HE CHRONIC fatigue syndrome (CFS) is an idio-pathic illness characterized by a disab-ling sense of fatigue, which is markedly exacerbated by physical exertion, and a constellation of other symptoms, such as impairments in concentra-tion and short-term memory, sleep distur-bances, musculoskeletal pain, headaches, painful lymph nodes, and recurrent sore throats.1,2 Chronic fatigue syndrome has a profound impact on the functional status of patients,3,4 and while complete recovery does occur in a small minority, most patients ex-perience functional limitations that persist for years.5 Thus, finding an effective treat-ment for CFS is a high priority.

A large number of pharmaceutical and medicinal agents have been touted as benefi-cial in CFS.6 However, only a few of these agents have been subjected to testing in random-ized, placebo-controlled trials. The selec-tion of drugs for these trials has been influ-enced by prevailing hypotheses regarding the cause or pathogenesis of CFS, eg, per-sistent viral infection,7 immunologic or al-lergic disorders,8,11 vitamin deficiency,12 or depression.13 Even though clinical benefit has been reported in some of these tri-als,6,10 concerns about study methods have precluded their general acceptance.

Recently, a study supporting the hy-pothesis that CFS is associated with neur-ally mediated hypotension14 has attracted much research attention. The observation, in this same study, that 9 of 23 patients treated primarily with fludrocortisone acetate and increased dietary salt reported complete or nearly complete resolution of all CFS symptoms within 1 month of be-ginning treatment also has attracted the attention of many patients with CFS and practitioners alike. Fludrocortisone and in-creased dietary sodium were administered with the aim of increasing blood volume, thereby preventing the initiation of a patho-logic autonomic cardiovascular reflex pro-posed to underlie neurally mediated hypo-tension.14 Although this study was not placebo controlled and additional drugs were given to some patients, the robust na-ture of the response of the patients led us to believe that the benefits observed were not due to placebo effect or the addition of additional drugs.

**Objective:** To provide a preliminary assessment of the efficacy and safety of fludrocortisone acetate treatment of chronic fatigue syndrome.

**Design:** A placebo-controlled, double-blind, random-allocation crossover trial of 6 weeks of fludrocortisone.

**Setting:** An outpatient clinical trials unit.

**Patients:** Twenty-five participants with chronic fatigue syndrome (mean age, 40 years; 19 [76%] women; mean duration of illness, 7.0 years) were recruited from a research clinic registry. Five patients withdrew from the trial.

**Interventions:** All participants were scheduled to receive fludrocortisone acetate (0.1-0.2 mg) or a placebo for 6 weeks in each treatment.

**Main Outcome Measures:** Self-administered questionnaires were completed at the beginning and end of each treatment arm that asked patients to rate the severity of their symptoms on a visual analogue scale. The Medical Outcomes Study 36-Item Short-Form Health Survey, a re-designed, placebo-controlled trial of unselected patients with chronic fatigue syndrome.

**Results:** At baseline, the study participants reported symptom severity greater than 5 for most symptoms, and all had evidence of marked functional impairments. No improvement was observed in the severity of any symptom or in any test of function for the 20 participants who completed both arms of the trial. Blood pressure and heart rate readings were unaffected by treatment, and plasma norepinephrine levels did not differ from those of a healthy control group. The incidence of adverse experiences was similar in the fludrocortisone and placebo arms of the trial.

**Conclusion:** Low-dose fludrocortisone does not provide sufficient benefit to be evident in a preliminary blinded trial of unselected patients with chronic fatigue syndrome.

Arch Intern Med. 1998;158:908-914
**PATIENTS AND METHODS**

**PROTOCOL**

Patients were recruited from a research program established in July 1988 at Hennepin County Medical Center, Minneapolis, Minn (the Minnesota Regional CFS Research Program), or from the Park Nicollet Clinic CFS Program, St Louis Park, Minn, established in 1989. The diagnosis of CFS had been determined in all of the patients in the registries of these 2 programs according to the criteria for the case definition of CFS. Questionnaires were mailed to the patients in these registries in January and February 1996 in which patients were asked about their potential interest in participating in a placebo-controlled, crossover study of fludrocortisone, and information was obtained regarding their eligibility. Exclusion criteria (which were not divulged in the questionnaire) were fatigue severity during the preceding 1 month of less than 5, scored on a 10-cm visual analogue scale from 0 (“not present”) to 10 (“couldn’t be worse”), or taking fludrocortisone or another medication that could confound interpretation of the results (ie, antihypertensives, antidepressants, anxiolytics, or corticosteroids).

Informed consent was obtained from subjects who enrolled in the treatment trial under an investigational protocol approved by the institutional review boards at Hennepin County Medical Center and Park Nicollet Clinic. Patients were randomly assigned initially to receive fludrocortisone or a placebo for 6 weeks, followed by a 6-week washout interval and then entry into the opposite arm of the study. Treatment phases lasted 6 weeks each. Allocation to the initial arm was random to minimize the effect of order in this study. The initial dose of fludrocortisone acetate was 0.1 mg, 1 tablet orally. If the patient reported no improvement in fatigue after the first 2 weeks of treatment, the dose of drug (or placebo) was doubled. Patients were instructed not to make any dietary changes, including their salt intake, during the study.

The primary outcomes were changes in symptom severity and functional status. To assess symptom severity, patients were asked at the beginning and end of each 6-week treatment arm of the trial to rate on a self-administered questionnaire the level of each symptom during the past 1 month on a visual analogue scale from 0 (“no problem”) to 10 (“couldn’t be worse”). The level of postexercise fatigue (distance before exhausted) was rated on a 5-point scale with the following answer options: 1, 1 block; 2, 1 to 3 blocks; 3, 3 to 6 blocks; 4, 1 to 3 miles; and 5, 3 miles or more. Functional status was assessed at the beginning and end of each 6-week treatment arm of the trial by means of the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36), a self-administered questionnaire that measures functional status and well-being during the past 1 month. Mood status was assessed within the same time frame with the Positive and Negative Affect Schedule, a short mood scale developed to evaluate positive affect and negative affect. Positive affect is the degree to which a person feels enthusiastic, alert, and active, while negative affect is a dimension of subjective distress and unpleasurable engagement. At the beginning and end of each arm of the study, a Hick paradigm reaction time test, which measures speed of cognitive processing, was administered by trained research personnel. Also, patients were asked to walk on a treadmill, set at a speed of 1 mph, for a maximum of 30 minutes. Patients were instructed that they could stop walking before 30 minutes if they felt too exhausted to continue. Time to exhaustion to carry out a placebo-controlled study of fludrocortisone in CFS. Because patients with neurally mediated hypotension are reported to develop high concentrations of circulating catecholamines, we also determined plasma nor-epinephrine (NE) levels at baseline in our patients. We hypothesized that patients with CFS would have elevated NE levels and that if clinical improvements were observed, they would correlate inversely with pretreatment NE levels.

**RESULTS**

**PARTICIPANT FLOW AND FOLLOW-UP**

Questionnaires were mailed to all 261 patients who were enrolled in the registries of the Minnesota Regional CFS Research Program (210 patients) or the Park Nicollet Clinic CFS Program (51 patients) (Figure). A total of 120 patients responded, 77 of whom were interested in participating. Of these, 47 patients were judged ineligible because they reported a fatigue severity score of less than 5 (11 patients), were taking fludrocortisone (5 patients) or another potentially confounding medication (26 patients), or were unable to participate for logistical reasons (5 patients). Of the remaining 30 eligible patients, 25 were selected for the treatment trial (20 patients from the Minnesota Regional CFS Research Program and 5 from the Park Nicollet Clinic CFS Program) on the basis of the order in which their responses to the mailed questionnaire were received. Of the 25 study participants, all were white and had an average ±SD age of 39.7 ± 10.9 years. Nineteen (76%) were female. They had been suffering from CFS for a mean of 7.0 ± 4.9 years, and the onset of illness was described as an acute infectious disease–like episode in 22 (88%) of patients. No significant differences were found when these patient characteristics were compared with those of the 190 CFS patients in the Minnesota Regional CFS Research Program registry who did not participate in the study.

Of the 25 participants, 5 withdrew from the study (Figure). Three patients who withdrew were receiving fludrocortisone and 1 was receiving placebo at the time of withdrawal. All 4 of these cases were in the initial arm of the study. The fifth patient dropped out during the washout period because of family problems. Reasons for withdrawal from the study in the other 4 patients were worsening symptoms (1 patient each reported markedly increased fatigue, headaches, or insomnia), and 1 patient withdrew from the study because she was scheduled for ovarian surgery. These 5 patients were excluded from evaluation of treatment efficacy.

For the 20 patients who completed both arms of the trial, in 8 cases the dose of fludrocortisone was doubled at the 2-week time point after initiation of therapy because of lack of improvement in fatigue, whereas the number of capsules was doubled in 11 cases when patients...
(minutes) was recorded by research personnel. Blood pressure and heart rate were also recorded at the termination of the exercise (treadmill) test. For patients who remained in the study, supine, standing, and postexercise blood pressure and heart rate were recorded at all subsequent visits.

At the initial (baseline) visit, supine (after resting for 15 minutes), standing (after assuming an upright posture for 5 minutes), and postexercise (at the termination of the treadmill test) blood pressure and heart rate were recorded and venous blood samples were obtained at these same times for determination of NE levels. Plasma was assayed for NE by means of high-performance liquid chromatography at the Heart Failure Research Center, Biochemistry Laboratory, University of Minnesota, Minneapolis (intra-assay and interassay coefficients of variation, 4.7% and 7.7%, respectively). To ascertain whether the patients with CFS had elevated plasma NE levels at baseline, which might point to chronic hypovolemia, data on NE levels from a healthy control group (mean ± SD age, 31 ± 13 years; 95% male; n=274) were provided by the University of Minnesota Heart Failure Research Center.

A sample size of 25 subjects was projected for this study on the basis of an estimate that we would be able to detect a 30% change in symptom severity or functional status, as determined by SF-36, assuming α=.05 and β=.80 and an attrition rate similar to that reported by Bou-Holaigah et al. A 30% study effect was considered to be clinically relevant. All data analyses were completed with SPSS 6.01 for Windows (SPSS Inc, Chicago, Ill; 1994). Descriptive statistics were completed to determine the characteristics of the study sample and to ensure that the data fit the assumptions of the statistical tests. For each of the treatment comparison analyses, change scores were calculated as the differences between baseline and follow-up values within a treatment arm. The t test for paired observations was used to compare the mean change score differences between fludrocortisone and placebo arms of the study.

**Assignment**

A simple random assignment table was derived by means of SPSS 6.01 for Windows. Randomization was completed in the Drug Evaluation Unit by an individual other than the project research assistant.

**Masking**

Fludrocortisone acetate (Florinef, Apothecon, Princeton, NJ) was prepared by placing a 0.1-mg tablet into an empty, size 1, light-blue, opaque gelatin capsule (Apothecary Products Inc, Burnsville, Minn) and filled with a sufficient quantity of lactose. Placebo was prepared by filling identical capsules with lactose. This provided treatments that were similar in appearance and taste. Patients were instructed not to open the capsules. To blind the investigators and the patients, pharmacists prepared the capsules. Allocation schedules were maintained by administrative staff in the Drug Evaluation Unit. The code was not broken until the termination of the study. The study was conducted by a double-blind design. Management of the allocation/randomization list and the fludrocortisone and similar-appearing placebo capsules were kept by research staff not involved with the patients. Clinical research staff and patients were blind to treatment conditions. Data analysts were given group assignment data necessary for comparisons but were unaware of which group was fludrocortisone and which was placebo.

were receiving the placebo. Of the participants who received increased doses, 5 did so on both arms of the study.

**Analysis**

The effects of treatment on symptoms are given in Table 1. At the initiation of treatment in both arms of the study, the severity of most of the symptoms associated with CFS was high (ie, >5 for fatigue, unrefreshing sleep, myalgias, impaired concentration, forgetfulness, confusion, and headaches). On average, the patients reported they could not walk more than 2 to 3 blocks before feeling exhausted. Lightheadedness, a symptom routinely associated with neurally mediated hypotension, was also scored on average as greater than 5 on a visual analogue scale. When the changes in severity of each of the symptoms listed in Table 1 were analyzed, no significant improvement was seen in either the fludrocortisone or the placebo arm of the study. Also, when the changes during fludrocortisone treatment were compared with those with placebo, no significant differences were observed. Fludrocortisone-treated patients did report a reduction in lightheadedness (Table 1), which is a common symptom in patients with neurally mediated hypotension, although this reduction was not statistically significant (P=.06). The effects of treatment on functional status are given in Table 2. No significant improvements were found in any of the functional domains assessed by the SF-36, either when the fludrocortisone and placebo arms of the study were analyzed independently or when the changes between the fludrocortisone and placebo arms were compared. Also, no statistically significant improvements were seen in mood state (assessed by the Positive and Negative Affect Scale), in the speed of cognitive processing (evaluated by the reaction time test), or in the amount of time the patients could walk on a treadmill at 1 mph for up to 30 minutes. At the beginning and the end of the fludrocortisone arm of the study, 12 patients each walked for the 30-minute limit, whereas 12 and 9 patients receiving placebo could achieve this time limit at the beginning and the end of treatment, respectively.

Blood pressure and heart rate readings and plasma NE levels were obtained on all 25 study participants at the initial (baseline) assessment (Table 3). Although increases in heart rate occurred, no significant changes were noted in systolic or diastolic blood pressure readings after patients assumed a standing position for 5 minutes or after they walked on the treadmill for a maximum of 30 minutes or until they stopped because of exhaustion (Table 3). Supine plasma NE levels increased from a mean (±SD) of 1632 ± 608 nmol/L to 2780 ± 953 nmol/L and 2933 ± 1050 nmol/L after standing and exercise, respectively. When the supine plasma NE levels of the 25 patients with CFS were compared with those of a healthy control group (1613 ± 632 nmol/L; n=274), no significant difference was found. The
response of plasma NE to standing was comparable with that generally reported during upright tilting, which has the same effect on baroreflex as does active standing.\textsuperscript{20} No data were found regarding the effects of an extremely low-level exercise protocol such as the one used here on plasma NE level. However, since other studies suggest a close correlation between exercise intensity and sympathetic nervous system activation,\textsuperscript{21} it is not likely that this protocol would be associated with significant increases in plasma NE level.

When the effects of treatment on blood pressure and heart rate (measured in the supine and standing positions and at the end of the treadmill test) were evaluated, no significant differences were observed in these measures when the changes on fludrocortisone and placebo arms were analyzed independently or when the changes in the fludrocortisone arm were compared with those in the placebo arm (Table 4). Also, the blood pressure readings at the termination of the exercise test were not different from those at rest or standing for subjects in the fludrocortisone and placebo arms of the study (Table 4).

Adverse events were reported by 8 (32\%) of the participants. The incidence of adverse events was similar in the fludrocortisone and the placebo arms of the study. Six adverse events were reported during the active arm of the study, and 5 such events were reported during the placebo arm. One participant reported 2 events (chest tightness and severe headache) and 1 patient reported 3 events (severe headache in the fludrocortisone arm; racing pulse and increased anxiety while taking placebo). The participant with chest pain was treated by the subject’s primary care provider as probable muscle tightness. All adverse events were resolved; only 2 subjects dropped from the study because of adverse events (1 for racing pulse and 1 for severe headache, both while in the placebo arm).

The study design called for patients to make no dietary changes while in the study, including their usual amounts of dietary salt. Using visual analogue scales to measure salt intake (0, never; 10, always), subjects reported no change in salt use during preparation of food while taking placebo (t=0.56, P=.58), while a slight increase was noted while using fludrocortisone (t=2.16, P=.04). For salt added to food at the table, there was a trend for less consumption at follow-up in the placebo group (t = 1.93, P = .07) and no observed effect in the fludrocortisone group (t = 0.73, P = .48).

### Table 1. Effect of Treatment on Symptom Severity\textsuperscript{*}

<table>
<thead>
<tr>
<th>Measurement†</th>
<th>Fludrocortisone Acetate</th>
<th>Placebo</th>
<th>P‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pretreatment</td>
<td>Posttreatment</td>
<td>Pretreatment</td>
</tr>
<tr>
<td>Chronic fatigue syndrome symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>7.4 ± 1.6</td>
<td>7.5 ± 1.2</td>
<td>7.1 ± 1.6</td>
</tr>
<tr>
<td>Unrefreshing sleep</td>
<td>8.2 ± 1.7</td>
<td>7.7 ± 2.0</td>
<td>7.1 ± 1.7</td>
</tr>
<tr>
<td>Muscle pains</td>
<td>6.1 ± 2.9</td>
<td>5.8 ± 3.1</td>
<td>5.9 ± 2.7</td>
</tr>
<tr>
<td>Inability to concentrate</td>
<td>6.1 ± 2.6</td>
<td>5.2 ± 2.5</td>
<td>6.1 ± 2.6</td>
</tr>
<tr>
<td>Headaches</td>
<td>6.0 ± 2.6</td>
<td>6.0 ± 2.6</td>
<td>6.2 ± 2.4</td>
</tr>
<tr>
<td>Forgetfulness</td>
<td>5.9 ± 2.6</td>
<td>4.7 ± 2.7</td>
<td>6.2 ± 2.3</td>
</tr>
<tr>
<td>Confusion</td>
<td>5.1 ± 2.7</td>
<td>4.3 ± 2.7</td>
<td>5.4 ± 3.0</td>
</tr>
<tr>
<td>Joint pains</td>
<td>5.1 ± 3.5</td>
<td>4.8 ± 3.8</td>
<td>4.3 ± 3.6</td>
</tr>
<tr>
<td>Painful lymph nodes</td>
<td>4.0 ± 3.5</td>
<td>3.5 ± 3.3</td>
<td>3.9 ± 3.6</td>
</tr>
<tr>
<td>Sore throat</td>
<td>3.2 ± 2.8</td>
<td>3.1 ± 2.1</td>
<td>3.0 ± 2.7</td>
</tr>
<tr>
<td>Distance before exhausted</td>
<td>2.5 ± 1.2</td>
<td>2.7 ± 1.0</td>
<td>2.5 ± 1.1</td>
</tr>
<tr>
<td>Other symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lightheadedness</td>
<td>5.3 ± 2.8</td>
<td>4.0 ± 2.3</td>
<td>5.1 ± 3.0</td>
</tr>
<tr>
<td>Depression</td>
<td>2.5 ± 2.2</td>
<td>2.2 ± 2.3</td>
<td>3.0 ± 2.2</td>
</tr>
</tbody>
</table>

\textsuperscript{*}Data are for the 20 patients who completed both the active (fludrocortisone) and placebo arms of the study.

\textsuperscript{†}All measures are from a 10-cm visual analog scale, except distance, with 0 being “no problem” and 10 being “the worst it could be.” Distance before exhausted was measured on a 5-point scale with the following answer options: 1, 1 block; 2, 1 to 3 blocks; 3, 3 to 8 blocks; 4, 1 to 3 miles; and 5, 3 miles or more. Values are mean ± SD.

\textsuperscript{‡}Comparisons are between the active vs the placebo arms of the study (ie, the changes between the initiation and the completion of the 6 weeks of treatment with fludrocortisone vs placebo).
The present double-blind, randomized, placebo-controlled trial of fludrocortisone was motivated by the highly promising results of the pilot study reported in 1995 by Bou-Holaigah et al. The 23 patients enrolled in their study had symptoms the authors postulated were attributable to neurally mediated hypotension. Consistent with this autonomic nervous system disorder, 22 (96%) of their patients had an abnormal response to an upright tilt-table test (ie, a significant fall in blood pressure). Four patients withdrew from their study, leaving 19 participants who were followed up for a mean duration of 24 weeks. All of these patients received fludrocortisone acetate (0.1-0.2 mg),22 the dosage used in the present study, and this was the only medication taken by the patients in the study. Because this single medication was the only intervention, the authors believed that the positive results could be explained by a placebo effect. However, the authors felt it was important to establish whether fludrocortisone administration was effective in a controlled trial. They therefore conducted the present study in a double-blind, randomized, placebo-controlled manner.

Comment

The present double-blind, randomized, placebo-controlled trial of fludrocortisone was motivated by the highly promising results of the pilot study reported in 1995 by Bou-Holaigah et al. The 23 patients enrolled in their study had symptoms the authors postulated were attributable to neurally mediated hypotension. Consistent with this autonomic nervous system disorder, 22 (96%) of their patients had an abnormal response to an upright tilt-table test (ie, a significant fall in blood pressure). Four patients withdrew from their study, leaving 19 participants who were followed up for a mean duration of 24 weeks. All of these patients received fludrocortisone acetate (0.1-0.2 mg),22 the dosage used in the present study, and this was the only medication taken by the patients in the study. Because this single medication was the only intervention, the authors believed that the positive results could be explained by a placebo effect. However, the authors felt it was important to establish whether fludrocortisone administration was effective in a controlled trial. They therefore conducted the present study in a double-blind, randomized, placebo-controlled manner.
Second, while our trial was placebo controlled, the number of participants may have been too small to detect a significant improvement, especially in a subset of patients that may have been overrepresented in the trial of Bou-Holaigah et al. Even though the clinical characteristics (age, sex, duration of illness, and degree of functional impairment) of the patients in the 2 studies appear to be similar, Bou-Holaigah et al were studying the potential association between CFS and neurally mediated hypotension, and their methods for patient recruitment may have selected for those with features of this disorder.

The hallmarks of neurally mediated hypotension are parasympathetic overactivity coupled with sympathetic withdrawal, leading to syncope or near-syncpne. The stimuli that provoke these pathological responses are various and may include inadequate central blood volume, abnormal reflex responses to decreased central blood volume, and emotional distress. Upright tilt-table testing has been used to diagnose neurally mediated hypotension in patients without other causes for syncope, but it is important to note that many normal subjects faint during this test, particularly if aggressive stimulation protocols with isoproterenol are used. Abnormal tilt-testing responses were found in 22 of the 23 patients who entered the study of Bou-Holaigah et al,14 and in a later report by these investigators,23 95 of 100 consecutive patients with a diagnosis of CFS were found to have abnormal responses to upright tilt testing.

If abnormal tilt-test responses are found in almost all patients with CFS,23 and a pathophysiological connection exists between neurally mediated hypotension and CFS, then tilt-table testing would not distinguish likely responders to therapy directed at neurally mediated hypotension (eg, volume expansion). For this reason, we did not use tilt-table tests. However, we did look for evidence of neurally mediated hypotension—like abnormalities, specifically, elevated resting plasma NE levels, which might point to chronic hypovolemia, or increased NE responses to standing and exercise, which again might point to mild hypovolemia or abnormal reflex responses to postural changes or with exercise. We found no evidence of abnormality in either baseline plasma NE levels or the responses of NE to standing or walking. These patients therefore did not show evidence of a major abnormality in 1 aspect of the proposed afferent limb purported to contribute to neurally mediated hypotension or in the integrated reflex responses to posture change or activity. We wonder, therefore, whether the nearly universal abnormalities in tilt testing found in patients with CFS by Bou-Holaigah et al14 are a reflection of deconditioning secondary to decreased activity, which might arise from long-standing CFS, rather than reflecting an entirely separate pathophysiological entity (ie, neurally mediated hypotension). The lack of response to the same volume-expanding agent used by Bou-Holaigah et al14 supports this possibility.

It is also possible that in contrast to the evidence of Bou-Holaigah et al,23 only a small subset of patients with CFS have neurally mediated hypotension, as would be suggested by the recent report of Freeman and Komaroff,24 who found that only 25% of patients with CFS selected on the basis of having symptoms referable to the autonomic nervous system had positive tilt-table tests. Thus, fludrocortisone therapy could prove beneficial in this subset of patients, and a randomized trial of fludrocortisone in patients with CFS with and without abnormal results of tilt tests should be considered to test this hypothesis.

A third factor that complicates the comparison of the outcomes of our patients and those of Bou-Holaigah et al14 is that different methods were used to evaluate the effects of treatment on symptoms and function. Bou-Holaigah et al assessed changes in symptoms after initiating therapy by means of scoring systems that rated (1) general sense of well-being; (2) fatigue, lightheadedness, and cognitive difficulties (worse, better, about the same); (3) the degree of cognitive dysfunction (by the Wood Mental Fatigue Inventory)25; and (4) an Activity Restriction Index, which they designed for their study. In the present study, a self-administered questionnaire was used that asked patients to rate on a visual analogue scale the severity of each CFS

Table 4. Effects of Treatment on Blood Pressure and Heart Rate*

<table>
<thead>
<tr>
<th></th>
<th>Fludrocortisone Acetate</th>
<th></th>
<th>Placebo</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pretreatment</td>
<td>Posttreatment</td>
<td>Pretreatment</td>
<td>Posttreatment</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Systolic blood pressure, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine</td>
<td>116.2 ± 11.8</td>
<td>120.0 ± 10.4</td>
<td>115.1 ± 11.4</td>
<td>115.3 ± 12.3</td>
</tr>
<tr>
<td>Standing</td>
<td>113.7 ± 13.1</td>
<td>119.0 ± 12.6</td>
<td>110.4 ± 11.5</td>
<td>113.6 ± 14.8</td>
</tr>
<tr>
<td>Postexercise</td>
<td>116.7 ± 15.7</td>
<td>124.0 ± 14.1</td>
<td>114.9 ± 14.3</td>
<td>115.6 ± 17.7</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine</td>
<td>81.6 ± 7.7</td>
<td>81.9 ± 8.0</td>
<td>79.7 ± 7.7</td>
<td>77.2 ± 8.5</td>
</tr>
<tr>
<td>Standing</td>
<td>83.5 ± 9.5</td>
<td>84.7 ± 9.8</td>
<td>80.3 ± 6.7</td>
<td>82.9 ± 10.1</td>
</tr>
<tr>
<td>Postexercise</td>
<td>81.2 ± 9.0</td>
<td>86.4 ± 9.5</td>
<td>81.5 ± 9.7</td>
<td>81.4 ± 9.7</td>
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<tr>
<td>Heart rate, beats/min</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Supine</td>
<td>72.3 ± 11.2</td>
<td>73.6 ± 10.0</td>
<td>69.9 ± 7.4</td>
<td>72.5 ± 8.7</td>
</tr>
<tr>
<td>Standing</td>
<td>81.6 ± 10.6</td>
<td>82.0 ± 9.7</td>
<td>81.3 ± 11.0</td>
<td>84.7 ± 11.5</td>
</tr>
<tr>
<td>Postexercise</td>
<td>90.5 ± 11.8</td>
<td>93.0 ± 14.8</td>
<td>96.2 ± 13.0</td>
<td>94.3 ± 10.7</td>
</tr>
</tbody>
</table>

* Data are for the 20 patients who completed both the active (fludrocortisone) and placebo arms of the study. Supine readings were recorded after resting for 15 minutes, standing readings were recorded after assuming an erect posture for 5 minutes, and postexercise readings were recorded at the end of the treadmill test (walking at 1 mph until feeling exhausted or for 30 minutes maximum). Values are mean ± SD.

† Comparisons are between the active vs the placebo arms of the study (ie, the changes between initiation and the completion of the 6 weeks of treatment with fludrocortisone vs placebo).
symptom. No significant improvements were observed in the severity of any of these symptoms. To assess function, the SF-36 was used to quantify functional activities (physical, social, and role functions), as well as emotional and general well-being, pain, and energy or fatigue. Like the patients of Komaroff et al. and Buchwald et al., our patients had marked functional impairments. Previous research has indicated that patients with CFS have normally low levels of positive affect but relatively normal levels of negative affect. Subjects were also given a Hick paradigm reaction time test, a measure of speed of cognitive processing that has been found to be slowed in CFS. The scores on the SF-36, Positive and Negative Affect Schedule, and reaction time test were virtually identical before and after treatment. Finally, the time that patients could walk on a treadmill, at a speed of 1 mph for a maximum of 30 minutes, was measured. Although the patients walked for a longer time at the end of fludrocortisone treatment, ie, 22.8 ± 9.2 minutes vs 19.3 ± 11.2 minutes before treatment, this increase was not statistically significant. Nevertheless, this 2.5-minute difference could represent a clinically significant effect. This seems unlikely, however, given the large variability in the observed treadmill exercise times.

While the results of our study cannot be considered definitive regarding the therapeutic role of fludrocortisone in CFS, the lack of benefit should serve as a cautionary note regarding the routine use of fludrocortisone in the treatment of CFS and should by inference raise a question about the hypothetical linkage to neurally mediated hypotension. The important questions left unanswered by any study thus far are the following: (1) What fraction of unselected patients with CFS, seeking attention in primary care practices (rather than in referral centers), have neurally mediated hypotension? (2) How often are symptoms suggesting neurally mediated hypotension correlated with autonomic nervous system evidence of neurally mediated hypotension? (3) Do the treatments for neurally mediated hypotension, in patients with CFS and neurally mediated hypotension, improve any of the symptoms of CFS and, if so, which symptoms?

CONCLUSIONS

The need for randomized, placebo-controlled trials of fludrocortisone and other therapies directed at treating posturally mediated hypotension in patients with CFS was clearly recognized by Bou-Holaigah et al. The results of the present study showing no improvement with fludrocortisone underscore the need for further placebo-controlled trials involving larger numbers of patients. Nonetheless, larger doses of fludrocortisone or the addition of other drugs or salt to the treatment regimen could prove harmful. Thus, until the results of larger randomized, placebo-controlled trials are published, we recommend that this form of therapy not be prescribed for CFS. Also, until the contribution of neurally mediated hypotension to the pathophysiology of CFS is established, upright tilt-table testing should not be used routinely in the examination of patients with this idiosyncratic illness.

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