**Background:** Chronic fatigue syndrome (CFS) is a disabling illness of persistent fatigue. Recent studies have shown that patients with CFS have an increased prevalence of nonallergic rhinitis. Inflammation of the nasal passages due to allergic rhinitis can cause nasal congestion resulting in an increased number of sleep disturbances and daytime fatigue. While topical nasal corticosteroids have been shown to alleviate nasal obstruction effectively in patients with rhinitis who do not have CFS, it is unknown whether topical nasal corticosteroids will reduce CFS symptoms.

**Study Objective:** The purpose of this study is to determine whether topical nasal corticosteroids will reduce daytime sleepiness in patients with CFS and rhinitis.

**Methods:** Twenty-eight of 31 subjects with rhinitis and a diagnosis of CFS completed the double-blind, randomized, placebo-controlled trial. Two subjects failed screening, and 3 subjects withdrew from the study prior to its completion. Subjects were randomized according to Balaam’s crossover design, and one of the following interventions was used for each group in the study: 8-week treatment with a topical nasal corticosteroid, 8-week treatment with a placebo saline spray, 4-week treatment with a topical nasal corticosteroid followed by a 4-week treatment with a placebo saline spray, or a 4-week treatment with a placebo saline spray followed by a 4-week treatment with a topical nasal corticosteroid. Data focusing on rhinitis symptoms, severity of chronic fatigue symptoms, and quality of life were gathered at biweekly office visits and with daily diaries.

**Results:** The results indicated that daytime sleepiness was reduced when patients with rhinitis and CFS were treated with topical nasal corticosteroids. The severity of associated CFS symptoms, specifically fatigue, muscle pain, post-exertional fatigue, and daily activity, did not improve with treatment.

**Conclusion:** Treating the symptoms of rhinitis in patients with CFS does not appear to alleviate daytime fatigue or associated nasal, musculoskeletal, or cognitive complaints. Therefore, it is unlikely that aggressive treatment of such symptoms with topical nasal corticosteroids will provide significant benefit to patients with CFS who do not have allergic rhinitis. These results indicate that the nonallergic rhinitis seen in patients with CFS may arise from a mechanism other than chronic inflammation.

Patients with chronic fatigue syndrome (CFS) have severe, idiopathic fatigue that is often accompanied by myriad nonspecific symptoms, such as myalgia, low-grade fever, headaches, and decreased cognition. In addition, data have shown a high incidence of the symptoms of rhinitis in patients who have CFS.1 Given that allergic rhinitis has been linked to daytime somnolence, chronic nonallergic rhinitis may also contribute to the mechanisms of CFS.2-4 It is our hypothesis that alleviating the nasal obstruction caused by allergic rhinitis may reduce daytime fatigue and somnolence in patients with CFS.

Although investigators1 have reported a high incidence of nonallergic rhinitis in patients with CFS, there are no data to suggest that treating patients for rhinitis may in fact reduce the symptoms of CFS. Topical nasal corticosteroids have been shown to relieve nasal congestion effectively in patients with allergic rhinitis.4-10 Evidence obtained from acoustic rhinometry, rhinomanometry, and nasal peak inspiratory flow rates have demonstrated reduced nasal congestion, as well as increased nasal patency. Studies have also shown that topical

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nasal corticosteroids have reduced daytime sleepiness in patients with allergic rhinitis.4–10 Given this evidence, it is possible that alleviating nasal obstruction in patients with CFS may reduce their symptoms of daytime fatigue.

Methods

The study was conducted as a crossover trial using Balaam’s design for randomization (Figure), a hybrid of a crossover and a parallel design. Subjects were assigned to one of four sequences: active only, placebo only, active then placebo, or placebo then active. In this study design, variability was controlled by having each subject serve as his or her own control. This design is more powerful than a traditional parallel trial and hence allows for a smaller sample size. However, such a design requires more subjects than a traditional crossover trial so that any carryover effect can be estimated (ie, the residual effect of prior treatment after a subject has crossed over to the second phase of the treatment sequence when dictated by the study’s design). This estimation of treatment differences is unbiased even in the presence of unequal carryover effects.

Advertisement with the approval from the institutional review board at Pennsylvania State University’s Hershey Medical Center was used to recruit study subjects. Subjects were required to be between ages 18 years and 65 years and to have the symptoms of nasal congestion, or nonallergic or perennial rhinitis. The severity of each subject’s rhinitis symptoms was determined by a subjective rhinitis severity score determined by asking the patient to rank on a scale of 0 (none) to 3 (severe) the symptoms of runny nose, nasal congestion, sneezing, itching eyes, and itching nose, throat, palate, or ears during the previous 2 weeks.

Twenty-eight patients with CFS were selected through the screening process on the basis of predetermined inclusion and exclusion criteria. Inclusion criteria were modeled after the Centers for Disease Control and Prevention’s (CDC) criteria for a diagnosis of CFS.11,12 These criteria were separated into 2 major criteria and 9 minor criteria. Selection was based on fulfilling both major criteria and at least 4 of the 9 minor criteria. Major criteria were:

- Unexplained severe fatigue of at least 6 months’ duration that is not alleviated by rest and impairs daily activity by at least 50%.
- Clinical conditions that may produce similar fatigue must be excluded.

The following minor criteria were also evaluated:

- arthralgias;
- decreased cognition, alertness, or memory;
- generalized headaches;
- low-grade fever;
- lymphadenopathy;
- myalgias;
- severe, postexertional fatigue;
- sore throat; or
- unrefreshing sleep.

Subjects were excluded based on the presence of sleep apnea, obesity, nasal polyps, recent upper respiratory tract infection, deviated septum, seasonal allergic rhinitis, asthma, or other respiratory diseases.

The 28 subjects were also evaluated for atopic illness based on skin prick (epicutaneous) testing for the following allergens: dog, cat, cockroach, fungi (ie, Alternaria), both types of house dust mite, and 10 seasonal allergens. All subjects who tested positive for seasonal allergens were excluded from this study to avoid symptom changes as a result of season changes. Fifteen subjects with perennial allergic rhinitis but no seasonal allergies and 13 subjects with nonallergic rhinitis and negative skin tests were randomized.

Seven patients were randomly assigned to each of the four study sequences, and a total of five physician office visits were required. At the first office visit, patients’ fulfillment of the CDC criteria for CFS was confirmed. Patients were then evaluated based on the results of their skin tests, and they were randomly assigned to one of the four treatment regimens.

Patients were reevaluated on visits conducted on weeks 2, 4, 6, and 8. During week 4, patients were crossed over to the second treatment regimen if one was determined in the study design for their particular randomized sequence. Active treatment consisted of a topical nasal corticosteroid (flunisolide). The placebo was a saline spray. Both treatment regimens were self-administered intranasally, two sprays twice daily.

During the 8-week trial, patients’ compliance and symptoms were monitored through the following measures and instruments: focused questionnaires (eg, rhinitis severity score), the Epworth Sleepiness Scale,13 the University of Pennsylvania Functional Outcomes of Sleep Quality of Life Survey (UPFQOS), and daily diaries.

Figure. Balaam’s crossover design for randomization. Seven subjects completed each arm of this study (N = 28).
Latency Test). The last questionnaire, the UPFOSS, is a when compared with objective tests (eg, Multiple Sleep Epworth Sleepiness Scale is a daily survey that ranks the likelihood of falling asleep during different daily activities. This questionnaire that asked patients to rank each of their symptoms—including runny nose; nasal stuffiness; sneezing; itching eyes; and itching nose, throat, and/or palate—during the previous 2 weeks on a scale of 0 (none) to 4 (severe).4 The rhinitis severity score was obtained through a separate questionnaire that asked patients to rank each of their symptoms—including runny nose; nasal stuffiness; sneezing; itching eyes; and itching nose, throat, and/or palate—during the previous 2 weeks on a scale of 0 (none) to 3 (severe). The results of the rhinitis severity score, the Epworth Sleepiness Scale, and the daily diary were summarized from the last 2 weeks of each 4-week treatment sequence, corresponding to the third and fifth office visits. A summary score was collected for each variable by taking an average of each patient’s ratings that dealt with the variable. The Mixed Procedure (PROC MIXED) in Statistical Analysis System (1997, SAS Institute Inc, Cary, NC) was used to analyze the data, with the summary score being the response variable. We analyzed these data to compare the five symptoms on the rhinitis severity score, three questions about reduction of symptoms due to treatment and the Epworth Sleepiness Scale, and four symptoms from the daily diary between placebo saline spray and topical nasal corticosteroid (flunisolide). The UPFOSS was analyzed on the basis of averaging scores based on the parameters of general productivity, social outcome, daily activity level, vigilance, and quality of intimate relationships, as well as a total score. The UPFOSS is an instrument developed for sleep apnea to determine the extent of daytime somnolence.

### Results

Twenty-eight patients were recruited. Their demographic characteristics are noted in Table 1. The analysis of symptoms on the Chronic Fatigue Syndrome Severity Rating showed no significant difference between active and placebo treatment regimens (Table 2). The data from the rhinitis severity score, UPFOSS, and daily diaries also showed no significant difference between active and placebo treatment regimens (Table 3). Analysis of daytime fatigue by daily diary scores showed significant improvement on one question of daytime sleepiness. However, no other significant difference was found on any other outcomes of the sleep diary (Table 3). Results of the Epworth Sleep Scale showed a reduction of sleep symptoms in the active treatment group (8.48, active; 11.66, placebo). However, this was not statistically significant (P = .08).

### Comment

Past research has suggested that rhinitis, in particular allergic rhinitis, can cause nasal obstruction resulting in fragmented sleep and daytime somnolence. Furthermore, it has been shown that topical nasal corticosteroids are effective in treating patients with daytime somnolence by alleviating nasal congestion caused by allergic rhinitis. Given that topical nasal corticosteroids have also been shown to be an effective treatment modality for patients with nonallergic rhinitis, it would be reasonable to postulate that in a subset of patients with CFS and rhinitis, excess daytime fatigue could result from a disruptive sleep pattern due to obstructed nasal passages. However, the findings of this study suggest that the symptoms of CFS cannot be effectively reduced in the majority of patients with CFS by simply reducing nasal inflammation with topical nasal corticosteroids.

As a further point of interest, rhinitis symptoms did not improve with treatment in this study. Given that topical nasal

### Statistical Methods

The number of subjects recruited was based on 28 subjects necessary to have an 80% chance of having a statistical improvement of somnolence with treatment at a level of significance of .05. Data from the rhinitis severity score, the Epworth Sleepiness Scale, and the daily diary were summarized from the last 2 weeks of each 4-week treatment sequence, corresponding to the third and fifth office visits. A summary score was collected for each variable by taking an average of each patient’s ratings that dealt with the variable. The Mixed Procedure (PROC MIXED) in Statistical Analysis System (1997, SAS Institute Inc, Cary, NC) was used to analyze the data, with the summary score being the response variable. We analyzed these data to compare the five symptoms on the rhinitis severity score, three questions about reduction of symptoms due to treatment and the Epworth Sleepiness Scale, and four symptoms from the daily diary between placebo saline spray and topical nasal corticosteroid (flunisolide). The UPFOSS was analyzed on the basis of averaging scores based on the parameters of general productivity, social outcome, daily activity level, vigilance, and quality of intimate relationships, as well as a total score. The UPFOSS is an instrument developed for sleep apnea to determine the extent of daytime somnolence.

### Table 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>8 (29)</td>
</tr>
<tr>
<td>Women</td>
<td>20 (71)</td>
</tr>
<tr>
<td>Rhinitis</td>
<td></td>
</tr>
<tr>
<td>Perennial</td>
<td>15 (54)</td>
</tr>
<tr>
<td>Nonallergic</td>
<td>13 (46)</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>46.2</td>
</tr>
<tr>
<td>Median</td>
<td>47</td>
</tr>
<tr>
<td>Range</td>
<td>31–62</td>
</tr>
</tbody>
</table>

### Table 2

<table>
<thead>
<tr>
<th>Flunisolide (Active)</th>
<th>Saline Spray (Placebo)</th>
<th>Difference</th>
<th>SE</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>14.96</td>
<td>18.13</td>
<td>−3.17</td>
<td>2.2</td>
<td>.16*</td>
</tr>
</tbody>
</table>

* No statistically significant effect was noted.

A rhinitis severity score was obtained through a separate questionnaire that asked patients to rank each of their symptoms—including runny nose; nasal stuffiness; sneezing; itching eyes; and itching nose, throat, and/or palate—during the previous 2 weeks on a scale of 0 (none) to 3 (severe). The Epworth Sleepiness Scale is a daily survey that ranks the likelihood of falling asleep during different daily activities. This instrument was chosen to evaluate daytime fatigue because it has been shown to be a valid determinant of sleepiness. Some others—such as the Multiple Sleep Latency Test—have been shown to be valid determinants of sleepiness when compared with objective tests (eg, Multiple Sleep Latency Test). The last questionnaire, the UPFOSS, is a detailed analysis of a patient’s daytime fatigue and how it affects daily activities, including work, school, and relationships. Daily diaries evaluated nasal symptoms, daytime fatigue, nocturnal sleep, and response to medications on two separate scales: one measured severity while the other measured reduction of symptoms. The diary was based on a 0 (none) to 4 (severe) scale.4

### Table 3

The analysis of symptoms of general productivity, social outcome, daily activity level, vigilance, and quality of intimate relationships, as well as a total score.
Corticosteroids have been shown to reduce rhinitis complaints in both allergic rhinitis and nonallergic rhinitis sufferers effectively, these findings may suggest that the rhinitis associated with CFS may result from a mechanism other than chronic inflammation. This conclusion is supported by reports that markers of nasal inflammation such as IgE, lysozyme, leukocyte elastase, and eosinophil cationic protein are not increased in patients with fibromyalgia or CFS as compared with normal healthy control subjects and subjects with allergic rhinitis or cystic fibrosis. Studies by Numata et al17 have shown that nasal lavage isolated from patients with idiopathic or vaso-motor rhinitis shows no significant differences compared with that in healthy control subjects in the number of eosinophils, the percentage of EG2-positive cells, the eosinophil-to-neutrophil ratio in nasal lavage, the eosinophil-to-epithelial cell ratio, or the percentage of EG2-positive cells. Numata et al17 concluded that inflammatory cells were not involved in idiopathic rhinitis. These findings suggest that a similar noninflammatory mechanism may contribute to the rhinitis seen in patients with CFS.

### Table 3

Effects of Topical Nasal Corticosteroids: Subjects With Chronic Fatigue Syndrome

<table>
<thead>
<tr>
<th>Measure or Instrument</th>
<th>Flunisolide (Active)</th>
<th>Saline Spray (Placebo)</th>
<th>Difference</th>
<th>SE</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhinitis severity scores</td>
<td>3.32</td>
<td>3.33</td>
<td>0.01</td>
<td>0.76</td>
<td>0.99</td>
</tr>
<tr>
<td>Runny nose</td>
<td>0.64</td>
<td>0.58</td>
<td>0.06</td>
<td>0.23</td>
<td>0.81</td>
</tr>
<tr>
<td>Nasal stuffiness</td>
<td>0.97</td>
<td>1.25</td>
<td>0.28</td>
<td>0.24</td>
<td>0.25</td>
</tr>
<tr>
<td>Sneezing</td>
<td>0.48</td>
<td>0.47</td>
<td>0.01</td>
<td>0.17</td>
<td>0.93</td>
</tr>
<tr>
<td>Itchy, watery eyes</td>
<td>0.53</td>
<td>0.62</td>
<td>0.09</td>
<td>0.22</td>
<td>0.71</td>
</tr>
<tr>
<td>Itchy nose, throat, palate, or ears</td>
<td>0.68</td>
<td>0.43</td>
<td>0.25</td>
<td>0.24</td>
<td>0.30</td>
</tr>
<tr>
<td>Epworth Sleepiness Scale</td>
<td>8.48</td>
<td>11.66</td>
<td>3.18</td>
<td>1.73</td>
<td>0.08</td>
</tr>
<tr>
<td>General productivity</td>
<td>3.02</td>
<td>2.71</td>
<td>0.31</td>
<td>0.21</td>
<td>0.14</td>
</tr>
<tr>
<td>Social outcome</td>
<td>3.05</td>
<td>3.02</td>
<td>0.03</td>
<td>0.23</td>
<td>0.89</td>
</tr>
<tr>
<td>Activity level</td>
<td>2.39</td>
<td>2.10</td>
<td>0.29</td>
<td>0.21</td>
<td>0.19</td>
</tr>
<tr>
<td>Vigilance</td>
<td>2.71</td>
<td>2.42</td>
<td>0.29</td>
<td>0.27</td>
<td>0.31</td>
</tr>
<tr>
<td>Intimate relationship or sexual activity</td>
<td>2.05</td>
<td>2.32</td>
<td>0.27</td>
<td>0.47</td>
<td>0.57</td>
</tr>
</tbody>
</table>

*The only significant difference between the groups is noted in reduced daytime sleepiness by diary.*
Last, between 15% and 30% of patients with CFS would be expected to have allergic rhinitis by chance alone. Treatment of patients for this rhinitis may be beneficial to improve quality of life, and therefore, assessment and treatment of patients with CFS for allergic rhinitis is indicated—especially because the fatigue and somnolence associated with allergic rhinitis may respond to topical nasal corticosteroids. However, further research, investigating the mechanism and effective therapy for rhinitis in patients with CFS, is warranted to determine the role and treatment modality for rhinitis and somnolence in patients with CFS.

References


