# Fludrocortisone Acetate to Treat Neurally Mediated Hypotension in Chronic Fatigue Syndrome

## A Randomized Controlled Trial

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**Context** Patients with chronic fatigue syndrome (CFS) are more likely than healthy persons to develop neurally mediated hypotension (NMH) in response to prolonged orthostatic stress.

**Objective** To examine the efficacy of fludrocortisone acetate as monotherapy for adults with both CFS and NMH.

**Design** Randomized, double-blind, placebo-controlled trial conducted between March 1996 and February 1999.

**Setting** Two tertiary referral centers in the United States.

**Patients** One hundred individuals aged 18 to 50 years who satisfied Centers for Disease Control and Prevention criteria for CFS and had NMH provoked during a 2-stage tilt-table test. Eighty-three subjects had adequate outcome data to assess efficacy.

**Intervention** Subjects were randomly assigned to receive fludrocortisone acetate, titrated to 0.1 mg/d (n=50) or matching placebo (n=50) for 9 weeks, followed by 2 weeks of observation after discontinuation of therapy.

**Main Outcome Measure** Proportion of subjects in each group with at least a 15-point improvement on a 100-point global wellness scale.

**Results** Baseline demographic and illness characteristics between the groups were similar; CFS had been present for at least 3 years in 71%. Using an intention-to-treat analysis, 7 subjects (14%) treated with fludrocortisone experienced at least a 15-point improvement in their wellness scores compared with 5 (10%) among placebo recipients ($P=.76$). No differences were observed in several other symptom scores or in the proportion with normal follow-up tilt test results at the end of the treatment period.

**Conclusions** In our study of adults with CFS, fludrocortisone as monotherapy for NMH was no more efficacious than placebo for amelioration of symptoms. Failure to identify symptomatic improvement with fludrocortisone does not disprove the hypothesis that NMH could be contributing to some of the symptoms of CFS. Further studies are needed to determine whether other medications or combination therapy are more effective in treating orthostatic intolerance in patients with CFS.

*JAMA. 2001;285:52-59* www.jama.com

CHRONIC FATIGUE SYNDROME (CFS) is a relatively common condition of unclear origin.[1,2] Its clinical features closely resemble disorders referred to in past decades as neurasthenia, neuromyasthenia, effort syndrome, or myalgic encephalopathy. As currently defined, CFS is estimated to affect as many as 400 per 100 000 adults.[3] It also occurs in children, but valid data on age-specific prevalence in childhood are not available. The natural history of CFS has not been fully elucidated, but the potential for prolonged illness, associated with substantial impairment of function, has been emphasized in recent studies.[4,5] Various medications are used in practice for treatment of headaches, insomnia, myalgias, or other symptoms of CFS, but no consistently effective, readily available, safe, and affordable pharmacologic therapy has been identified for the disorder as a whole.

Chronic fatigue has long been recognized as a symptom of autonomic nervous system dysfunction.[6,7] Recent work has emphasized an association between CFS and neurally mediated hy-

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potension (NMH), a disorder in the regulation of blood pressure under orthostatic stress, also known as vasovagal hypotension, delayed orthostatic hypotension, neurocardiogenic syncope, or vasodepressor syncope.[8-14] Related forms of chronic orthostatic intolerance have also been described in adolescents and adults with prolonged fatigue or CFS.[15-18]

Preliminary reports of improvement in CFS symptoms when the hypotension is treated led us to hypothesize that the orthostatic intolerance is a potentially reversible cause of CFS symptoms.[8,9] In this article we report the results of a large randomized, placebo-controlled trial conducted at 2 centers, undertaken to assess whether treatment with fludrocortisone acetate would lead to improvement in general well-being and in orthostatic tolerance among those with CFS and documented NMH.

## METHODS

### Selection of Subjects

Subjects were eligible for inclusion in the trial if they were aged 18 to 50 years and satisfied the 1994 Centers for Disease Control and Prevention (CDC) criteria for the diagnosis of CFS[1] and had NMH diagnosed during a 2-stage tilt-table test, as described below. The CDC criteria for CFS require a careful clinical evaluation to exclude other plausible causes of fatigue and to specify that otherwise unexplained fatigue must be present for at least 6 months and must be associated with 4 or more of the following symptoms: impaired memory or concentration, sore throat, tender cervical or axillary lymph nodes, muscle pain, multijoint pain, new headaches, unrefreshing sleep, and postexertional malaise.[1]

Individuals were screened for eligibility and managed during the course of the study by each of the 2 study sites, the Laboratory for Clinical Investigation at the National Institute of Allergy and Infectious Disease and the Johns Hopkins Hospital. Individuals with CFS were recruited from the registry of subjects who had participated in other CFS studies at the National Institutes of Health and through notices about the study appearing in patient advocacy publications, local newspapers, and Internet postings. To ensure that they satisfied criteria for CFS, study applicants completed a detailed screening form about their medical history. The regular physicians of individuals who met eligibility requirements for the study were asked to confirm that there were no other plausible causes of fatigue on physical examination or on blood testing performed within the preceding 6 months, as well as to affirm that the person was likely to be able to tolerate the study procedures. Those who passed this level of screening were scheduled for tilt-table testing. In the 2 weeks before testing, subjects completed a Beck Depression Inventory on 2 occasions.

All subjects had to have at least moderate severity of illness as determined by a score of 65 or less on a unidimensional global wellness scale at the time of submission of the screening application.[19] This global wellness scale asks individuals to rate how they feel on a scale of 0 to 100, with 0 representing dying, and 100 representing feeling as good as one could imagine. All participants were able to walk without assistance.

Subjects were excluded if they had a history of conditions that could be exacerbated by fludrocortisone or by tilt-table testing, including hypertension, ischemic heart disease, structural heart disease (except mitral valve prolapse), documented significant dysrhythmia, known intolerance of fludrocortisone, serum creatinine levels higher than 106 µmol/L, diabetes, peripheral neuropathy, hepatic disease, or glaucoma. Individuals were also excluded if they had ever taken fludrocortisone acetate at a dosage of at least 0.1 mg/d for 2 or more weeks, or if in the 2 weeks before entry they had taken the following drugs known or suspected to interfere with the results of tilt-table testing: tricyclic antidepressants in doses higher than the equivalent of 25 mg/d of amitriptyline hydrochloride, trazodone hydrochloride, serotonin reuptake inhibitors, acetazolamide sodium or other diuretics, oral mineralocorticoids or glucocorticoids, other drugs used in the treatment of NMH (eg, β-receptor antagonists, disopyramide phosphate, calcium channel antagonists, methylphenidate hydrochloride, dextroamphetamine, midodrine hydrochloride, theophylline, ephedrine), systemic antifungal azoles, sumatriptan succinate, or drugs with uncertain effects on blood pressure used by some physicians in patients with CFS, such as Kutapressin (a liver extract), coenzyme Q10, niacin, and cyanocobalamin injections. Individuals were excluded if they were enrolled concurrently in another CFS therapy study, if they had depression or other psychiatric diagnoses requiring therapy, or if they actively abused illicit drugs or alcohol. The study protocol was approved by the institutional review boards of the 2 participating centers. All subjects gave written informed consent.

### Study Design

Eligible subjects with NMH were stratified by study center and by disease duration ($<3$ vs $\geq 3$ years), then randomly assigned to receive fludrocortisone or placebo. The study pharmacy generated the randomization sequence from a table of random numbers. Treatment began approximately 2 weeks after the screening tilt-table test. Each gelatin capsule of fludrocortisone acetate contained 0.025 mg of the study medication and a methylcellulose filler. The starting dosage was 1 capsule of 0.025 mg/d for a week, then increased to 2 capsules of 0.05 mg/d for a week, and finally increased to 4 capsules of 0.025 mg/d for the remaining 7 weeks of treatment, a dosage associated with good clinical effect in our open treatment experience (P.C.R. and H.C., unpublished data, 1995). The placebo capsules contained methylcellulose only; the number of capsules per day was increased in an identical sequence. Subjects were advised to drink at least 2 L of fluid per day but were asked not to change their usual sodium chloride intake during the study. Because fludrocortisone increases urinary potassium

excretion, both groups also received tablets of potassium chloride, 10 mEq/d, from the onset of treatment. If adverse effects emerged, subjects were instructed by study nurses to reduce the dosage to the most recently tolerated amount. In the ninth week, while still taking the study medication, subjects underwent repeat tilt-table testing. Subjects were followed up for 2 weeks after discontinuation of study drug, following completion of the 9-week treatment period.

### Measures of Outcome

The following self-rating instruments were used to assess subjects' physical and emotional symptoms and level of function: the wellness score, a valid and reliable single-item scale used in other studies of CFS, which has been shown to correlate well with other widely used self-rating instruments,[9] and to be sensitive to clinical improvement in CFS patients[9,19,20]; the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36), which examines physical functioning, role limitations because of physical health, bodily pain, social functioning, general mental health, role limitations because of emotional problems, vitality, and general health perceptions[21]; the Beck Depression Inventory, a self-administered scale of depression[22]; the Wood Mental Fatigue Inventory, a disease-specific questionnaire, which asks subjects to rate 9 mental fatigue symptoms, in which higher scores indicate worse cognitive difficulty[23]; the Profile of Mood States questionnaire, a standardized instrument for the quantitative measurement of anger, anxiety, confusion, depression, fatigue, and vigor[24]; and the Duke Activity Status Index.[25] Subjects completed the wellness score each day from 2 weeks before the tilt test until the end of the study, and they completed the other measures at 2 weeks and 1 week before the initial tilt-table test, then at weeks 1, 4, 8, and 11 of the study. Adverse effects from the study drug were rated by the subjects at weeks 1 through 4, 6, and 8. Subjects were contacted by the study nurses at weeks 2, 4, and 6 to review each subject's progress through the trial.

### Blinding and Compliance

Subjects were not informed of the study drug assignment until after the final trial data had been analyzed. Clinical investigators remained unaware of the treatment group assignment during the analysis phase until after the grouped study results had been examined, at which point the treatment code was revealed. Personnel supervising the follow-up tilt-table tests were unaware of the treatment group assignments and of the reported wellness scores. The latter were mailed directly to the data center by the subjects, who were asked during week 7 of treatment to state which study drug they thought they were receiving. Subjects were judged to be compliant with study medication if they recorded taking at least 50% of the recommended study dose every week from week 3 onward.

### Sample Size Determination

The primary study outcome measure was the proportion of subjects with a 15-point improvement in mean daily wellness scores. The pretreatment period wellness score—the mean score in the 7 days before the tilt test—was compared with the mean daily score from the start of week 5 of treatment until 3 days before the second tilt test. The latter period was thought most likely to represent the period of maximal therapeutic effect. Any subject with at least 7 days of wellness data after the start of week 5 was considered to have provided adequate data for assessing the outcome of the intervention.

From data generated using the wellness score during a trial of low-dose hydrocortisone for CFS,[20] we estimated that no more than 10% of placebo recipients would experience a 15-point improvement in the wellness score over the period of the trial, and that a 15-point improvement was clinically meaningful to subjects with CFS. From pilot data using fludrocortisone in those with CFS and NMH, we estimated a 35% improvement in the treatment arm. Assuming a drop-out rate of 14% and a power of 0.8, with an $\alpha$ level of .05 for a 2-sided test, we estimated a need for 50 subjects per group.

### Statistical Analysis

Independent samples *t* tests or Mann-Whitney *U* tests were used to compare continuous data between groups, and $\chi^2$ or Fisher exact tests were used to compare categorical data. An O'Brien-Fleming group sequential procedure with 1 interim examination of the data was used to evaluate treatment efficacy, with the overall significance established at .05. For all other comparisons, a *P* value of .01 was established to protect against type I errors due to multiple comparisons. All data entry and analysis were conducted at the EMMES Corp, a statistical analysis and data management company based in Potomac, Md. At 2 points during the trial, the safety of study procedures was reviewed by a data safety and monitoring board. At these intervals, the treatment groups were identified only by a coded variable. At the second interval, after outcome data were available from 65 subjects, the board and study statisticians examined efficacy, but study investigators remained blinded.

### Tilt Testing Protocol

All tilt-table tests were performed at the Johns Hopkins Hospital. Subjects were transported from the hospital entrance to the tilt laboratory by wheelchair to reduce differences between subjects in physical exertion immediately before the test. A peripheral intravenous catheter was inserted after local infiltration of the venipuncture site with buffered lidocaine, and fluids were administered at 10 mL/h to allow isoproterenol hydrochloride infusion in stage 2 if needed. The tilt-table test was performed in the morning after a minimum of 4 hours of fasting, in a room with a controlled temperature of 22°C.

Each subject was positioned supine on the tilt table, loosely restrained by safety straps, with a footboard for weight bearing, and remained supine for 15 minutes before the tilt test be-

gan. During the test, visual stimulation and other conversation were kept to a minimum, and subjects were asked to remain motionless. Blood pressure was measured using an automated blood pressure cuff with the arm resting at the subject's side. Heart rate was monitored continuously.

Stage 1 of the test involved upright tilt to 70° for up to 45 minutes. Blood pressure, heart rate, heart rhythm, and symptoms were recorded every 5 minutes while supine, 1 minute after upright tilt, and every 5 minutes thereafter. When symptoms became severe, when heart rate dropped, or when heart rhythm changed, blood pressure was recorded each minute. If stage 1 of the test was tolerated and hypotension was not provoked, the subject was returned to the supine position and received by infusion 2 µg/min of isoproterenol hydrochloride for 10 minutes. The table was then brought to the upright 70° position for a maximum of 15 minutes more (stage 2). The test was terminated at the request of the subject, if the heart rate exceeded 180/min for 2 minutes despite reduction in the rate of isoproterenol infusion to 1 µg/min, or if hypotension or syncope occurred. After the tilt test, all subjects received at least 1 L of normal saline solution intravenously for 30 to 60 minutes.

The baseline heart rate and blood pressure values for the tilt test were the mean of the 10- and 15-minute supine readings. *Neurally mediated hypotension* was defined as a 25-mm Hg reduction in systolic blood pressure from the baseline supine values, sustained for at least 1 minute, with no associated increase in heart rate, and accompanied by symptoms of presyncope. *Presyncope* was defined by the presence of premonitory symptoms and signs of imminent syncope such as severe weakness, lightheadedness, nausea, or diaphoresis.[26] It was not necessary for syncope to occur for the test to be considered abnormal. For analytic purposes, when no blood pressure reading could be obtained at the time of syncope, the blood pressure was recorded as 40/0 mm Hg. *Postural tachycardia syndrome* was defined as the occurrence of orthostatic symptoms in association with either a 30/min increase in heart rate from baseline within 10 minutes of being tilted upright, sustained for 1 minute or more or a heart rate of higher than 120/min in the same period.[27,28] The tilt test was not stopped if the subject developed postural tachycardia syndrome; as a result, subjects could be classified as having NMH, postural tachycardia syndrome, or both.

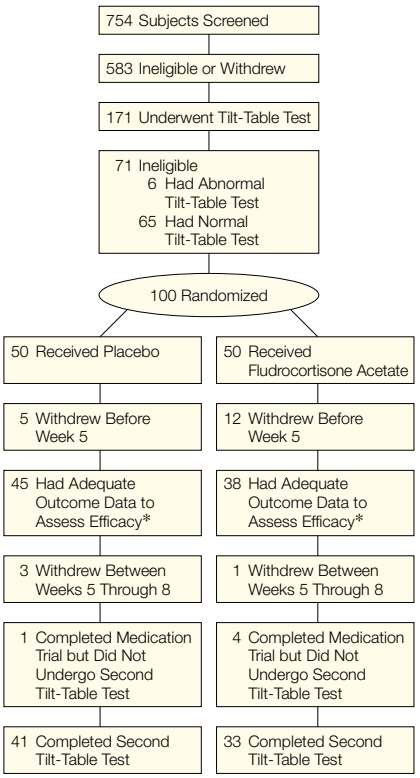
## RESULTS

### Subject Enrollment

As illustrated in FIGURE 1, of the 754 applications received, 583 did not undergo tilt-table testing for the following reasons: 86 were accepted for the study but either were not interested in enrolling or were unavailable, 32 were outside the age criteria for the study, 52 did not meet criteria for CFS, 68 had wellness scores higher than 65, 58 had medical and 38 had psychiatric illnesses that excluded them from participation, 162 were excluded on the basis of their past or current medications (selective serotonin-reuptake inhibitors in 90, fludrocortisone for at least 2 weeks in 26, β-adrenergic antagonists in 9, and other excluded medications in 37); for 65 subjects the screening forms were incomplete, and 22 were ineligible due to other causes.

Of those who passed the preliminary screening, 171 underwent tilt-table testing between March 1996 and February 1999. One hundred six (62%) had NMH provoked during tilt testing, 39 of whom (37%) also met criteria for postural tachycardia syndrome. An additional 7 subjects (4%) met criteria for postural tachycardia syndrome in the absence of hypotension. Six subjects with NMH were judged ineligible at the time of tilt testing, 1 because the mean wellness score in the 2 weeks immediately before tilt testing was 90, 2 because of psychiatric exclusions that became evident at the time of testing, 2 because they had started new medications between the time of screening application and tilt testing, and 1 because of the development of an unrelated medical illness. This left 100 subjects for enrollment. Sixty-seven of the enrolled subjects had developed NMH in stage 1 of the tilt test.

**Figure 1.** Subject Flow Through the Trial




*Those with wellness scores for at least 7 days of the final 4 weeks of the treatment period were considered as having adequate outcome data.

Overall, 21 subjects withdrew from the study prematurely (8 placebo, 13 fludrocortisone). However, wellness scores for 4 of these subjects (3 placebo, 1 fludrocortisone) were available for at least 7 days of the final 4 weeks of the treatment period. This left 83 subjects with adequate wellness scores for evaluation of efficacy (45 placebo, 38 fludrocortisone). One subject in each group withdrew early due to the development of hypertension, and 1 in each group withdrew early due to unwillingness to comply further with study procedures. One patient in the placebo group developed panic symptoms and tachycardia, 1 had increased fatigue, 1 stopped taking the study medication after the first dose because of severe light-

headedness, fatigue, and diaphoresis, and 3 further placebo recipients withdrew early because they were unimproved. In the fludrocortisone group, 4 additional subjects developed depression that had resolved within days of discontinuing the medication, 1 had worse headaches, and 2 developed new abdominal discomfort. Of the 4 remaining subjects who withdrew from the fludrocortisone group, 1 had an unrelated medical illness that warranted withdrawal, 1 was randomized but later found to have a major depression and did not receive medication, and 2 had worsening symptoms.

Demographic and clinical variables were similar between groups at entry (TABLE 1 and TABLE 2), except for a higher score on the physical function subscale of the SF-36 for those in the fludrocortisone arm. There were no clinically important differences in baseline characteristics between the 32 subjects enrolled at the National Institutes of Health and the 68 enrolled at the Johns Hopkins site.

**Table 1.** Baseline Demographic Characteristics of Randomized Participants by Treatment*

| Characteristic | Placebo (n = 50) | Fludrocortisone Acetate (n = 50) | *P* Value |
|---|---|---|---|
| Age, mean (SD), y | 37.3 (9.3) | 36.2 (7.4) | .50 |
| Age ≥30 y | 82 | 76 | .62 |
| Weight, mean (SD), kg | 69.5 (16.4) | 68.4 (10.7) | .72 |
| White | 96 | 100 | .50 |
| Women | 66 | 66 | >.99 |
| Currently working | 53 | 56 | .84 |
| On disability | 8 | 20 | .08 |
| Duration of CFS, mean (SD), y | 6.0 (4.9) | 6.9 (6.4) | .40 |
| Duration of CFS ≥3 y | 72 | 70 | .83 |

*CFS indicates chronic fatigue syndrome. Data are presented as percentages unless otherwise indicated.

## Primary Outcomes

Using an intention-to-treat analysis, there was no significant difference in the proportion of subjects with at least a 15-point improvement in wellness scores over the course of the study (Table 2); this degree of improvement was evident in only 14% of subjects in the fludrocortisone group compared with 10% of those in the placebo group. The

**Table 2.** Outcome Measures at Baseline and on Treatment*

| | Placebo (n = 50) | | Fludrocortisone Acetate (n = 50) | | *P* Value | |
|---|---|---|---|---|---|---|
| Outcome | Baseline | Receiving Treatment | Baseline | Receiving Treatment | Baseline | Receiving Treatment |
| **Primary Outcomes** | | | | | | |
| Wellness score | 40.7 (16.3) | 43.1 (17.6)† | 46.8 (16.0) | 50.4 (18.2)‡ | .06 | .07 |
| Score improvement, No. (%) | | | | | | |
| 5 Points | . . . | 17 (34) | . . . | 14 (28) | . . . | .52 |
| 10 Points | . . . | 6 (12) | . . . | 9 (18) | . . . | .58 |
| 15 Points | . . . | 5 (10) | . . . | 7 (14) | . . . | .76 |
| 20 Points | . . . | 3 (6) | . . . | 5 (10) | . . . | .72 |
| **Secondary Outcomes** | | | | | | |
| Wood Mental Fatigue Inventory | 18.3 (8.2) | 13.3 (9.6) | 16.3 (9.7) | 14.1 (10.9) | .28 | .73 |
| Beck Depression Inventory | 15.0 (5.5) | 10.8 (6.8) | 14.7 (8.2) | 10.4 (7.2) | .82 | .82 |
| POMS vigor subscale | 6.7 (4.3) | 8.6 (6.7) | 7.9 (4.7) | 8.8 (6.1) | .20 | .91 |
| POMS fatigue subscale | 21.3 (4.6) | 16.4 (7.9) | 19.6 (5.1) | 16.2 (7.3) | .08 | .93 |
| SF-36 physical function | 45.1 (22.7) | 51.4 (27.8) | 54.8 (22.5) | 58.9 (21.9) | .04 | .18 |
| SF-36 mental health | 66.3 (16.3) | 69.8 (16.3) | 63.7 (18.1) | 68.6 (19.1) | .45 | .75 |
| Duke Activity Status Index | 5.0 (6.2) | 6.7 (7.3) | 7.8 (9.3) | 9.2 (10.6) | .09 | .23 |
| **Tilt-Table Test Outcomes** | | | | | | |
| Heart rate, beats/min | 69.8 (9.8) | 69.3 (9.2) | 70.7 (8.4) | 69.0 (8.8) | .64 | .90 |
| Systolic blood pressure, mm Hg | 117.7 (13.1) | 113.7 (10.0) | 115.8 (11.9) | 117.5 (9.6) | .46 | .11 |
| Diastolic blood pressure, mm Hg | 75.0 (7.2) | 73.4 (7.4) | 72.4 (6.7) | 73.3 (6.6) | .06 | .93 |
| NMH in stage 1, No. | 33 | 17 | 34 | 20 | .83 | .16 |
| NMH in stage 2, No. | 17 | 14 | 16 | 6 | . . . | . . . |
| Normal in both stages, No. | . . . | 9 | . . . | 4 | . . . | . . . |
| Refused stage 2, No. | . . . | 1 | . . . | 3 | . . . | . . . |
| No follow-up tilt, No. | . . . | 1 | . . . | 5 | . . . | . . . |

*POMS indicates Profile of Mood States; SF-36, Medical Outcomes Study 36-Item Short Form Health Survey; NMH, neurally mediated hypotension; and ellipses, not applicable. Data are presented as mean (SD) unless otherwise indicated. *P* values are for comparisons between the placebo and treatment groups at baseline and then during treatment.
†Number of participants is 45.
‡Number of participants is 38.

distribution of wellness scores at baseline approached statistical significance (mean [SD], 46.8 [16.0] in the fludrocortisone group vs 40.7 [16.3] in the placebo group, $P=.06$). However, the mean (SD) change in wellness scores from the pretreatment to the treatment periods was not significant: 3.8 (11.5) for the fludrocortisone group vs 2.7 (10.0) for the placebo group ($P=.71$).

As shown in FIGURE 2, changes in wellness scores between pretreatment and treatment periods varied considerably for the entire study population, and the changes were not related either to treatment assignment or to the pretreatment wellness score. There was no difference between rates of 15-point improvement in the wellness scores in those whose CFS had been present less than 3 years (4/15 improved in the fludrocortisone group vs 0/14 in the placebo group) or who were younger than 30 years (3/12 improved in the fludrocortisone group vs 0/9 in the placebo group), but the study had inadequate statistical power to detect true differences between these subgroups. Among those who tolerated and were compliant with the study medications, 7 (21.2%) of 33 subjects in the fludrocortisone group experienced at least a 15-point improvement in the wellness score compared with 5 (11.6%) of 43 in the placebo group ($P=.41$). Similarly, no differences were noted among those who received the full dose of the study medication (4 capsules per day) for the duration of the trial.

### Secondary Outcomes

No differences were noted between groups in any of the other self-rating instrument scores during the treatment period. The baseline wellness score correlated well ($r>0.3$) with the Profile of Mood States vigor subscale, the SF-36 physical function subscale, the Wood Mental Fatigue Inventory, and the Profile of Mood States fatigue subscale at baseline, moderately well with the Duke Activity Status Index ($r=0.25$) and the Beck Depression Inventory ($r=-0.28$), but not at all with the mental health component of the SF-36 ($r=-0.01$). No differences in supine blood pressure were noted between groups at baseline or at the time of repeat tilt-table testing in the ninth week of treatment. For those who had an abnormal stage 1 tilt-table test result, the mean (SD) change in wellness score from baseline was 5.8 (13.4) in the fludrocortisone group vs 5.9 (9.5) in the placebo group.

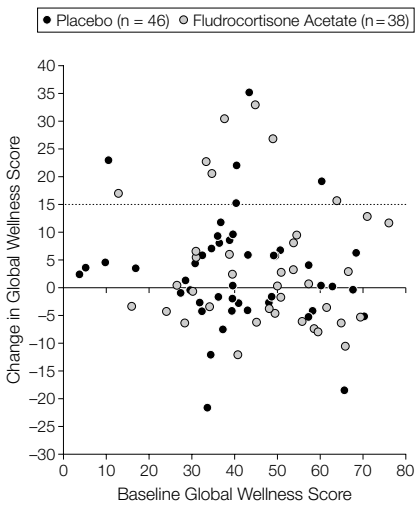
In the 2 weeks following discontinuation of the study drug after week 9 of treatment, the mean (SD) wellness score in the fludrocortisone group decreased by 5.1 (6.5) compared with a reduction of only 1.0 (5.6) in the placebo group ($P=.005$). The degree of change in the 2 weeks off treatment was similar between groups for those who had experienced at least a 15-point improvement in the wellness score over the course of the study: 10.9 (8.1) vs 10.7 (8.0), respectively.

### Adverse Events

No serious adverse events occurred during tilt-table testing. During the treatment phase, no subject had an important adverse effect that lasted long after discontinuation of the study medication. Specifically, no subject had a change in systolic blood pressure of more than 40 mm Hg on treatment, although 1 subject in the placebo group developed moderate hypertension (162/94 mm Hg). Only 1 subject in the placebo group gained more than 5 kg during the study. Overall, mean (SD) weight increased 1.2 (1.6) kg in the placebo group compared with 1.1 (1.6) kg in the fludrocortisone group. No subject developed depression requiring antidepressant medication during the treatment period. At least 1 adverse effect was reported during the study by 71% of placebo and 61% of fludrocortisone recipients (data not shown).

The study groups did not differ with regard to serum potassium levels between baseline and the time of the second tilt test, but the mean (SD) serum sodium concentration was higher during treatment in those receiving fludrocortisone (141.9 [2.0] vs 140.3 [2.3] mEq/L; $P=.003$). The study nurses reduced the study drug dosage below 0.1 mg/d for 12 placebo subjects and 10 fludrocortisone subjects due to suspected medication intolerance, suggesting that subjects were truly unaware of their treatment assignment early in the study. When asked at the 7-week point of therapy which intervention they thought they were receiving, the correct treatment assignment was identified by 42%, whereas 49% identified the incorrect one.

**Figure 2.** Change in Global Wellness Score




Data compare during-treatment scores with the pretreatment baseline scores. The treatment period wellness score was the mean of the daily wellness scores from the start of week 5 of treatment until 3 days before the follow-up table-tilt test. Data also include 1 subject in the placebo group who had 6 days of wellness data but who did not meet the criteria for inclusion in the analysis outcomes. The dotted line indicates a 15-point improvement in mean daily wellness score, the magnitude of change considered to be clinically meaningful.

## COMMENT

The results of this randomized, double-blind, placebo-controlled trial indicate that fludrocortisone is not efficacious when used alone for the treatment of NMH in adults with CFS. Only 14% of those randomly assigned to receive fludrocortisone reported a clinically meaningful improvement in their general sense of well-being, not significantly different from the 10% rate in the placebo arm. The study had an 81% power to detect a 25% higher rate of 15-point improvement in wellness scores

in the fludrocortisone group; a study with an 80% power to detect a 15% higher rate of 15-point improvement would have required a study size of approximately 200 subjects. There was no evidence of a beneficial effect for fludrocortisone among those who were fully compliant with the study medication, or if the analysis considered less meaningful changes in wellness scores.

Our results are similar to those obtained by Peterson and colleagues.[29] In their crossover trial, CFS patients who were assumed but not proved to have NMH received either placebo or 0.1 to 0.2 mg/d of fludrocortisone acetate for 6 weeks; 20 of 25 enrolled subjects completed both arms of the trial. No significant improvements were noted in symptom scores, the SF-36 scale, or physiologic measurements. Two other recent randomized trials have shown that individuals with CFS experience a modest clinical improvement after treatment with hydrocortisone,[20,30] which has combined glucocorticoid and mineralocorticoid effects. Although it is possible that the improvements noted in these trials could be attributed to the mineralocorticoid effect of hydrocortisone, our study and that of Peterson and colleagues provide little support for this view.

This study was designed to address whether NMH has a pathophysiologic role in the genesis of CFS symptoms. We reasoned that if NMH were a cause of CFS symptoms, then adequate therapy of the orthostatic intolerance would cause a global improvement in well-being. Because fludrocortisone did not provide adequate treatment of the NMH in persons with CFS, as measured by the response to repeated tilt-table testing, it provided an inadequate test of the hypothesis that NMH is a cause of some CFS symptoms. Since this study was designed, no pharmacological agents had been defined in randomized controlled trials as effective treatments for NMH. We chose to study fludrocortisone because it had been used for several decades in patients with orthostatic hypotension,[31,32] and on the basis of several case series in patients with syncope or CFS,[9,33,34] as well as one comparative trial suggesting its utility in younger patients with recurrent neurally mediated syncope.[35] Since this trial began, however, at least 4 randomized placebo-controlled trials have been conducted among patients with recurrent syncope due to NMH. These studies identified atenolol,[36] enalapril,[37] midodrine,[38] and paroxetine hydrochloride[39] as efficacious. Given the overlap in tilt test responses between those with recurrent syncope and those with CFS, further investigation of these medications is warranted to determine whether they will improve both the orthostatic tolerance and quality of life of those with CFS.

Several aspects of the study methods deserve further comment. The treatment of NMH usually begins with an adequate salt and fluid intake, avoidance of provocative stimuli such as prolonged standing and warm environments, as well as adoption of physical maneuvers to improve venous return to the heart.[40-43] All study subjects were advised to drink 2 L of fluid per day. We elected not to teach physical maneuvers or to recommend an increased intake of sodium chloride because any beneficial effect that accrued as a result in the placebo group would have reduced the likelihood of detecting a therapeutic benefit from the active study medication. It remains to be seen whether fludrocortisone will prove useful in combination with either an increased intake of sodium chloride or other therapies directed at NMH, but we elected not to study combination therapy because of the increased risk that treatment group assignment would be more obvious to study subjects. For similar reasons, we chose to keep the study dose of fludrocortisone acetate at 0.1 mg/d, which had appeared adequate in our open treatment experience, although dosages of 0.1 to 0.4 mg/d are often recommended. A limitation of the study was that compliance was measured by self-report and that we did not include a pill count or measure fludrocortisone directly to assess compliance.

Other studies of individuals with CFS have reported a low rate of spontaneous improvement among those with a longer duration of prestudy illness.[5] In our study, 71% of subjects had been ill for 3 years or more, similar to the duration of illness of subjects in other CFS treatment trials. It is possible that 1 or more associated illness characteristics make this group more refractory to medical therapy. Subjects with CFS for less than 3 years in our study were evenly distributed between the fludrocortisone and placebo groups. Nonetheless, because of the limited number of subjects in this subgroup, we were unable to exclude true improvements due to fludrocortisone. A small but nonsignificant difference was also present between fludrocortisone and placebo for the subgroup of subjects younger than 30 years, suggesting that these groups warrant increased attention in future studies of medications for those with CFS.

The reported prevalence of NMH in other studies has varied somewhat, between 22% and 96%, depending on the age of the patients, the form of orthostatic stress, its duration, the period of pretest fasting, the environmental conditions at the time of the test, and concurrent dietary or medical treatments. In the 7 studies published thus far in which CFS patients and healthy controls were studied using the same tilt test protocol, 6 have identified a higher prevalence of hypotension among those with CFS.[9,11,14,17,44-46] Our study screened a much larger group of subjects with CFS than have been included in previous studies. Although we cannot exclude a bias in self-referral of subjects with orthostatic symptoms, 66% of study subjects with CFS developed NMH, postural tachycardia syndrome, or both in response to a 2-stage tilt test. Although our trial focused on treatment, the pathophysiology of orthostatic intolerance among patients with CFS deserves further attention in future studies.

**Author Contributions:** Dr Rowe participated in the study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript; provided critical revision of the manuscript for important intellectual content, and statistical expertise; obtained funding, and supervised conduct of the study.
Dr Calkins participated in the study concept and design, acquisition of data, analysis and interpretation of data; provided critical revision of the manuscript for important intellectual content; obtained funding; and supervised conduct of the study.
Ms DeBusk participated in acquisition of data; pro-

vided critical revision of the manuscript for important intellectual content and administrative, technical, or material support; and supervised conduct of the study.
Dr McKenzie participated in the study concept and design, provided critical revision of the manuscript for important intellectual content, and supervised conduct of the study.
Dr Anand participated in acquisition of data, analysis and interpretation of data, and drafting of the manuscript and provided critical revision of the manuscript for important intellectual content and statistical expertise.
Dr Sharma participated in the study concept and design and acquisition of data, provided critical revision of the manuscript for important intellectual content; and provided administrative, technical, or material support.
Dr Cuccherini participated in acquisition of and analysis and interpretation of data and provided critical revision of the manuscript for important intellectual content, and administrative, technical, or material support.
Dr Soto participated in the acquisition of data, analysis and interpretation of data, and drafting of the manuscript; provided critical revision of the manuscript for important intellectual content, statistical expertise, and administrative, technical, or material support.
Ms Hohman participated in the acquisition of data and drafting of the manuscript and provided administrative, technical, or material support; obtained funding; and supervised conduct of the study.
Ms Snader participated in the study concept and design and acquisition of data; provided critical revision of the manuscript for important intellectual content and administrative, technical, or material support; and supervised conduct of the study.
Ms Lucas participated in analysis and interpretation of data; provided critical revision of the manuscript for important intellectual content, and statistical expertise.
Dr Wolff participated in the acquisition, analysis, and interpretation of data, drafting of the manuscript, and provided statistical expertise.
Dr Straus participated in the study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, provided critical revision of the manuscript for important intellectual content, statistical expertise, and administrative, technical, or material support; and supervised conduct of the study.

**Funding/Support:** This work was funded in part by grant AI 39500 from the National Institute of Allergy and Infectious Diseases (Dr Rowe) and by grant NCRR, RR00052 from the National Institutes of Health in support of the Johns Hopkins Outpatient General Clinical Research Center. The Chronic Fatigue Immune Dysfunction Syndrome Association of America Inc, provided a bridging grant to the investigators at the Johns Hopkins Hospital.

**Acknowledgment:** We thank the following individuals who served as the data safety and monitoring board for this trial: Adolfo Correa, MD, PhD (Chair), John H. Lawrence III, MD, John G. Bartlett, MD, and John A. Kastor, MD. We thank Jackie Kaczmarczyk, Marlene Wright, Phyllis Barr, Carol Tunin, PhD, Mark Van Raden, MA, and Leigh Sawyer, DVM, MPH, for their help with this study.

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