Original Investigation

Disease Mechanisms and Clonidine Treatment in Adolescent Chronic Fatigue Syndrome

A Combined Cross-sectional and Randomized Clinical Trial

Dag Sulheim, MD; Even Fagermoen, MD; Anette Winger, RN, MA; Anders Mikal Andersen, BSc; Kristin Godang, BSc; Fredrik Müller, MD, PhD; Peter C. Rowe, MD, PhD; J. Philip Saul, MD; Eva Skovlund, PhD; Merete Glenne Øie, PhD; Vegard Bruun Wyller, MD, PhD

IMPORTANCE Chronic fatigue syndrome (CFS) is a disabling condition with unknown disease mechanisms and few treatment options.

OBJECTIVE To explore the pathophysiology of CFS and assess clonidine hydrochloride pharmacotherapy in adolescents with CFS by using a hypothesis that patients with CFS have enhanced sympathetic activity and that sympatho-inhibition by clonidine would improve symptoms and function.

DESIGN, SETTING, AND PARTICIPANTS Participants were enrolled from a single referral center recruiting nationwide in Norway. A referred sample of 176 adolescents with CFS was assessed for eligibility; 120 were included (34 males and 86 females; mean age, 15.4 years). A volunteer sample of 68 healthy adolescents serving as controls was included (22 males and 46 females; mean age, 15.1 years). The CSF patients and healthy controls were assessed cross-sectionally at baseline. Thereafter, patients with CFS were randomized 1:1 to treatment with low-dose clonidine or placebo for 9 weeks and monitored for 30 weeks; double-blinding was provided. Data were collected from March 2010 until October 2012 as part of the Norwegian Study of Chronic Fatigue Syndrome in Adolescents: Pathophysiology and Intervention Trial.

INTERVENTIONS Clonidine hydrochloride capsules (25 µg or 50 µg twice daily for body weight <35 kg or >35 kg, respectively) vs placebo capsules for 9 weeks.

MAIN OUTCOMES AND MEASURES Number of steps per day.

RESULTS At baseline, patients with CFS had a lower number of steps per day ($P < .001$), digit span backward score ($P = .002$), and urinary cortisol to creatinine ratio ($P = .001$), and a higher fatigue score ($P < .001$), heart rate responsiveness ($P = .02$), plasma norepinephrine level ($P < .001$), and serum C-reactive protein concentration ($P = .04$) compared with healthy controls. There were no significant differences regarding blood microbiology evaluation. During intervention, the clonidine group had a lower number of steps per day (mean difference, −637 steps; $P = .07$), lower plasma norepinephrine level (mean difference, −42 pg/mL; $P = .01$), and lower serum C-reactive protein concentration (mean ratio, 0.69; $P = .02$) compared with the CFS placebo group.

CONCLUSIONS AND RELEVANCE Adolescent CFS is associated with enhanced sympathetic nervous activity, low-grade systemic inflammation, attenuated hypothalamus-pituitary-adrenal axis function, cognitive impairment, and large activity reduction, but not with common microorganisms. Low-dose clonidine attenuates sympathetic outflow and systemic inflammation in CFS but has a concomitant negative effect on physical activity; thus, sympathetic and inflammatory enhancement may be compensatory mechanisms. Low-dose clonidine is not clinically useful in CFS.

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Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Vegard Bruun Wyller, MD, PhD, Department of Paediatrics, Akershus University Hospital, N-1478 Lørenskog, Nordbyhagen, Norway (brwylle@online.no).

Chronic fatigue syndrome (CFS) is characterized by unexplained, long-lasting, disabling fatigue accompanied by pain, cognitive impairment, orthostatic intolerance, and other symptoms.[1,2] Chronic fatigue syndrome is an important cause of disability among adolescents and may have detrimental effects on psychosocial and academic development[3] as well as family functioning.[4] The adolescent CFS prevalence is estimated at 0.1% to 1.0%.[5-7] Cognitive behavioral therapy has a beneficial effect,[8] but no safe and effective pharmacotherapy has been documented.

The pathophysiology of CFS remains poorly understood. Previous adolescent studies[9-11] reported enhanced sympathetic and attenuated parasympathetic cardiovascular nervous activity, possibly explaining symptoms and disability.[12] Low-grade systemic inflammation[13,14] and attenuation of the hypothalamus-pituitary-adrenal axis [15,16] have also been documented in some studies. Neuropsychological studies[17-19] suggest slight impairments of executive control functions; the details remain to be explored.

One study[20] suggested that all of these features might be attributed to a persistent stress response or "sustained arousal" (Supplement [eFigure 1]). This model complies with other CFS models[21] and rests on contemporary stress theories.[22,23] Sustained arousal might be caused by infections,[24] which seem to be precipitating factors in CFS.[25,26] However, the precise role of microorganisms in CFS remains unclear.

Clonidine hydrochloride is a centrally acting agonist to the α_2-adrenergic receptor.[27] Clonidine inhibits sympathetic nervous activity and enhances parasympathetic nervous activity, thereby lowering heart rate and blood pressure.[28] In addition, clonidine might have anti-inflammatory properties,[29] as well as a beneficial effect on executive functions during conditions of high arousal in primates,[30] in line with a previous CFS study.[31]

The aim of the present study was 2-fold: (1) explore the pathophysiology of CFS and (2) assess the effect of low-dose clonidine treatment in adolescent CFS. We hypothesized that enhanced sympathetic activity is an important part of CFS pathophysiology and that sympatho-inhibition by clonidine would improve symptoms and function.

Methods

Patients With CFS

The Department of Paediatrics at Oslo University Hospital is a national referral center in Norway for young patients with CFS. For the present study, all 20 hospital pediatric departments in Norway, as well as primary care pediatricians and general practitioners, were invited to refer patients with CFS aged 12 to 18 years consecutively to our department. The referring units were required to confirm that the patient did not have any medical or psychiatric disorder that might explain the fatigue and that they had experienced no concurrent demanding life event.

In agreement with clinical guidelines,[2,32] we applied a broad case definition requiring 3 months of unexplained disabling, chronic/relapsing fatigue of new onset (Supplement [eMethods]). We did not require that patients meet any other accompanying symptom criteria.

Healthy Controls

A group of healthy adolescents with a comparable distribution of sex and age were recruited from local schools to serve as a control group for the cross-sectional comparison. Controls were not matched to cases on any variable. No chronic disease and no regular use of pharmaceutical agents were allowed.

Study Design

This study is part of the NorCAPITAL-project (The Norwegian Study of Chronic Fatigue Syndrome in Adolescents: Pathophysiology and Intervention Trial) (Supplement [eFigure 2 and eAppendix]), which has been approved by the Norwegian National Committee for Ethics in Medical Research and the Norwegian Medicines Agency (Supplement [eMethods]). Data were collected between March 1, 2010, and October 15, 2012. Written informed consent was obtained from all participants or from parents or next of kin if required. Each participant received a gift certificate worth NKr 200 after each completed in-hospital assessment.

This study combined a cross-sectional and a randomized clinical design: (1) patients with CFS and healthy controls underwent a baseline investigational program at our research unit, and (2) patients with CFS were randomized to 9 weeks of treatment with oral clonidine capsules or placebo capsules in a 1:1 ratio by using a computer-based routine for stratified randomization (block size: 4) (**Figure 1**). A disease duration of 18 months (the median disease duration in a previous follow-up study[33]) served as the stratification criterion.

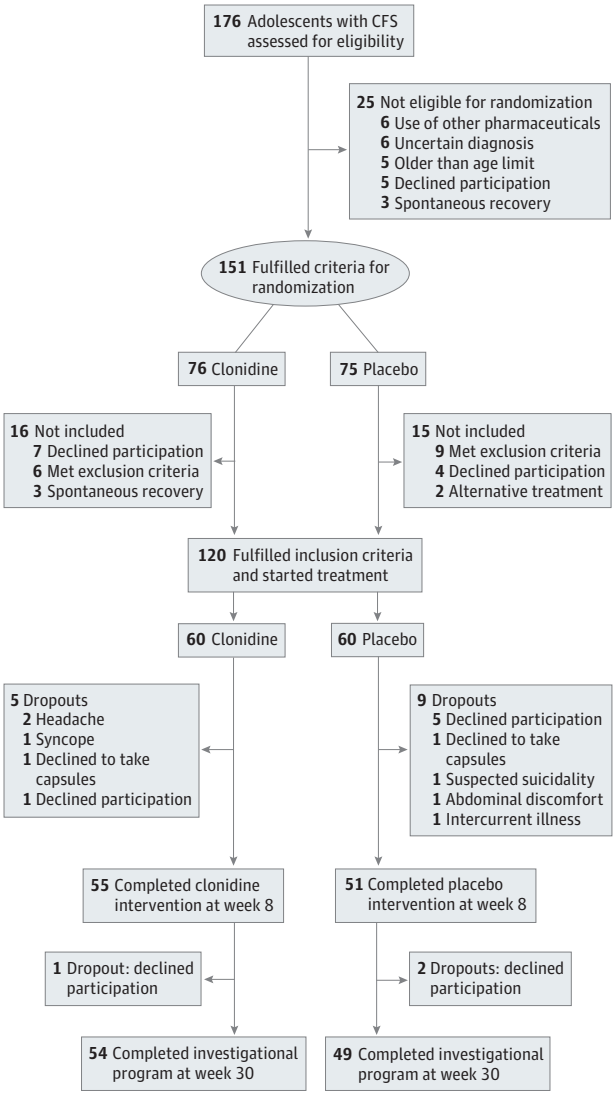
The intervention part of the trial followed a modified intention-to-treat approach.[34] Pharmacy routines required randomization to be carried out at least 1 day before the study drug was dispensed to each patient. However, a separate clinical encounter to assess eligibility was not feasible. Instead, patients fulfilling prespecified criteria (Supplement [eTable 1]) were consecutively randomized after receipt of the referral form (Supplement [eMethods]). A few weeks after randomization, patients were clinically assessed at our research unit (by D.S. or E.F.), after which a decision on enrollment was made (Supplement [eTable 2]). Special attention was directed toward excluding patients with depression as a primary cause of fatigue.

Outcome was assessed by an investigational program identical to the baseline program at weeks 8 and 30. Patients and researchers were blinded to treatment allocation at all stages (Supplement [eTable 7]).

Investigational Program

A 1-day in-hospital assessment included clinical examination, blood sampling (antecubital venous puncture), 20° head-up tilt test, and cognitive tests and always began between 7:30 AM and 9:30 AM (Supplement [eMethods]). All participants were instructed to fast overnight and abstain from tobacco products and caffeine for at least 48 hours, to bring a morning spot urine sample in a sterile container, and

Figure 1. Flowchart of the Randomized Clinical Trial Section of the Study



A total of 176 patients with chronic fatigue syndrome (CFS) were assessed for eligibility, 151 fulfilled criteria for randomization and 120 fulfilled the inclusion criteria and started treatment: 60 were allocated to clonidine, and 60 to placebo. At week 8, a total of 55 patients had completed the clonidine intervention and 51 had completed the placebo intervention. At week 30, a total of 54 vs 49 patients, respectively, had completed the investigational program.

to apply the local anesthetic lidocaine, 2.5%, and prilocaine, 2.5% (EMLA; AstraZeneca), on the skin in the antecubital area 1 hour before the blood sampling. At week 8, patients with CFS were told to postpone taking their prescribed morning dose of the study drug until after blood sampling and the head-up tilt test. All procedures were carried out in a quiet room in a fixed sequence and by the same 3 researchers (D.S., E.F., and A.W.).

After the in-hospital assessment, daily physical activity was monitored during 7 consecutive days using an accelerometer device (activPAL; PAL Technologies Ltd). In addition, a self-administered questionnaire was completed.

Intervention

Tablets containing 25 µg of clonidine hydrochloride (Catapresan; Boehringer Ingelheim) were enclosed in orange opaque, demolition-resistant lactose capsules (Apoteket Produktion and Laboratorier). Empty capsules were used as placebo comparators.

Clonidine lowers blood pressure dose dependently,[35,36] possibly increasing the risk of adverse effects in patients with CFS who already experience orthostatic intolerance.[9] Therefore, clonidine dosages were chosen to yield plasma concentrations within the lower range of what is considered clinically effective. Based on a previous pilot study,[37] the following algorithm was used:

- Patient weight greater than 35 kg: 2 capsules twice daily for 8 weeks (ie, clonidine, 50 µg twice daily, in the intervention group); and
- Patient weight less than 35 kg: 1 capsule twice daily for 8 weeks (ie, clonidine, 25 µg twice daily, in the intervention group).

Therapy was initiated 1 week after the baseline investigational program. One-half of the dose was given during the first 3 days to minimize introductory adverse effects. After 8 weeks of the full dose, the dose was halved for 1 additional week to avoid rebound effects, after which treatment was discontinued.

At therapy initiation, each patient was supplied with a defined number of capsules. The residual number at week 8 was counted, and an index of adherence was calculated. Clonidine plasma concentration was measured at weeks 3 and 8.

Outcomes

The primary efficacy end point was the mean number of steps per day, obtained by an accelerometer recording (Supplement [eMethods and eTable 3]). Secondary efficacy end points (Supplement [eTable 4]) were

- Functional Disability Inventory total sum score,
- Chalder Fatigue Questionnaire total sum score,
- Karolinska Sleep Questionnaire insomnia score,
- CFS symptom inventory hypersensitivity score,
- Brief Pain Inventory average pain score,
- Digit span backward test total sum score,
- Heart rate responsiveness during head-up tilt test,
- Plasma norepinephrine concentration,
- Urinary free cortisol to creatinine ratio, and
- Serum C-reactive protein (CRP) concentration.

Adverse Events

Supine and upright blood pressure and heart rate were considered the most important safety end points. A questionnaire charted the frequencies of 21 possible adverse effects of clonidine on a 1 to 5 Likert scale (ranging from never/rarely present to present all of the time) and was completed by interview at week 8. In addition, patients were routinely interviewed by telephone about adverse effects at weeks 2, 4, and 6.

Statistical Analysis

The mean (SD) number of steps per day approximates 10 000 (4000) in healthy adolescents.[38] An increment of 2500 steps per day for the CFS clonidine group was considered clinically

significant, as suggested from an adult study.[39] The power calculation suggested that a total of 106 patients was to be included (significance level, .05, power, 0.9) (Supplement [eResults]). The drop-out rate was estimated at 10%, yielding a target enrollment of 120 patients.

Patients with CFS were compared with healthy controls by applying *t*, Mann-Whitney, χ^2, or Fisher exact tests as appropriate. The outcome of clonidine intervention was assessed by general linear models (analysis of covariance), adjusting for baseline values and disease duration; we performed both modified intention-to-treat analyses and per-protocol analyses (Supplement [eTable 9]). Separate tests were conducted for all outcome variables at weeks 8 and 30, and a multiple imputation procedure was used to handle missing observations. The net intervention effect was calculated from the parameters of the fitted general linear model. Differential effects in subgroups were explored by including relevant interaction terms. In the clonidine group, dose-response relationships were explored by multiple linear regression analyses.

Statistical software (SPSS; SPSS Inc.) was used for all analyses. All tests were carried out 2-sided, and $P \leq .05$ was considered statistically significant. No correction for multiple comparisons was applied.

Results

Study Populations

A total of 176 adolescents with CFS were referred and assessed for eligibility (Figure 1). Of these, 151 fulfilled randomization criteria and 120 fulfilled the inclusion criteria (34 males and 86 females; mean age, 15.4 years), completed the investigational program, and started treatment (60 in each treatment group). Of the 120 patients, 88 individuals (73.3%) satisfied the Fukuda criteria from the International Chronic Fatigue Syndrome Study Group,[1] and 49 patients (40.8%) had depressive symptoms indicating a possible comorbid mood disorder.[40]

A total of 68 healthy individuals were included as a control group (22 males 46 females; mean age, 15.1 years). Thirty-nine of these adolescents completed a full investigational program, and 29 underwent only laboratory analyses.

Healthy Control Comparisons

Compared with healthy controls, patients with CFS had significantly lower number of steps per day, insomnia score, digit span backward score, and urinary cortisol to creatinine ratio. In addition, patients with CFS had higher disability score, fatigue score, average pain score, hypersensitivity score, heart rate responsiveness, and plasma norepinephrine and serum CRP concentration levels (**Table 1**). All differences remained significant when controlling for depressive symptoms except the digit span backward score ($P = .06$) and serum CRP ($P = .27$). Supine and upright heart rates were higher in the CFS group, whereas blood pressures were similar. No significant differences were found for sex, age, body mass index, family characteristics, and blood hematology, biochemistry, and microbiology studies (Table 1 and Supplement [eTable 8]).

Intervention

Fourteen patients with CFS dropped out before week 8 (5 in the clonidine group, 9 in the placebo group), and an additional 3 withdrew prior to week 30 (Figure 1 and Supplement [eTable 5 and eTable 6]). The mean index of adherence was 93% (clonidine group) and 92% (placebo group). At week 8 in the clonidine group, the mean plasma concentration of clonidine was 0.24 µg/L. The estimated mean steady-state concentration (trough value) was 0.23 µg/L.

Outcome

During intervention, the number of steps per day increased in the placebo group but not in the clonidine group, resulting in an estimated mean difference of −637 steps ($P = .07$) at week 8 (**Table 2** and **Figure 2**). Plasma norepinephrine and serum CRP levels decreased in the clonidine group (mean difference, −42 pg/mL; $P = .01$; mean ratio, 0.69; $P = .02$; respectively) (to convert norepinephrine values to picomoles per liter, multiply by 5.914). No other interventional effects on efficacy variables were found. At week 8, the clonidine group had slightly but significantly lower supine and upright heart rates compared with the placebo group ($P = .03$ and $P = .03$, respectively). No other effects on cardiovascular safety end points were demonstrated. At week 30, the 2 groups were similar across all end points except for lower heart rate responsiveness in the clonidine group ($P = .03$). The results of per-protocol analyses were closely similar to the modified intention-to-treat analyses (Supplement [eTable 9]).

Clonidine plasma concentration was negatively associated with the number of steps per day and positively associated with the fatigue score (Supplement [eTable 10]). No other dose-response relationships were detected apart from a negative association between the estimated steady-state concentration and the insomnia score (ie, insomnia problems increased with concentrations). No differential outcome related to the 2 predefined subgroups (adherence to the Fukuda criteria and presence of depressive symptoms) was found.

Adverse Events

In the clonidine group, one patient fainted and another patient was found to have a peptic duodenal ulcer immediately after the intervention period. Sleepiness and dizziness when rising were significantly more common in the clonidine group, but there was no significant difference in the total number of self-reported adverse effects (Supplement [eTable 11]).

Discussion

There were 2 primary findings of this study. First, adolescent CFS is associated with enhanced sympathetic nervous activity, low-grade systemic inflammation, attenuated hypothalamus-pituitary-adrenal axis function, slight cognitive impairment, and large activity reduction, but not with common

Table 1. Background Characteristics

Characteristic	Mean (SD)			
	CFS Patients, Baseline			
	Clonidine Group (n = 60)	Placebo Group (n = 60)	Healthy Controls (n = 68)	*P* Value (CFS Patients vs Controls)[a]
Sex, No. (%)				
Male	13 (22)	21 (35)	22 (32)	.56
Female	47 (78)	39 (65)	46 (68)	
Age, y	15.2 (1.5)	15.5 (1.6)	15.1 (1.6)	.18
BMI	21.6 (4.4)	21.5 (4.0)	20.6 (3.7)	.12
Symptoms suggesting mood disorder, No. (%)				
No	34 (57)	36 (60)	34 (92)	<.001
Yes	26 (43)	23 (39)	3 (8)	
Adheres to Fukuda criteria, No. (%)[b]				
No	14 (24)	15 (26)	NA	
Yes	45 (76)	43 (74)		
Disease duration, median (range), mo	17.5 (4-72)	18 (5-104)	NA	
Efficacy variables, baseline				
No. of steps per day	4670 (2277)	4564 (2524)	10 302 (3667)	<.001
FDI total sum score	24.0 (9.2)	23.1 (9.2)	1.6 (3.1)	<.001
CFQ total sum score	19.1 (6.4)	19.2 (6.1)	9.3 (4.6)	<.001
BPI average pain score	4.8 (2.1)	4.3 (2.1)	2.5 (1.8)	<.001
KSQ insomnia score	3.4 (1.0)	3.5 (0.9)	4.9 (0.9)	<.001
Symptom inventory hypersensitivity score	2.9 (1.2)	2.8 (1.3)	1.1 (0.2)	<.001
Digit span backward total sum score	5.8 (1.9)	6.0 (2.0)	6.9 (2.0)	.002
Heart rate responsiveness, beats/min	5.2 (3.8)	4.8 (4.8)	3.2 (3.4)	.02
Plasma norepinephrine, pg/mL	343 (140)	327 (123)	251 (74)	<.001
Urine cortisol to creatinine ratio, median (IQR), µg to mg	13.5 (12.5)	9.3 (8.3)	17.0 (19.2)	.001
Serum CRP, median (IQR), mg/L	0.50 (0.97)	0.39 (0.96)	0.35 (0.46)	.04
Safety variables, baseline				
Supine SBP, mm Hg	112 (10)	114 (9)	113 (7)	.67
Supine DBP, mm Hg	62 (9)	65 (10)	63 (7)	.50
Supine heart rate, beats/min	75 (13)	76 (13)	68 (11)	.002
Upright SPB, mm Hg	116 (15)	117 (11)	117 (9)	.64
Upright DPB, mm Hg	74 (11)	75 (12)	71 (9)	.11
Upright heart rate, beats/min	95 (18)	94 (19)	86 (14)	.003

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BPI, Brief Pain Inventory; CFS, chronic fatigue syndrome; CFQ, Chalder Fatigue Questionnaire; CRP, C-reactive protein; DBP, diastolic blood pressure; FDI, Functional Disability Inventory; IQR, interquartile range; KSQ, Karolinska Sleep Questionnaire; NA, not applicable; SBP, systolic blood pressure.

SI conversion factors: To convert CRP to nanomoles per liter, multiply by 9.524; urine cortisol to creatinine ratio to micromoles per mole, multiply by 0.3122; norepinephrine to picomoles per liter, multiply by 5.914.

[a] *P* values were based on χ^2 test, Fisher exact test, *t* test, or Mann-Whitney test, as appropriate.

[b] Fukuda criteria are CFS diagnostic criteria from the International Chronic Fatigue Syndrome Study Group.[1]

microorganisms. Second, clonidine attenuates sympathetic outflow and systemic inflammation in CFS, but has a concomitant negative effect on physical activity.

Sympathetic Nervous Activity

Compared with the controls, patients with CFS had increased levels of plasma norepinephrine, as well as a higher heart rate (supine and upright) and heart rate responsiveness, indicating sympathetic enhancement. Increased plasma norepinephrine is a conspicuous finding, confirming previous results,[11] and is consistent with a report of high plasma neuropeptide Y levels.[41] Sympathetic enhancement might result from physical deconditioning. In the present study, however, neither plasma norepinephrine level nor heart rate responsiveness was associated with the number of steps per day in patients with CFS (Supplement [eTable 12]).

In patients with CFS, lowering norepinephrine levels with clonidine was associated with lower physical activity than the activity with placebo. Thus, clonidine appeared to eliminate a relatively strong placebo effect, and the observed differences resolved when the study drug was discontinued. A recent study[42] suggested that sympathetic activation is a predictor of the placebo response.

Inflammation

Clonidine lowered both plasma norepinephrine and serum CRP levels in patients with CFS, suggesting that enhanced sympathetic nervous activity might be the cause of low-grade systemic inflammation. Catecholaminergic stimulation of lymphocytes has been shown[43] to promote secretion of the cytokine interleukin 6, which in turn enhances CRP synthesis. Alternatively, the anti-inflammatory effect of clonidine

Table 2. Outcome of Clonidine Intervention: Modified Intention-to-Treat Analyses[a]

Efficacy Variable	Week 8 (During Treatment)	Week 30 (After Treatment)
Steps per day, No.		
Clonidine group, mean	4631	4682
Placebo group, mean	5212	4652
Difference (95% CI)	−637 (−1328 to 53)	119 (−796 to 1035)
P value (clonidine vs placebo)	.07	.80
FDI total sum score		
Clonidine group, mean	21.4	17.5
Placebo group, mean	20.7	16.8
Difference (95% CI)	0.2 (−10.3 to 10.8)	0.2 (−13.3 to13.6)
P value (clonidine vs placebo)	.97	.98
CFQ total sum score		
Clonidine group, mean	17.9	11.1
Placebo group, mean	16.4	13.5
Difference (95% CI)	1.7 (−2.3 to 5.6)	0.5 (−14.7 to 15.7)
P value (clonidine vs placebo)	.24	.95
BPI average pain score		
Clonidine group, mean	4.1	3.8
Placebo group, mean	3.4	3.3
Difference (95% CI)	0.5 (−0.16 to 1.16)	0.4 (−0.4 to 1.1)
P value (clonidine vs placebo)	.14	.32
KSQ insomnia score		
Clonidine group, mean	3.7	3.6
Placebo group, mean	3.8	3.6
Difference (95% CI)	0.1 (−0.4 to 0.2)	0.1 (−0.3 to 0.4)
P value (clonidine vs placebo)	.54	.74
Symptom inventory hypersensitivity score		
Clonidine group, mean	2.6	2.6
Placebo group, mean	2.4	2.6
Difference (95% CI)	0.1 (−0.2 to 0.5)	−0.03 (−0.4 to 0.3)
P value (clonidine vs placebo)	.42	.84
Digit span backward total sum score		
Clonidine group, mean	5.8	5.9
Placebo group, mean	6.2	6.7
Difference (95% CI)	− 0.1 (−0.6 to 0.5)	−0.5 (−1.2 to 0.1)
P value (clonidine vs placebo)	.80	.10
Heart rate responsiveness, beats/min		
Clonidine group, mean	5.0	4.2
Placebo group, mean	4.9	5.2
Difference (95% CI)	−0.1 (−1.3 to 1.1)	−1.5 (−2.8 to 0.1)
P value (clonidine vs placebo)	.90	.03
Plasma norepinephrine, pg/mL		
Clonidine group, mean	262	296
Placebo group, mean	288	298
Difference (95% CI)	−42 (−75 to −9)	−9 (−51 to 32)
P value (clonidine vs placebo)	.01	.66
Urine cortisol to creatinine ratio, µg/dL to mg/dL		
Clonidine group, mean	12.2	12.5
Placebo group, mean	13.5	12.8
Ratio (95% CI)	0.79 (0.59 to 1.01)	0.95 (0.68 to 1.33)
P value (clonidine vs placebo)	.13	.77

(continued)

Table 2. Outcome of Clonidine Intervention: Modified Intention-to-Treat Analyses[a] (continued)

Efficacy Variable	Week 8 (During Treatment)	Week 30 (After Treatment)
Serum CRP, mg/L		
Clonidine group, mean	0.55	0.85
Placebo group, mean	0.77	0.79
Ratio (95% CI)	0.69 (0.50 to 0.94)	1.1 (0.8 to 1.5)
P value (clonidine vs placebo)	.02	.66
Safety Variables		
Supine SBP, mm Hg		
Clonidine group, mean	112	113
Placebo group, mean	110	113
Difference (95% CI)	1.5 (−0.93 to 4.0)	1.5 (−1.2 to 4.1)
P value (clonidine vs placebo)	.22	.28
Supine DBP, mm Hg		
Clonidine group, mean	61	60
Placebo group, mean	61	61
Difference (95% CI)	1.6 (−0.72 to 3.9)	0.8 (−2.0 to 3.5)
P value (clonidine vs placebo)	.17	.59
Supine heart rate, beats/min		
Clonidine group, mean	69	73
Placebo group, mean	73	72
Difference (95% CI)	−3.0 (−5.8 to −0.3)	0.8 (−2.0 to 3.9)
P value (clonidine vs placebo)	.03	.56
Upright SPB, mm Hg		
Clonidine group, mean	115	117
Placebo group, mean	116	118
Difference (95% CI)	−0.7 (−3.57 to 3.44)	−0.2 (−3.7 to 3.4)
P value (clonidine vs placebo)	.97	.92
Upright DPB, mm Hg		
Clonidine group, mean	70	70
Placebo group, mean	70	70
Difference (95% CI)	0.6 (−2.9 to 4.2)	0.3 (−2.7 to 3.2)
P value (clonidine vs placebo)	.72	.85
Upright heart rate, beats/min		
Clonidine group, mean	90	94
Placebo group, mean	96	98
Difference (95% CI)	−5.8 (−11.0 to −1.0)	−3.4 (−8.9 to 2.0)
P value (clonidine vs placebo)	.03	.22

Abbreviations: See Table 1.

SI conversion factors: To convert CRP to nanomoles per liter, multiply by 9.524; urine cortisol to creatinine ratio to micromoles per mole, multiply by 0.3122; norepinephrine to picomoles per liter, multiply by 5.914.

[a] All analyses were based on multiple imputation of missing values. Means and differences at weeks 8 and 30 were estimated from the variables of the general linear model. Model diagnostics were performed by visual inspection of residual plots. For urine cortisol to creatinine ratio and serum CRP, modeling was performed on natural log–transformed variables; geometric means and ratios instead of differences are reported. Randomization was carried out before enrollment; thus, not all randomized patients received treatment (Figure 1).

might be the result of enhanced parasympathetic activity,[28] which suppresses the transcription factor nuclear factor κB in macrophages and thereby lowers secretion of proinflammatory cytokines.[44] Increased nuclear factor κB activity has been reported[45] in CFS.

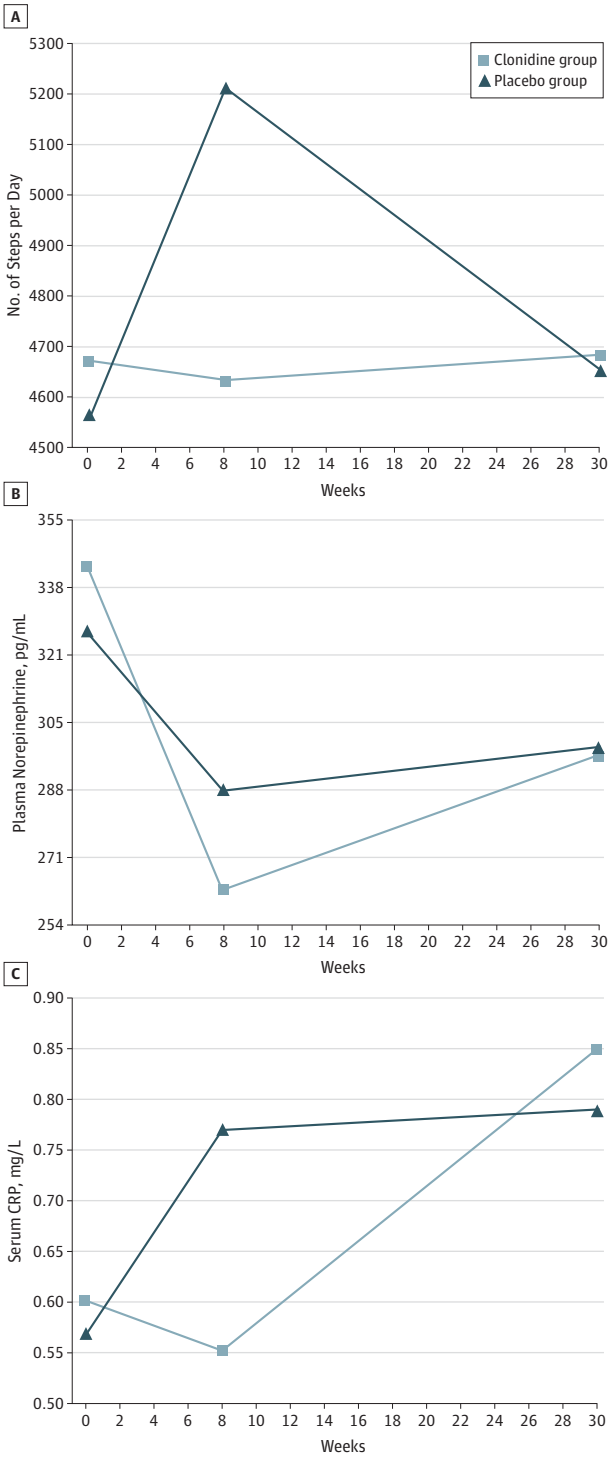
The present study confirms findings from some studies[15,16] of low urinary free cortisol in CFS. Systemic inflammation in CFS has been attributed to hypothalamus-pituitary-adrenal axis attenuation.[13] This possibility seems less likely in light of the present results, because urinary free cortisol concentration tended to decrease during clonidine intervention.

Low-grade systemic inflammation also might be caused by ongoing or reactivation of infections, but the present study does not suggest an increased presence of common microorganisms in CFS, a finding that is consistent with other reports.[46] However, our finding of elevated CRP levels in CFS might be partly explained by the coexistence of depressive symptoms, because controlling for such symptoms leveled out CRP differences between patients and controls.

Hemodynamics

Clonidine did not lower blood pressure or heart rate responsiveness and had a minimal effect on supine and upright heart rates. Furthermore, a dose-response relationship could not be demonstrated. These findings contrast with those of previous studies[35,36] in which similar dosages and plasma concentrations of clonidine had a significant and dose-dependent effect on blood pressure and heart rate. A potential plasma-expanding effect of clonidine might offset blood

Figure 2. Changes of Efficacy Variables During the Intervention Period



A, Number of steps per day: the placebo group had an increment in steps per day during the intervention period (an expected placebo effect), whereas no increment (no placebo effect) was demonstrable in the clonidine group. B, Plasma norepinephrine: the clonidine group had a stronger decrease in plasma norepinephrine compared to the placebo group. C, Serum C-reactive protein (CRP): the clonidine group had a slight decrease in CRP concentration, whereas the concentration increased in the placebo group. To convert CRP to nanomoles per liter, multiply by 9.524; norepinephrine to picomoles per liter, multiply by 5.914.

pressure reduction, but a previous study[47] and our own data on body weight and hemoglobin concentration (Supplement [eTable 13]) do not support this possibility. A more likely explanation might be altered adrenergic receptor density, which is consistent with a recent report[48] of abnormal α_2-receptor protein transcription in CFS. Alteration of pharmacodynamics might also explain the association between high clonidine concentration and insomnia problems in the present study despite the well-known sedative effect of clonidine and the lack of clonidine's effect on working memory.[31]

Clinical Implications

Low-dose clonidine is not clinically useful in adolescent CFS, and alternative therapeutic strategies should be explored. The results further suggest that neither sympathetic enhancement nor low-grade systemic inflammation contributes to symptoms and disability in CFS, as postulated in the sustained arousal model.[20] The differences between the patients and the controls were small, especially for CRP levels. Sympathetic enhancement and inflammation might instead be compensatory mechanisms, because suppression of these responses in the clonidine group was associated with a poorer clinical outcome.

Strengths and Limitations

This study had good adherence and a low drop-out rate, in line with other studies in the field.[8] The wide inclusion criteria suggest generalizability to the population of adolescents with CFS referred to pediatric care. Because only 2 patients had disease duration between 3 and 6 months, the results should be generalizable to populations in which more than 6 months of fatigue is required.

The single-center design and the fact that our inclusion criteria are not identical to common international standards might reduce generalizability. However, subgrouping (Fukuda criteria and comorbid depressive symptoms) did not suggest a differential response to the intervention. The results might also apply to adults with CFS because previous research does not suggest important differences in pathophysiology.

The prevalence of comorbid depressive symptoms among patients with CFS was higher than in a comparable study.[49] It is possible that we included some patients with primary depression rather than CFS; ideally, a formal psychiatric interview should have been conducted. However, a more likely explanation is low discriminant validity of the applied depression inventory, because several single items assess symptoms that are common in both depression and CFS.[40]

We used a low clonidine dosage, and the study would have benefited from a more thorough pilot study of dosage algorithms. The negative effect of clonidine on physical activity and fatigue might be the result of pharmacologic effects other than sympathetic/inflammatory attenuation. Because of the multiple statistical tests used for analyses, *P* values close to the limit of significance ($P \leq .05$) should be interpreted with caution.

Conclusions

Adolescent CFS is associated with enhanced sympathetic nervous activity, attenuated hypothalamus-pituitary-adrenal axis, low-grade systemic inflammation, slight cognitive impairment, and large activity reduction, but not with common microorganisms. Sympathetic enhancement might cause inflammation, but neither sympathetic enhancement nor inflammation appears to contribute to physical disability or fatigue. Low-dose clonidine is not a clinically useful therapy in adolescent CFS; rather, it appears that the autonomic and inflammatory processes that clonidine blocks may have beneficial effects.

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Author Affiliations: Department of Paediatrics, Oslo University Hospital, Oslo, Norway (Sulheim, Wyller); Department of Paediatrics, Lillehammer County Hospital, Lillehammer, Norway (Sulheim); Institute of Clinical Medicine, Medical Faculty, University of Oslo, Oslo, Norway (Fagermoen, Winger); Department of Anesthesiology and Critical Care, Oslo University Hospital, Oslo, Norway (Fagermoen); Institute of Nursing Sciences, Oslo and Akershus University College of Applied Sciences, Oslo, Norway (Winger); Department of Pharmacology, Oslo University Hospital, Oslo, Norway (Andersen); Section of Specialized Endocrinology, Department of Endocrinology, Oslo University Hospital Rikshospitalet, Oslo, Norway (Godang); Department of Microbiology, Oslo University Hospital, Oslo, Norway (Müller); Department of Pediatrics, the Johns Hopkins University School of Medicine, Baltimore, Maryland (Rowe); Department of Pediatrics, Medical University of South Carolina, Charleston (Saul); School of Pharmacy, University of Oslo, Oslo, Norway (Skovlund); Norwegian Institute of Public Health, Oslo, Norway (Skovlund); Department of Psychology, University of Oslo, Oslo, Norway (Øie); Innlandet Hospital Trust, Lillehammer, Norway (Øie); Division of Medicine and Laboratory Sciences, Medical Faculty, University of Oslo, Oslo, Norway (Wyller); Department of Paediatrics, Akershus University Hospital, Nordbyhagen, Norway (Wyller).

Author Contributions: Drs Sulheim and Fagermoen contributed equally to this study. Dr Wyller had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Sulheim, Fagermoen, Winger, Godang, Rowe, Saul, Øie, Wyller.
Acquisition of data: Sulheim, Fagermoen, Winger, Andersen.
Analysis and interpretation of data: Sulheim, Fagermoen, Godang, Müller, Rowe, Saul, Skovlund, Øie, Wyller.
Drafting of the manuscript: Sulheim, Fagermoen, Godang.
Critical revision of the manuscript for important intellectual content: Fagermoen, Winger, Andersen, Müller, Rowe, Saul, Skovlund, Øie, Wyller.
Statistical analysis: Sulheim, Fagermoen, Skovlund, Wyller.
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REFERENCES

1. Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A; International Chronic Fatigue Syndrome Study Group. The chronic fatigue syndrome: a comprehensive approach to its definition and study. *Ann Intern Med*. 1994;121(12):953-959.

2. Royal College of Paediatrics and Child Health. *Evidence Based Guidelines for the Management of CFS/ME (Chronic Fatigue Syndrome/Myalgic Encephalopathy) in Children and Young Adults*. London, England: Royal College of Paediatrics and Child Health; 2004.

3. Kennedy G, Underwood C, Belch JJ. Physical and functional impact of chronic fatigue syndrome/myalgic encephalomyelitis in childhood. *Pediatrics*. 2010;125(6):e1324-e1330. doi:10.1542/peds.2009-2644.

4. Missen A, Hollingworth W, Eaton N, Crawley E. The financial and psychological impacts on mothers of children with chronic fatigue syndrome (CFS/ME). *Child Care Health Dev*. 2012;38(4):505-512.

5. Nijhof SL, Maijer K, Bleijenberg G, Uiterwaal CS, Kimpen JL, van de Putte EM. Adolescent chronic fatigue syndrome: prevalence, incidence, and morbidity. *Pediatrics*. 2011;127(5):e1169-e1175. doi:10.1542/peds.2010-1147.

6. Crawley EM, Emond AM, Sterne JA. Unidentified chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) is a major cause of school absence: surveillance outcomes from school-based clinics. *BMJ Open*. 2011;1(2):e000252. doi:10.1136/bmjopen-2011-000252.

7. Jason LA, Bell DS, Rowe K, et al. A pediatric case definition for chronic fatigue syndrome. *J Chronic Fatigue Syndr*. 2006;13(2/3):1-44.

8. Nijhof SL, Bleijenberg G, Uiterwaal CS, Kimpen JL, van de Putte EM. Effectiveness of internet-based cognitive behavioural treatment for adolescents with chronic fatigue syndrome (FITNET): a randomised controlled trial. *Lancet*. 2012;379(9824):1412-1418.

9. Wyller VB, Due R, Saul JP, Amlie JP, Thaulow E. Usefulness of an abnormal cardiovascular response during low-grade head-up tilt-test for discriminating adolescents with chronic fatigue from healthy controls. *Am J Cardiol*. 2007;99(7):997-1001.

10. Wyller VB, Barbieri R, Thaulow E, Saul JP. Enhanced vagal withdrawal during mild orthostatic stress in adolescents with chronic fatigue. *Ann Noninvasive Electrocardiol*. 2008;13(1):67-73.

11. Wyller VB, Godang K, Mørkrid L, Saul JP, Thaulow E, Walløe L. Abnormal thermoregulatory responses in adolescents with chronic fatigue syndrome: relation to clinical symptoms. *Pediatrics*. 2007;120(1):e129-e137. doi:10.1542/peds.2006-2759.

12. Wyller VB, Helland IB. Relationship between autonomic cardiovascular control, case definition, clinical symptoms, and functional disability in adolescent chronic fatigue syndrome: an exploratory study. *Biopsychosoc Med*. 2013;7(1):5. doi:10.1186/1751-0759-7-5.

13. Klimas NG, Broderick G, Fletcher MA. Biomarkers for chronic fatigue. *Brain Behav Immun*. 2012;26(8):1202-1210.

14. Raison CL, Lin JM, Reeves WC. Association of peripheral inflammatory markers with chronic fatigue in a population-based sample. *Brain Behav Immun*. 2009;23(3):327-337.

15. Papadopoulos AS, Cleare AJ. Hypothalamic-pituitary-adrenal axis dysfunction in chronic fatigue syndrome. *Nat Rev Endocrinol*. 2012;8(1):22-32.

16. Segal TY, Hindmarsh PC, Viner RM. Disturbed adrenal function in adolescents with chronic fatigue syndrome. *J Pediatr Endocrinol Metab*. 2005;18(3):295-301.

17. Majer M, Welberg LA, Capuron L, Miller AH, Pagnoni G, Reeves WC. Neuropsychological performance in persons with chronic fatigue syndrome: results from a population-based study. *Psychosom Med*. 2008;70(7):829-836.

18. DeLuca J, Johnson SK, Ellis SP, Natelson BH. Cognitive functioning is impaired in patients with chronic fatigue syndrome devoid of psychiatric disease. *J Neurol Neurosurg Psychiatry*. 1997;62(2):151-155.

19. Haig-Ferguson A, Tucker P, Eaton N, Hunt L, Crawley E. Memory and attention problems in children with chronic fatigue syndrome or myalgic encephalopathy. *Arch Dis Child*. 2009;94(10):757-762.

20. Wyller VB, Eriksen HR, Malterud K. Can sustained arousal explain the chronic fatigue syndrome? *Behav Brain Funct*. 2009;5:10. doi:10.1186/1744-9081-5-10.

21. Maloney EM, Boneva R, Nater UM, Reeves WC. Chronic fatigue syndrome and high allostatic load: results from a population-based case-control study in Georgia. *Psychosom Med*. 2009;71(5):549-556.

22. McEwen BS. Protective and damaging effects of stress mediators: central role of the brain. *Dialogues Clin Neurosci*. 2006;8(4):367-381.

23. Ursin H, Eriksen HR. Sensitization, subjective health complaints, and sustained arousal. *Ann N Y Acad Sci*. 2001;933:119-129.

24. Kadota Y, Cooper G, Burton AR, et al. Autonomic hyper-vigilance in post-infective fatigue syndrome. *Biol Psychol*. 2010;85(1):97-103.

25. Hickie I, Davenport T, Wakefield D, et al; Dubbo Infection Outcomes Study Group. Post-infective and chronic fatigue syndromes precipitated by viral and non-viral pathogens: prospective cohort study. *BMJ*. 2006;333(7568):575-581.

26. Katz BZ, Shiraishi Y, Mears CJ, Binns HJ, Taylor R. Chronic fatigue syndrome after infectious mononucleosis in adolescents. *Pediatrics*. 2009;124(1):189-193.

27. Szabo B. Imidazoline antihypertensive drugs: a critical review on their mechanism of action. *Pharmacol Ther*. 2002;93(1):1-35.

28. Cividjian A, Toader E, Wesseling KH, Karemaker JM, McAllen R, Quintin L. Effect of clonidine on cardiac baroreflex delay in humans and rats. *Am J Physiol Regul Integr Comp Physiol*. 2011;300(4):R949-R957.

29. Kim MH, Hahn TH. The effect of clonidine pretreatment on the perioperative proinflammatory cytokines, cortisol, and ACTH responses in patients undergoing total abdominal hysterectomy. *Anesth Analg*. 2000;90(6):1441-1444.

30. Kim S, Bobeica I, Gamo NJ, Arnsten AF, Lee D. Effects of α-2A adrenergic receptor agonist on time and risk preference in primates. *Psychopharmacology (Berl)*. 2012;219(2):363-375.

31. Morriss RK, Robson MJ, Deakin JF. Neuropsychological performance and noradrenaline function in chronic fatigue syndrome under conditions of high arousal. *Psychopharmacology (Berl)*. 2002;163(2):166-173.

32. National Institute for Health and Clinical Excellence. *Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (or Encephalopathy): Diagnosis and Management of CFS/ME in Adults and Children: NICE Clinical Guideline. No. 53.* London, England: National Institute for Health and Clinical Excellence; 2007.

33. Sulheim D, Hurum H, Helland IB. Adolescent chronic fatigue syndrome; a follow-up study displays concurrent improvement of circulatory abnormalities and clinical symptoms. *Biopsychosoc Med*. 2012;6:10. doi:10.1186/1751-0759-6-10. Medline:22436201

34. *ICH Topic E 9: Statistical Principles for Clinical Guidelines.* London, England: European Medicines Agency; 1998.

35. Anavekar SN, Howes LG, Jarrott B, Syrjanen M, Conway EL, Louis WJ. Pharmacokinetics and antihypertensive effects of low dose clonidine during chronic therapy. *J Clin Pharmacol*. 1989;29(4):321-326.

36. Veith RC, Best JD, Halter JB. Dose-dependent suppression of norepinephrine appearance rate in plasma by clonidine in man. *J Clin Endocrinol Metab*. 1984;59(1):151-155.

37. Fagermoen E, Sulheim D, Winger A, et al. Clonidine in the treatment of adolescent chronic fatigue syndrome: a pilot study for the NorCAPITAL trial. *BMC Res Notes*. 2012;5:418. doi:10.1186/1756-0500-5-418.

38. Strycker LA, Duncan SC, Chaumeton NR, Duncan TE, Toobert DJ. Reliability of pedometer data in samples of youth and older women. *Int J Behav Nutr Phys Act*. 2007;4:4. doi:10.1186/1479-5868-4-4.

39. Newton JL, Pairman J, Hallsworth K, Moore S, Plötz T, Trenell MI. Physical activity intensity but not sedentary activity is reduced in chronic fatigue syndrome and is associated with autonomic regulation. *QJM*. 2011;104(8):681-687.

40. Daviss WB, Birmaher B, Melhem NA, Axelson DA, Michaels SM, Brent DA. Criterion validity of the Mood and Feelings Questionnaire for depressive episodes in clinic and non-clinic subjects. *J Child Psychol Psychiatry*. 2006;47(9):927-934.

41. Fletcher MA, Rosenthal M, Antoni M, et al. Plasma neuropeptide Y: a biomarker for symptom severity in chronic fatigue syndrome. *Behav Brain Funct*. 2010;6:76.

42. Ober K, Benson S, Vogelsang M, et al. Plasma noradrenaline and state anxiety levels predict placebo response in learned immunosuppression. *Clin Pharmacol Ther*. 2012;91(2):220-226.

43. Cole SW, Arevalo JM, Takahashi R, et al. Computational identification of gene-social environment interaction at the human IL6 locus. *Proc Natl Acad Sci U S A*. 2010;107(12):5681-5686.

44. Rosas-Ballina M, Tracey KJ. The neurology of the immune system: neural reflexes regulate immunity. *Neuron*. 2009;64(1):28-32.

45. Maes M, Mihaylova I, Bosmans E. Not in the mind of neurasthenic lazybones but in the cell nucleus: patients with chronic fatigue syndrome have increased production of nuclear factor kappa beta. *Neuro Endocrinol Lett*. 2007;28(4):456-462.

46. Cameron B, Flamand L, Juwana H, et al. Serological and virological investigation of the role of the herpesviruses EBV, CMV and HHV-6 in post-infective fatigue syndrome. *J Med Virol*. 2010;82(10):1684-1688.

47. Thananopavarn C, Golub MS, Eggena P, Barrett JD, Sambhi MP. Clonidine, a centrally acting sympathetic inhibitor, as monotherapy for mild to moderate hypertension. *Am J Cardiol*. 1982;49(1):153-158.

48. Light AR, Bateman L, Jo D, et al. Gene expression alterations at baseline and following moderate exercise in patients with chronic fatigue syndrome and fibromyalgia syndrome. *J Intern Med*. 2012;271(1):64-81.

49. Bould H, Collin SM, Lewis G, Rimes K, Crawley E. Depression in paediatric chronic fatigue syndrome. *Arch Dis Child*. 2013;98(6):425-428.