muscular pain was significantly worse at baseline and after placebo than after treatment with methylphenidate. The degree of postexertional malaise and sleeping disturbance improved after patients were treated with methylphenidate compared with baseline and placebo. In comparison with baseline, the degree of joint pain improved significantly only after treatment with methylphenidate, but there was no significant difference between the 2 interventions.

Possible Side Effects

The laboratory analyses did not change over the course of the study. The upper part of Table 2 shows the effect of the different interventions on some parameters of the patients in comparison with baseline. The small differences noted were not judged clinically significant.

The lower part of Table 2 shows the side effects of the interventions. Overall, none of the interventions caused an important increase in complaints. Moreover, sleep disturbance, dizziness, akathisia, and chest pain were significantly less frequently reported after methylphenidate compared with baseline, but no difference was observed between both treatment conditions. Dry mouth was the only complaint that was significantly more frequent after treatment with methylphenidate compared with baseline and treatment with placebo.

Comparing Responders Versus Nonresponders

There were no differences at baseline in age, sex, duration of symptoms, QOL, depression, anxiety, the degree of concentration disturbances, the degree of general emotional

Table 1 Values of and differences between the different measurement points

Measurement	Baseline (BL) Mean ± SD	Placebo (PL) Mean ± SD	Methylphenidate (MP) Mean ± SD	Mean differences					
				Mean MP – BL (95% CI)	P	Mean MP – PL (95% CI)	P	Mean PL – BL (95% CI)	P
Primary endpoints: fatigue and concentration disturbance									
VAS fatigue	7.5 ± 1.4	7.8 ± 1.5	6.7 ± 2.4	–.7 (–1.2; –.2)	.010	–1.0 (–1.7; –.4)	.001	.3 (–.1; .8)	.31
CIS total score	114.6 ± 14.8	112.5 ± 11.3	102.8 ± 22.4	–11.8 (–16.9; –6.7)	<.0001	–9.7 (–14.3; –5.1)	<.0001	–2.1 (–5.2; 1.0)	.16
Bodily fatigue	51.1 ± 5.2	49.7 ± 5.0	45.6 ± 9.7	–5.5 (–7.9; –3.1)	<.0001	–4.1 (–6.4; –1.9)	<.0001	–1.4 (–2.8; .1)	.064
Concentration	29.6 ± 5.5	28.1 ± 4.6	25.2 ± 7.3	–4.4 (–6.1; –2.7)	<.0001	–2.9 (–4.6; –1.2)	.001	–1.5 (–2.7; –.3)	.015
Motivation	17.2 ± 6.3	17.4 ± 5.5	15.9 ± 5.7	–1.3 (–2.5; –.1)	.029	–1.6 (–2.6; –.5)	.004	.23 (–.7; 1.2)	.63
Activity	16.8 ± 4.5	16.9 ± 3.4	15.8 ± 4.7	–1.0 (–2.3; .3)	.14	–1.1 (–2.1; –.2)	.019	.1 (–.7; 1.0)	.76
VAS concentration disturbance	7.1 ± 2.1	6.9 ± 2.5	5.7 ± 2.5	–1.3 (–2.0; –.7)	<.0001	–1.1 (–1.7; –.5)	<.0001	–.2 (–.4; .3)	.42
Secondary endpoints									
VAS happiness	5.9 ± 2.3	6.1 ± 2.2	6.2 ± 1.8	.3 (–.4; 1.0)	.33	–.1 (–.4; .7)	.67	.2 (–.4; .8)	.51
Health-related quality of life (SF-36)									
Physical factor	31.0 ± 12.2	34.3 ± 12.4	38.2 ± 17.1	7.2 (4.4; 10.2)	<.0001	3.9 (.4; 7.4)	.028	3.4 (1.0; 5.7)	.005
Physical functioning	48.6 ± 18.4	51.2 ± 18.7	52.8 ± 19.0	4.2 (.8; 7.7)	.018	1.6 (–1.2; 4.3)	.26	2.6 (–.7; 5.9)	.12
Bodily pain	36.0 ± 23.0	37.6 ± 20.8	40.4 ± 23.8	4.4 (–.4; 9.3)	.073	2.8 (–.7; 6.2)	.12	1.6 (–3.0; 6.3)	.48
General health	32.1 ± 14.7	38.2 ± 14.0	40.4 ± 18.7	8.3 (3.7; 12.8)	.001	2.2 (–4.0; 8.4)	.48	6.1 (2.1; 10.0)	.003
Role-physical*	0 (0-18.8)	0 (0-25.0)	0 (0-3.4)	NA	.004	NA	.04	NA	.22
Mental factor	48.7 ± 15.4	47.3 ± 16.7	51.8 ± 16.4	3.1 (–1.6; 7.7)	.19	4.4 (–.5; 9.4)	.076	–1.4 (4.5; 1.8)	.38
Mental health	56.8 ± 17.1	57.2 ± 17.1	56.0 ± 15.9	–.8 (–4.7; 3.1)	.69	–1.2 (–5.1; 2.7)	.53	.4 (–2.8; 3.7)	.80
Social functioning	40.4 ± 22.5	41.1 ± 20.9	45.1 ± 24.6	4.7 (–.2; 9.6)	.059	4.1 (–1.0; 9.2)	.11	.6 (–3.7; 4.9)	.77
Vitality	26.5 ± 13.7	29.1 ± 13.3	33.5 ± 18.3	7.0 (3.0; 11.0)	.001	4.4 (.6; 8.1)	.025	2.6 (–.8; 6.1)	.13
Role-emotional*	100 (33.3-100)	100 (33.3-100)	72.8 (33.3-100)	NA	.93	NA	.11	NA	.062
Mood/anxiety									
HADS Depressed mood	7.8 ± 3.9	7.7 ± 3.7	7.3 ± 3.8	–.5 (–1.2; .2)	.15	–.4 (–1.2; .4)	.31	–.1 (–.6; .4)	.67
HADS Anxious mood	8.4 ± 4.4	8.7 ± 4.7	8.3 ± 3.8	–.1 (–1.0; .8)	.84	–.3 (–1.3; .7)	.51	.2 (–.62; 1.1)	.60
Fukuda criteria									
VAS sore throat	3.4 ± 2.8	3.6 ± 3.0	3.2 ± 3.1	–.2 (–1.0; .5)	.58	–.4 (–1.1; .3)	.22	.2 (–.5; 1.0)	.57
VAS adenopathy	2.4 ± 2.8	2.2 ± 3.0	2.2 ± 2.8	–.2 (–.8; .5)	.57	.0 (–.8; .7)	.91	–.2 (–.8; .5)	.64
VAS muscle pain	6.9 ± 2.6	6.7 ± 2.6	6.1 ± 2.9	–.8 (–1.5; –.2)	.011	–.6 (–1.2; –.0)	.046	–.2 (–.7; .3)	.38
VAS joint pain	6.2 ± 3.0	5.8 ± 3.1	5.4 ± 3.1	–.8 (–1.5; –.1)	.019	–.4 (–1.1; .1)	.13	–.4 (–.9; .3)	.31
VAS headache	5.7 ± 3.0	5.1 ± 3.2	5.0 ± 3.2	–.7 (–1.6; .0)	.063	–.1 (–.8; .6)	.76	–.6 (–1.4; .1)	.078
VAS sleeping disturbance	6.1 ± 3.2	5.9 ± 2.8	5.3 ± 3.1	–.8 (–1.5; –.1)	.021	–.6 (–1.3; .1)	.093	–.2 (–.9; .4)	.50
VAS post-exertional malaise	5.4 ± 3.3	5.3 ± 3.3	4.8 ± 3.2	–.6 (–1.3; .0)	.051	–.5 (–1.3; .2)	.12	–.1 (–.8; .7)	.86

NA = not applicable.

*Values are presented as median (inter-quartile range).

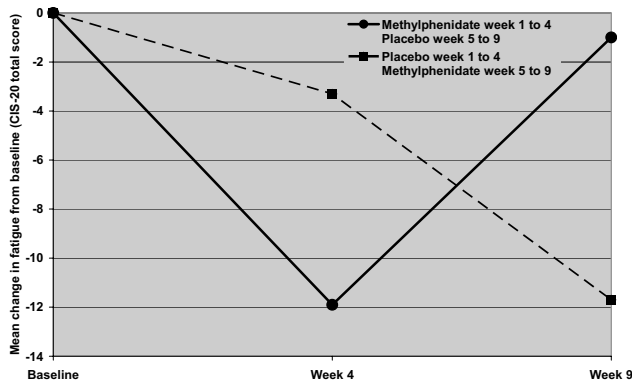


Figure 2 Mean change from baseline score on CIS-20 fatigue measure.

well-being, or the severity of the CDC minor criteria in responders versus nonresponders. However, the responders had a significantly lower total CIS-score at baseline (104 ± 19 vs 117 ± 13 , $P = .009$), although the differences between the subscales of the CIS were not statistically significant. The degree of fatigue at baseline, as measured from a VAS, was also significantly lower in responders versus nonresponders (6.6 ± 1.2 vs 7.6 ± 1.4 , $P = .04$).

DISCUSSION

Methylphenidate (20 mg/day for 4 weeks) significantly improved fatigue and concentration disturbances in patients with chronic fatigue syndrome compared with placebo-treatment. There was a significant effect on fatigue on both outcome instruments (VAS and CIS). The effect of methylphenidate was significant on all of the CIS subdimensions except for activity. Concentration disturbances measured with a VAS had also significantly improved after methyl-

phenidate. A clinically significant response was observed in 1 of every 6 patients treated with methylphenidate. Patients with less severe fatigue were more likely to respond to methylphenidate administration. Part of this relation might be due to our definition of responders, which included patients with a CIS score that had fallen to ≤ 76 . The likelihood to reach 76 is higher when the baseline CIS score is lower.

The physical functioning factor of quality of life was better after methylphenidate than at baseline or under placebo treatment, whereas there was no change in the mental functioning factor, except for vitality. Depressed and anxious mood did not change either. Hence, the improvement of fatigue was not due to an improvement of the general affect of the patient.

As could be expected, there was a certain (although smaller) placebo effect in our patients that was significant for the CIS Concentration subscale and for the SF-36 Physical Factor due to a significant improvement in the SF-36 General Health subscore. In a recent meta-analysis of controlled interventional trials in chronic fatigue syndrome patients, the pooled placebo response was 19.6%, lower than in other medical conditions. The authors linked the even lower placebo response for psychological-psychiatric interventions compared with drug therapy to patients' poor expectations.²⁶

An unexpected finding of our study was that muscle pain was scored significantly lower with methylphenidate than at baseline or with placebo. Other accompanying symptoms such as joint pain, sleeping disturbances, and postexertional malaise were also significantly better with methylphenidate treatment compared with baseline, but not compared with placebo treatment. The concern that sleeping disturbances would aggravate under methylphenidate was not observed.

Table 2 Effects of the interventions on the assessed parameters and the evolution of the possible side effects which changed significantly

Parameters	Baseline	Mean MP - BL	P value	Mean MP - PL	P value	Mean PL - BL	P value
	Mean \pm SD	(95% CI)		(95% CI)		(95% CI)	
Weight (Kg)	71.3 \pm 14.9	-.4 (-1; .1)	.14	.7 (2.4; -3.8)	.66	-1.1 (-4.1; 2.0)	.48
Systolic blood pressure (mmHg)	128 \pm 15	-1 (-4; 3)	.62	1 (-2; 4)	.38	-2 (-5; 1)	.17
Diastolic blood pressure (mmHg)	81 \pm 7	1 (-2; 4)	.42	4 (1; 7)	.005	-3 (-6; 0)	.049
Pulse rate (beats per minute)	72 \pm 8	5 (1; 9)	.008	2 (-1; 4)	.11	3 (0; 6)	.038
	Baseline n (%)	Placebo n (%)	Methylphenidate n (%)	MP - BL P value	MP - PL P value	PL - BL P value	
Possible side effects							
Sleeplessness	40 (67)	23 (38)	21 (35)	.001	.84	.002	
Dry mouth	23 (38)	18 (30)	34 (57)	.027	.001	.27	
Dizziness	42 (70)	38 (63)	30 (50)	.004	.077	.42	
Akathisia	42 (70)	34 (57)	29 (48)	.007	.33	.077	
Abdominal pain	32 (53)	23 (38)	28 (47)	.42	.13	.022	
Chest pain	26 (43)	25 (42)	17 (28)	.049	.077	1.00	

No differences were found for the other possible side effects (palpitations, agitation nervousness, loss of appetite, headaches, blurred sight, convulsions, muscle cramps, involuntary movements, nervous twitches, nausea, vomiting, skin rash, pruritus, urticaria, fever, joint pain, hair loss).

Side effects were not more frequently reported during methylphenidate, except for dry mouth.

The effects of methylphenidate on fatigue observed in our patients are not specific for chronic fatigue syndrome because similar effects have also been described for chronic organic disease-related fatigue. In three prospective open-label studies, methylphenidate had a beneficial effect on fatigue in patients with advanced cancer,¹³⁻¹⁵ Breitbart et al randomized 144 outpatients with human immunodeficiency virus disease and fatigue to double-blind treatment with methylphenidate, pemoline, or placebo. Forty-one percent of patients receiving methylphenidate and 36% of the patients receiving pemoline demonstrated significant improvement of fatigue compared with 15% of patients receiving placebo.¹⁶

Only one small pilot study has assessed the effects of an amphetamine-like drug in chronic fatigue syndrome. Olson et al used dexamphetamine and found improvement of fatigue severity in 9 of 10 patients, whereas there was no statistically significant change in functioning.²⁷

Methylphenidate's mechanism of action relies on blocking the dopamine and—to some extent—noradrenaline reuptake.^{28,29} Because amphetamine derivatives increase alertness and reduce the effects of sleep deprivation, an effect on both fatigue and concentration can be expected. In attention deficit and hyperactivity disorder, a marked improvement in concentration and attention has been demonstrated. Moreover, recent findings demonstrated that methylphenidate augments the saliency of a task or an event by increasing central, extra-cellular dopamine, which may in turn improve concentration, attention and performance.³⁰

Our understanding of the pathophysiology of chronic fatigue syndrome remains limited. As a possible stress-related disorder, based on subtle and interrelated neurobiological disturbances,¹¹ pathophysiological treatment of this syndrome is not evident. We do not know if the observed effects of methylphenidate in chronic fatigue syndrome are due to true interference with pathophysiological mechanisms or are purely symptomatic. Indeed, also, healthy persons are more alert while taking methylphenidate, which is exploited by some students during examination periods. Whatever the exact mechanisms of action of methylphenidate in chronic fatigue syndrome patients, treatment with this drug might be a valuable aid to the evidence-based treatment modalities cognitive-behavioral therapy and graded exercise. Future research in this field may focus on the use of other stimulants in chronic fatigue syndrome, such as slow-release formulations of methylphenidate or modafinil.

Some limitations and caveats of our study are noteworthy. The long-term effects of methylphenidate treatment in chronic fatigue syndrome patients are not yet known; does it remain active and free of side effects after months or even years of continuous intake? Treatment with methylphenidate is often continued for long periods of time in attention deficit and hyperactivity disorder, and in these patients

tolerance does not seem to be a major obstacle. There is currently very limited evidence for significant abuse, because reinforcing effects such as euphoria rarely occur.³¹ Finally, our results might not be applicable to the general chronic fatigue syndrome population because, for instance, we excluded patients using antidepressants.

In conclusion, our results show that during a 4-week treatment period, methylphenidate significantly improves fatigue and concentration in chronic fatigue syndrome patients. Further research is needed to confirm that methylphenidate remains effective and free of side effects at long term, and to investigate if the effect of methylphenidate in chronic fatigue syndrome is merely symptomatic, or if the drug interferes with the underlying pathophysiology.

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