A Randomized, Double-blind, Placebo-Controlled Trial of Psychostimulants for the Treatment of Fatigue in Ambulatory Patients With Human Immunodeficiency Virus Disease

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Background: Fatigue is a commonly encountered symptom of human immunodeficiency virus (HIV) disease, associated with significant psychological and functional morbidity and poor quality of life. Preliminary studies on the treatment of fatigue from the cancer and multiple sclerosis literature suggest that psychostimulants may be effective in reducing fatigue.

Objective: To compare the efficacy of 2 psychostimulant medications, methylphenidate hydrochloride (Ritalin) and pemoline (Cylert), with a placebo intervention for the treatment of fatigue in patients with HIV disease.

Methods: In this double-blind trial, 144 ambulatory patients with HIV disease and persistent and severe fatigue were randomized to treatment with methylphenidate, pemoline, or placebo. Medications were titrated up to a maximum dose of 60 mg of methylphenidate hydrochloride, 150 mg of pemoline, or 8 capsules of placebo daily. Fatigue was measured using 2 self-reported rating scales, the Piper Fatigue Scale (PFS) and the Visual Analogue Scale for Fatigue (VAS-F). We also used the timed isometric unilateral straight leg-raising task, a measure of muscular endurance. Quality-of-life and psychological well-being measures included the Beck Depression Inventory, the Brief Symptom Inventory, and the 36-Item Short-Form Medical Outcomes Study Health Status Survey. Side effects were monitored using the Systematic Assessment for Treatment Emergent Events and the Extra-pyramidal Symptom Rating Scale. All measures were rated weekly.

Results: One hundred nine subjects completed the 6-week trial; 15 patients (41%) receiving methylphenidate and 12 patients (36%) receiving pemoline demonstrated clinically significant improvement compared with 6 patients (15%) receiving placebo. Patients receiving methylphenidate or pemoline demonstrated significantly more improvement in fatigue on several self-reported rating scales (PFS total score, \( P = .04 \); affective subscale, \( P = .008 \); sensory subscale, \( P = .04 \); and VAS-F energy subscale, \( P = .02 \)). Analysis of the regression slopes by means of hierarchical linear modeling demonstrated a significantly greater rate of improvement in PFS total scores among patients receiving psychostimulants compared with the placebo group (\( P = .02 \)). There were no significant differences in the efficacy between methylphenidate and pemoline on any outcome measure studied. Improvement in fatigue was also significantly correlated with improvement in measures of depression, psychological distress, and overall quality of life. Severe side effects were relatively uncommon among this sample, and only hyperactivity or jitteriness occurred significantly more often among subjects receiving active medication.

Conclusions: Many patients with HIV- and acquired immunodeficiency syndrome–unrelated fatigue respond favorably to treatment with methylphenidate or pemoline. Both psychostimulants appear to be equally effective and significantly superior to placebo in decreasing fatigue severity with minimal side effects. Moreover, improvement of fatigue was significantly associated with improved quality of life and decreased levels of depression and psychological distress.

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Fatigue is a commonly encountered symptom of human immunodeficiency virus (HIV) disease, associated with significant psychological and functional morbidity and poor quality of life (QOL). Recent reports estimate that fatigue is a distressing symptom in as many as 40% to 50% of patients with acquired immunodeficiency syndrome (AIDS) and is even common among individuals with early asymptomatic HIV infection. For example, Longo and colleagues, using a semistructured interview to elicit the physical and psychological concerns of men with AIDS, noted that 41% of their sample described fatigue as a major physical concern. In a more comprehensive study of fatigue, Darko and colleagues found that more than 50% of their...
PATIENTS AND METHODS

PATIENTS

Ambulatory patients with HIV infection or AIDS were recruited from hospitals, outpatient clinics, and agencies serving HIV-infected individuals throughout the metropolitan New York City area. Advertisements were posted in these facilities offering $25 in exchange for participation in a study of QOL and physical symptoms (the nature of the study was not disclosed in these advertisements to minimize the possibility that patients would exaggerate their fatigue to participate). Patients who met inclusion and exclusion criteria were offered $23 for each follow-up visit to compensate for their time and travel expenses, and to maximize compliance with the study procedures.

Patients were eligible for study participation if they were seropositive for HIV, received ambulatory care at the time of study entry, were older than 18 years, spoke English fluently (because most instruments were only validated in English), and were able to swallow oral medications. In addition, all participants were required to have had persistent fatigue (for at least 2 weeks or more) that was rated 5 or greater on a numerical rating scale of 0 to 10. Patients were excluded if they reported active substance abuse or had urine toxicologic screening results that were positive for nonprescription controlled substances. Patients were also excluded if they had a diagnosis of a major depressive episode or cognitive impairment sufficient to preclude informed consent or data collection (ie, evidence of HIV-associated dementia complex of moderate or severe level of impairment), or if they reported insufficient fatigue. In addition, patients were excluded if they had medical contraindications, such as evidence of severe renal or hepatic disease (ie, creatinine levels or results of liver function tests exceeding twice normal limits) or a history of cardiac disease (ie, cardiac arrhythmia), seizure disorder, or psychosis, or if they were prescribed medications that were contraindicated (monoamine oxidase inhibitors, bupropion hydrochloride, guanethidine monosulfate, or other sympathomimetic agents). This research study was approved by the Memorial Sloan-Kettering Hospital Institutional Review Board, New York, NY. All participants provided written informed consent after a discussion of the risks and benefits of study participation.

PROCEDURE

After providing informed consent, all potential subjects underwent screening for inclusion and exclusion criteria using the Mini-Mental State Examination,20 the Structured Clinical Interview for Diagnosis (SCID), Non-Patient, HIV Version,21 and a battery of neuropsychological tests sensitive to detecting cognitive impairments caused by HIV-associated dementia. These measures included the digit symbol subtest from the Wechsler Adult Intelligence Scale–Revised,22 the Trail-Making Test,23 the Grooved Pegboard Test,24 and the Finger Tapping Test.25 Evidence of cognitive impairment on the Mini-Mental State Examination (scores <22) or on the battery of neuropsychological tests (ie, performance >1 SD below published norms on 3 of 4 tests) resulted in exclusion from the study. In addition, all participants were required to provide a urine sample for toxicologic screening (to rule out active substance abuse) and clinical laboratory testing (eg, complete blood cell count, chemistry screening panel including liver function tests) to screen and monitor for safe completion of the study.

All subjects who met inclusion and exclusion criteria were administered a battery of self-reported and observer-rated measures. These included 2 self-reported measures of fatigue, the Piper Fatigue Scale (PFS)26 and the Visual Analog Scale for Fatigue Severity (VAS-F),27 as well as a measure of muscular endurance, the timed isometric unilateral straight leg-raising task.28 Because validation data for the PFS is considerably stronger than for other measures of fatigue, we considered this measure our primary dependent variable. Patients were also rated on the Karnofsky Performance Status scale,29,30 to assess their overall functioning abilities. Measures of psychological well-being and QOL included the Beck Depression Inventory (BDI),31 the Brief Symptom Inventory,32 and the 36-Item Short-Form Medical Outcome Study Health Status Survey.33

After baseline data collection, subjects were randomized (using block randomization to ensure comparable numbers of HIV-infected patients with and without an AIDS diagnosis) to one of the 3 study arms and prescribed methylphenidate hydrochloride, 7.5 mg (1 capsule) twice daily; pemoline, 18.75 mg (1 capsule) twice daily; or placebo, 1 capsule twice daily, as their initial starting dose. Study sample of patients with AIDS had significant levels of fatigue compared with only 10% of HIV-seronegative control subjects. In their study, patients with AIDS reported significantly greater fatigue-related interference with work, self-care, and social and daily activities and spent a greater number of hours sleeping than controls.

Breitbart and colleagues also reported a high prevalence of fatigue among their sample of 427 ambulatory patients with AIDS. They classified 53% of their sample as having fatigue, and observed significant associations between fatigue and anemia, pain, total number of AIDS-related physical symptoms, and whether patients were currently receiving treatment for AIDS-related medical disorders. In addition, demographic variables such as sex and HIV transmission risk factor were significantly associated with fatigue in their sample (women and injection drug users were more likely to report fatigue). Patients with fatigue also reported significantly more depressive symptoms and psychological distress and significantly poorer QOL.

Fatigue in HIV disease, as in cancer and other medical conditions, is a complex multidimensional experience with diverse causes and correlates. Fatigue in patients with HIV disease has been associated with anemia, malnutrition and wasting, AIDS dementia and the consequences of central nervous system HIV infection, hypogonadism, HIV myopathy, elevated cytokine levels and sleep disturbance, depression, and pain. In addition, fatigue has been attributed to a variety of medications, chemotherapies, immunotherapies, radiation therapy, opportunistic infections, and cancers.

Fatigue management strategies are typically divided into those aimed at treating the underlying cause of fatigue and those aimed at treating fatigue directly. For example, Rabkin and colleagues observed improved fatigue after treatment of hypogonadism in their patients with AIDS. They classified 53% of their sample as having fatigue, and observed significant associations between fatigue and anemia, pain, total number of AIDS-related physical symptoms, and whether patients were currently receiving treatment for AIDS-related medical disorders. In addition, demographic variables such as sex and HIV transmission risk factor were significantly associated with fatigue in their sample (women and injection drug users were more likely to report fatigue). Patients with fatigue also reported significantly more depressive symptoms and psychological distress and significantly poorer QOL.

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participants and research staff were unaware of which medication subjects were prescribed (all medications were prepared in identical capsules, and randomization was completed by pharmacy personnel based on a random number table). Study patients were then seen weekly for 6 weeks, and were contacted by the research nurse (J.F.-E.) several times per week between weekly visits to monitor medication and side effects and to titrate medications as rapidly as possible to the maximum tolerated dose (or the maximum dose allowed by the study protocol, ie, 60 mg/d for methylphenidate hydrochloride, 150 mg/d for pemoline, and 8 capsules per day for placebo). At each weekly in-person visit, patients were asked to complete the entire battery of assessment measures (measures of fatigue and psychological well-being), with the exception of SCID interviews and the Mini-Mental State Examination, which were conducted only at baseline to assess exclusion criteria, and the neuropsychological test battery, which was conducted at baseline and at study completion. Side effects and adverse events were also rated during each weekly appointment, using the Systematic Assessment for Treatment Emergent Events (SAFTEE), a multifaceted measure assessing 26 adverse effects commonly observed in pharmacological interventions, the Extrapyramidal Side Effects Rating Scale, designed to identify the presence of tics or involuntary movements that may accompany psychostimulant medications (not assessed by the SAFTEE), and weekly ratings of weight to assess the impact of any appetite suppression that might result from psychostimulant therapy. Pill counts were also obtained weekly to ensure medication compliance. Patients were discontinued from study participation if they complained of intolerable side effects of study medications or required hospitalization for HIV-related medical problems (whether or not they were related to study medications).

STATISTICAL ANALYSIS

Fatigue data were analyzed in the following 2 different ways: first using change scores calculated from fatigue data obtained at baseline and at the completion of the 6-week trial, and second using hierarchical linear modeling to compare regression slopes of fatigue improvement. In the first set of analyses, all fatigue-related outcome measures (including total scores and subscale scores) were analyzed using a multivariate analysis of variance (MANOVA), considering improvement in measures of fatigue as the dependent variables and treatment arm as the primary independent variables. Subsequent analysis of covariance (ANCOVA) models were used to allow for the influence of additional covariates such as medication dosage and HIV/AIDS status. The second level of analysis, which included all subjects who completed at least 3 follow-up assessments, compared the regression slopes derived for individual subjects over time, with each slope reflecting the pattern of improvement due to treatment (hierarchical linear modeling). Because improvement in fatigue over time is not necessarily linear, regression models were fit to the overall slope of the improvement curves by transforming the time intervals to reflect the slope of improvement (this transformation resulted in essentially linear improvement curves; the data are nevertheless presented without this transformation to facilitate interpretation). These regression weights were then analyzed using an analysis of variance (ANOVA) model to assess whether differences existed across treatment arms with regard to the rate of improvement in fatigue observed across each group. Planned contrasts were conducted to compare patients prescribed active treatment with those taking a placebo, and then to compare the methylphenidate and pemoline groups. Finally, Pearson product-moment correlations between improvement in fatigue (change scores) and improvement in measures of psychological distress and QOL were also used to assess the impact of treatment on psychosocial functioning (statistical tests for these correlation coefficients were calculated using a Bonferroni correction). Power analyses were conducted before study initiation and indicated an optimal sample size of 40 subjects per group to yield a power of 0.84, assuming a moderate effect size of 0.37. Because no data were available for patients who refused to participate in the study (after randomization), an intent-to-treat analysis was not feasible. Instead, by using hierarchical linear modeling, we were able to include all subjects who completed at least 3 of the 7 assessment periods (baseline and 2 follow-up visits), thus allowing for the inclusion of subjects who withdrew from the study prematurely.

Given the potential utility of psychostimulants for the treatment of fatigue, we sought to investigate the ef-
ficiency and safety of these medications in patients with HIV and AIDS. This study used a randomized, double-blind, placebo-controlled method to compare 2 psychostimulants (methylphenidate and pemoline) for the treatment of fatigue. These medications were chosen because of the preliminary research suggesting their possible efficacy in improving symptoms of fatigue in patients with chronic illnesses. Although most research has focused on drugs such as methylphenidate or dextroamphetamine sulfate as the prototypical psychostimulants, we sought to compare a traditional psychostimulant (methylphenidate) with an alternative psychostimulant (pemoline) with fewer sympathomimetic effects and a side effect profile that may be better tolerated by medically ill patients. We also improved on previous methods by measuring fatigue with several multidimensional self-reported scales of fatigue, as well as physiological measurements, to assess the impact of these treatments on specific aspects of fatigue. Side effects were monitored by means of a comprehensive side effects rating scale to assess the safety and tolerability of these psychostimulants in this population. Finally, measures of psychological distress and QOL were included to assess the impact of effective treatment for fatigue. We hypothesized that both psychostimulants would be superior to placebo in reducing fatigue, and that reductions in fatigue would correspond to improved psychological well-being and QOL.

RESULTS

SAMPLE CHARACTERISTICS

Two hundred thirteen individuals underwent screening for possible study inclusion. Of these prospective subjects, 34 were excluded because of active substance abuse based on self-report or results of urine toxicologic screening (this number would likely have been considerably higher had subjects not been informed of the urine toxicologic screening at the time interviews were scheduled). An additional 6 subjects were excluded because of medical contraindications; 23, a diagnosis of a major depressive episode (based on SCID interviews); and 6, the presence of other psychiatric conditions (eg, dementia and history of mania or schizophrenia). The remaining 144 subjects were randomized to one of the 3 study arms. Of these 144 subjects, 109 completed the 6-week study (Figure 1). Six subjects were randomized but never began taking a study medication (ie, never arrived for the appointment at which medications were dispensed). Seven subjects were discontinued from the study because of medical complications that arose; 7, because of poor compliance with study procedures (eg, excessive missed doses or failure to attend follow-up appointments); 5, because of intolerable side effects; and 10, because of unknown reasons (ie, stopped participating in the study without informing study personnel as to the basis for this decision).

Table 1 presents the demographic characteristics of subjects who underwent evaluation for possible participation (subjects who underwent screening), those who met inclusion and exclusion criteria (subjects randomized), and the subset of participants who completed the 6-week study (study completers).

There were no significant differences (ie, P<.05) across the 3 study arms on any demographic or baseline clinical and medical variables (eg, sex, race, transmission risk factor, baseline fatigue score, hemoglobin level, Karnofsky Performance Status scale score, or BDI score), indicating that the randomization procedure successfully generated equivalent groups. Because there were no group differences, medical data are described for the entire sample rather than for each study arm. Most subjects (77/109 [70.6%]) met criteria for a diagnosis of AIDS based on 1993 criteria of the Centers for Disease Control and Prevention, although only 47 of these 77 subjects had a history of an AIDS-defining infection (category C disease, Table

Table 1. Demographic Characteristics of Study Participants

<table>
<thead>
<tr>
<th>Variable</th>
<th>Underwent Screening (n = 213)</th>
<th>Randomized (n = 144)</th>
<th>Completed Study (n = 109)</th>
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</thead>
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<tr>
<td>Sex</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>125 (58.7)</td>
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<td>69 (63.3)</td>
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<td>Female</td>
<td>88 (41.3)</td>
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<td>Race</td>
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<tr>
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<td>28 (19.4)</td>
<td>21 (19.3)</td>
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<td>African American</td>
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<td>78 (54.2)</td>
<td>60 (55.0)</td>
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<tr>
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<td>32 (22.2)</td>
<td>24 (22.0)</td>
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<tr>
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<td>6 (4.2)</td>
<td>4 (3.7)</td>
</tr>
<tr>
<td>Risk factor</td>
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<td></td>
<td></td>
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<tr>
<td>Homosexual</td>
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<td>31 (21.5)</td>
<td>26 (23.9)</td>
</tr>
<tr>
<td>Heterosexual</td>
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<td>56 (38.9)</td>
<td>41 (37.6)</td>
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<tr>
<td>Injection drug use</td>
<td>73 (34.3)</td>
<td>49 (34.0)</td>
<td>36 (33.0)</td>
</tr>
<tr>
<td>Other/unknown</td>
<td>15 (7.0)</td>
<td>8 (5.6)</td>
<td>6 (5.5)</td>
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<tr>
<td>CDC category†</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>34 (16.0)</td>
<td>31 (21.5)</td>
<td>22 (20.2)</td>
</tr>
<tr>
<td>B</td>
<td>60 (28.2)</td>
<td>56 (38.9)</td>
<td>40 (36.7)</td>
</tr>
<tr>
<td>C</td>
<td>68 (31.9)</td>
<td>57 (39.6)</td>
<td>47 (43.1)</td>
</tr>
<tr>
<td>Unknown</td>
<td>51 (23.9)</td>
<td>0</td>
<td>0</td>
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</table>

*Percentages have been rounded and may not total 100. CDC indicates Centers for Disease Control and Prevention, Atlanta, Ga.
†According to the criteria of the CDC.

Figure 1. Trial profile.
The average Karnofsky Performance Status scale score for the sample was 75.5 (SD = 9.3), with 80 (73.4%) of 109 subjects obtaining scores of 70 or better. The mean hemoglobin level for study participants was 134 g/L (SD = 18), and only 9 (8.3%) of 109 subjects who completed the study had entry hemoglobin levels below 110 g/L. Most subjects (86/109 [78.9%]) were receiving an antiretroviral medication; 64 (58.7%) were receiving combination therapies, including protease inhibitors. There were no significant group differences with regard to antiretroviral or protease inhibitor therapies. The average BDI score was 14.2 (SD = 7.2), indicating relatively mild level of depressive symptoms (particularly because several BDI items assess somatic symptoms that may correspond to symptoms of HIV disease rather than depression), and 21 of 109 subjects were prescribed concomitant antidepressant medications (primarily selective serotonin reuptake inhibitors). In addition, 6 patients (2 per study arm) were prescribed androgen replacement therapies. Medication compliance was also comparable across groups, with an overall total of 91% of the weekly pill counts revealing accurate medication dosing.

Analysis of the effectiveness of the blind was assessed by asking subjects, at the end of the 6-week trial, to guess whether they were receiving active drug or placebo. This analysis demonstrated that although patients prescribed a psychostimulant were in fact significantly more likely (P < .05) to guess that they were prescribed an active medication, most patients receiving a placebo also guessed (incorrectly) that they were prescribed a psychostimulant. Although relatively few patients receiving active drug believed they were taking a placebo (6/58 [10.3%]), most patients receiving placebo also held this belief (22/35 [62.9%]).

**Improvement in Fatigue Across Treatment Groups**

Univariate ANOVAs showed that the 3 treatment arms differed significantly in terms of improvement on the PFS total score (F = 3.59 [P = .04]; effect size, 0.25; 95% confidence interval [CI], 0.06-0.44), the affective subscale of the PFS (F = 5.06 [P = .008]; effect size, 0.28; 95% CI, 0.09-0.47), and the sensory subscale of the PFS (F = 3.39 [P = .04]; effect size, 0.24; 95% CI, 0.05-0.43). However, there were no significant group differences on the cognitive (F = 1.70 [P = .19]; effect size, 0.17; 95% CI, -0.02 to 0.36) or severity (F = 1.82 [P = .17]; effect size, 0.18; 95% CI, -0.01 to 0.37) subscales of the PFS. Improvement scores on the VAS-F also yielded no significant group differences on the total score (F = 1.61 [P = .21]; effect size, 0.17; 95% CI, -0.02 to 0.36) or the fatigue subscale (F = 0.77 [P = .47]; effect size, 0.12; 95% CI, -0.07 to 0.31). However, changes in the energy subscale of the VAS-F differed significantly across the 3 groups (F = 4.28 [P = .02]; effect size, 0.23; 95% CI, 0.04-0.42). A MANOVA assessing the impact of treatment on improvement in these measures of fatigue (using change scores as described above) demonstrated an overall significant effect for the set of fatigue measures and subscales (F = 1.79 [P = .04]).

Contrast analyses were used, first to compare the combined group subjects assigned to 1 of the 2 treatment arms (methylphenidate or pemoline) with those assigned to the placebo condition, and second to compare subjects prescribed methylphenidate with those prescribed pemoline. These analyses demonstrated a significant difference in improvement on the PFS total score and affective and sensory subscales, as well as the energy subscale of the VAS-F. The VAS-F total score also approached significance in this analysis (P = .06). There were no significant differences in improvement on any of these measures, however, between subjects prescribed methylphenidate vs those prescribed pemoline. The mean improvement scores across the 3 treatment groups are listed in **Table 2**.

We classified subjects as having demonstrated clinically significant improvement of fatigue if their PFS total score decreased by 5 points or more (the maximum possible improvement on this scale was 10 points) or their VAS-F total score decreased by 50 mm or more (the maximum possible improvement on this scale was 100 mm). Using this criterion, we observed a significant difference across study arms in the proportion of patients who showed clinically significant improvement (χ² = 6.52 [P = .04]). Of 37 patients taking methylphenidate, 15 (41%) demonstrated clinically significant improvement, compared with 12 (36%) of 33 patients taking pemoline and only 6 (15%) of 39 patients taking placebo.

A second phase of analysis, using hierarchical linear modeling, incorporated data from all 7 time points. Individual regression slopes were calculated separately for each subject in which total scores from the PFS and VAS-F were entered as dependent variables, and study week was entered as an independent variable. These regression slopes, which reflect the rate of improvement for each individual subject over time, were then compared across the treatment arm using an ANOVA model.
similar to that used to analyze the change in scores from baseline to the end of the study. Because of the nonlinear slope of these data, the time variable was transformed using an inverse function before calculating regression slopes (this transformation diminishes the slope of improvement in early weeks while increasing the slope during later weeks, thus effectively straightening an otherwise curvilinear improvement slope). This analysis, depicted in Figure 2, demonstrated a significantly more rapid decrease in PFS total scores for patients receiving methylphenidate or pemoline compared with subjects receiving placebo ($F_{2,116}=4.63$ [$P=.02$]). Contrast analyses revealed that patients receiving methylphenidate or pemoline improved significantly faster and more steadily than patients receiving placebo ($F_{1,116}=7.62$ [$P=.007$]), whereas no differences existed between active treatment groups ($F_{1,116}=0.46$ [$P=.51$]). Although a similar pattern of results emerged for VAS-F total scores (Figure 3), this difference was not statistically significant ($F_{2,116}=1.75$ [$P=.20$]). Contrast analyses comparing both stimulant groups with the placebo group, however, approached significance ($F_{1,116}=3.46$ [$P=.07$]), whereas no differences existed between active treatment groups ($F_{1,116}=0.09$ [$P=.78$]).

A post hoc ANCOVA was used to assess whether improvement patterns differed depending on disease severity (ie, seropositive for HIV vs diagnosis of AIDS), extent of depressive symptoms at baseline (the sample was divided between those with BDI scores $\leq$ 15 and $>15$), the presence of concomitant antidepressant medications, or demographic variables such as sex, race, or risk transmission factor. These analyses demonstrated no significant interaction effects ($P<.05$), indicating that the superiority of pharmacological interventions over placebo was unrelated to disease severity, extent of depressive symptoms, concomitant antidepressant medications, sex, race, or risk transmission factor.

Given that the goal of dosage titration was to determine the optimal dose at which fatigue improved without causing excessive side effects, we used end-of-study medication dosages as the best indicator of optimal dosing. The average dosage for patients receiving methylphenidate hydrochloride was 51.0 mg/d ($SD=12.6$), with dosages ranging from 15 to 60 mg/d. Of the 37 subjects receiving methylphenidate hydrochloride who completed the study, 22 (59.5%) were taking this maximum dose (which was the maximum allowed in our study protocol) and only 4 were receiving 30 mg/d or less. Thus, it is unclear how many of these 22 subjects would have responded even more completely with higher doses of methylphenidate. The average dosage for patients receiving pemoline was 96.0 mg/d ($SD=47.5$), with dosages ranging from 37.5 to 150 mg/d. Of the 33 subjects in the pemoline group, only 11 subjects were receiving the maximum dose allowed by study protocol, whereas 9 of the 33 subjects were receiving the minimum dose (37.5 mg/d).

## SIDE EFFECTS AND TOXICITY

The presence of side effects caused by study medication was assessed using the SAFTTEE and Extrapyramidal Side Effects Rating Scale during each weekly assessment. Only 5 subjects withdrew from study participation because of side effects. Two subjects were receiving methylphenidate; 2 subjects, pemoline; and 1 subject, placebo. One of the 2 patients prescribed methylphenidate cited excessive jitteriness as the primary reason for study withdrawal after 4 weeks. The second patient, who withdrew during the final week of study participation, cited a combination of symptoms including dry mouth, rapid heartbeat, difficulty sleeping, and hyperactivity. One of the 2 patients receiving pemoline, who withdrew after 2 weeks of study participation, complained of neuropathic pain that he attributed to the study medication. One patient prescribed placebo, who withdrew because of intolerable side effects after 5 weeks of study participation, complained of constipation and hyperactivity.

With regard to the overall rate of side effects experienced by subjects in the 3 treatment arms, the most commonly reported side effects were those related to hyperactivity and jitteriness (Table 3). In fact, the only side effect that differed (in prevalence) significantly across the 3 treatment arms was a summary variable consisting of both symptoms. Nearly half of the subjects receiving methylphenidate and pemoline reported experiencing one or both of these symptoms, whereas only one quarter of the subjects receiving placebo reported such symptoms ($\chi^2=6.96$; $n=131$ [$P=.04$]). There were no other significant differences ($P<.05$) across the 3 treatment arms in the rates of any side effects or symptoms (including other summary variables corresponding to sleep and gas-

![Figure 2. Improvement in fatigue over time, measured by means of the Piper Fatigue Scale.](image)

![Figure 3. Improvement in fatigue over time, measured by means of the Visual Analog Scale for Fatigue (VAS-F).](image)
given the frequency with which patients complained of feeling jittery or hyperactive, we examined the dosages at which these symptoms occurred and whether they responded to decreases in dosage or went away without any dosage change. Of those subjects reporting jitteriness as an side effect of medication, the average dosage at which subjects experienced this symptom was 35.36 mg/d (range, 15-60 mg/d) of methylphenidate. Eight of the 14 subjects in the methylphenidate arm who reported jitteriness experienced symptom relief, despite increasing their methylphenidate dosage, whereas an additional 2 subjects experienced relief at the same dosage at which the symptom started. Only 1 subject experienced symptom relief when the dosage was decreased, and an additional 3 subjects reported continued jitteriness despite medication changes. The average dosage at which hyperactivity was experienced was 35.00 mg/d (range, 15-60 mg/d), with 5 of these 11 subjects reporting symptom relief despite dosage increases. An additional 3 subjects reported symptom relief at the same dosage at which the symptom started, whereas 3 subjects required dosage decreases to alleviate their hyperactivity, and 1 subject did not experience any relief from this symptom.

Among subjects in the pemoline group, the average dosage at which jitteriness was experienced was 69.89 mg/d (range, 37.5-150 mg/d). Of the 11 subjects reporting this side effect, 10 experienced symptom relief despite equal or increased dosages of this medication, whereas one subject did not experience any symptom relief despite a reduction in dosage. The average dosage at which subjects in the pemoline group reported hyperactivity was 45.54 mg/d (range, 37.5-56.25 mg/d). Of the 7 subjects reporting this side effect, 6 experienced symptom relief despite equal or higher dosages of pemoline, whereas 1 subject required a decrease in dosage (from 56.25 mg/d to 37.5 mg/d) to alleviate hyperactivity. Data regarding the dosage of placebo at which side effects occurred were not analyzed.

**IMPACT OF TREATMENT ON PSYCHOLOGICAL DISTRESS AND QOL**

There were significant correlations between the change scores derived from baseline and end-of-study fatigue ratings (eg, degree of improvement in fatigue) and improvement in most measures of psychological functioning and QOL. As displayed in Table 4, changes in BDI scores were significantly correlated with improvement on the PFS (r = 0.41 [P < .001]) and VAS-F (r = 0.34 [P < .001]) total scores.
scores, indicating that as overall ratings of fatigue severity decreased, levels of depressive symptoms also decreased. The fatigue subscales most highly correlated with improvement in depressive symptoms were the severity and cognitive subscales of the PFS ($r=0.43$ and $r=0.38$, respectively) and the energy subscale of the VAS-F ($r=0.42$). The PFS affective and sensory subscales were less highly correlated with improvement on the BDI ($r=0.29$ and $r=0.30$, respectively) as was the VAS-F energy subscale ($r=0.09$).

Similarly, change scores derived from BSI Global Distress Index were significantly correlated with improvement on the PFS and VAS-F total scores ($r=0.37$ [P<.001] and $r=0.27$ [P<.001], respectively). The strongest correlations between fatigue improvement and reduced psychological distress were observed for the severity and cognitive subscales of the PFS ($r=0.34$ and $r=0.45$, respectively), whereas the PFS sensory and affective subscales and the VAS-F fatigue and energy subscales were less highly correlated ($r=0.30$, $r=0.22$, $r=0.28$, and $r=0.18$, respectively). Finally, improved overall QOL, as measured by many of the Medical Outcomes Study Health Status Survey subscales, were significantly correlated with changes in both the PFS and VAS-F total scores (Table 4). The strongest correlations between improved fatigue and changes in QOL were observed in the role functioning subscale ($r=0.32-0.48$ for 7 of 8 fatigue self-reported measures), indicating that improved fatigue had the strongest effect on physical activity.

This study, which to our knowledge represents the first double-blind placebo-controlled trial of psychostimulants for the treatment of fatigue in patients with HIV, demonstrates that many patients with HIV- and AIDS-related fatigue respond favorably to treatment with methylphenidate or pemoline. Both psychostimulants appear to be equally effective and significantly superior to placebo in decreasing fatigue severity with minimal side effects. Moreover, improved fatigue was significantly associated with improved QOL and decreased levels of depression and psychological distress. Thus, effective treatment for fatigue in patients with HIV disease is available and may offer substantial benefits for overall QOL in many patients. The use of psychostimulants in the clinical management of fatigue in patients with HIV disease is most appropriate as part of a comprehensive approach. This approach would include the identification and treatment of AIDS-related conditions that can cause fatigue, such as anemia, as well as the judicious use of combination antiretroviral therapies to reduce viral load and restore immune function.14

The degree of improvement due to psychostimulants, however, was not uniform across all measures of fatigue. The strongest, most consistent, and most statistically significant group differences were evident on our primary dependent variable, the PFS, a multidimensional self-reported scale that had the most extensive validation data of any fatigue measurement tool available. Somewhat more modest results were obtained using the VAS-F, a brief self-reported rating scale with somewhat less extensive validation data relative to the PFS. We found no evidence of a treatment effect on the physiological measurement used, the timed isometric unilateral straight leg-raising task. Despite these seemingly mixed results, we believe that these data nevertheless demonstrate a clinically and statistically significant treatment effect for psychostimulants compared with placebo, because significant results were obtained with the most reliable measures of fatigue used. Significant results were obtained for the total PFS score and 2 of the 4 PFS subscales (affective and sensory), as well as 1 of the 2 VAS-F subscales (energy). The remaining self-reported scales all followed a similar pattern, some of which approached statistical significance, supporting the conclusion that psychostimulants were effective in reducing fatigue. The only exception to this pattern emerged with our measure of muscular endurance, the timed isometric unilateral straight leg-raising task. Because this task simply measures the length of time patients can suspend their leg in the air, it is likely influenced by many factors other than fatigue (eg, degree of effort, motivation, physical discomfort, and strength). Although physiological measurements to assess fatigue are clearly desirable in fatigue intervention research, this task may be an inadequate and unreliable method for assessing fatigue.

The other factor that likely influenced the extent of significant findings observed was the sizable placebo effect evident in our data. Despite taking an inactive substance, this group demonstrated a rapid and consistent reduction in fatigue symptoms that, although somewhat less than that of subjects taking active medication, was nevertheless substantial. In fact, examination of the longitudinal data (Figures 1 and 2) reveals a substantial (and comparable) decrease in fatigue during the first week of study participation. During subsequent weeks, however, patients receiving active medication appear to have continued improvement, whereas no such pattern was evident for the placebo group (this pattern is most clearly evident in the PFS data displayed in Figure 1). Support for this apparent placebo effect is also demonstrated by the finding that most patients taking placebo believed that they were taking 1 of the 2 active medications and reported side effects (from placebo) that were roughly comparable to those reported by patients receiving active medication. Given the pattern of improvement described above, it may be that a longer study period is necessary to assess whether placebo-induced benefits can be maintained.

The nature and frequency of side effects among patients receiving placebo was not substantially (or significantly) different from those reported by patients receiving active medication. This finding, as well as the relatively mild nature of side effects reported, is particularly noteworthy given the extent of medical illness present in our study population. Of more than 135 patients treated in this study, only 5 withdrew because of intolerable side effects, and 1 of these 5 patients had received an inactive placebo. Of those side effects reported, the most common (and only side effects that were significantly more prevalent among patients receiving active medication) were jitteriness and hyperactivity, both of which are common side effects of psychostimulants. Although several other side effects occurred slightly more often among patients prescribed methylphenidate or pemoline, these diff-
ferential prevalence rates were small and not statistically significant. There have been no reports in the literature to date of any adverse effects of psychostimulants such as methylphenidate on immune function or disease progression in patients with HIV disease. Moreover, although recent concerns have been raised regarding the risk for acute liver failure in patients treated with pemoline, we observed no such reactions in our sample. Nevertheless, given the possibility of such adverse effects, clinicians should be aware of the Food and Drug Administration recommendations for informed consent when prescribing pemoline.37

One obvious confounding factor in this study concerns the possibility that the improvement in fatigue attributed to psychostimulant medications was in fact due to an antidepressant effect. Methylphenidate and pemoline have been noted to alleviate depressive symptoms in patients with medical illness,38–40 and fatigue is, of course, a common symptom of depression. Thus, the apparent benefits attributed to psychostimulants might reflect a more indirect influence of these medications on the patient’s depressive symptoms rather than a direct effect on fatigue. Of course, patients with a major depressive disorder were excluded from study participation specifically to minimize the possibility of such a confound; however, many study participants had some degree of depressive symptoms. The confound of antidepressant and antifatigue effects is further clouded by our observation that the strongest impact of medications was on the affective subscale of the PFS, presumably reflecting the fatigue items with the highest correspondence to mood. Given the multidimensional nature of fatigue, it is perhaps not surprising that psychostimulants would have the strongest effect on the affective dimension of fatigue. On the other hand, improvement in depressive symptoms (and other QOL measures) was less highly correlated with the affective subscale of the PFS, and much more highly correlated with overall fatigue improvement (total scores on the PFS and VAS-F) and fatigue severity (ie, the severity subscale of the PFS). Thus, it appears likely that the antidepressant effects observed were more likely to reflect the positive impact of decreased fatigue severity rather than a more direct antidepressant effect of these medications.

Despite the encouraging results described herein, a number of limitations must be acknowledged in this study. First, the time frame used to study treatment effects (6 weeks) limits any assessment of whether continued treatment with psychostimulants would result in a further decline in fatigue symptoms or even a maintenance of those gains achieved. Although we might speculate that continued treatment would result in sustained or even additional improvement in fatigue for patients actually taking medications, but that these gains might gradually erode in patients taking a placebo, such speculation is untested. However, to our knowledge, this 6-week study represents the longest trial of psychostimulants published to date in the literature. It is also possible that patients with HIV or AIDS might develop a tolerance for psychostimulant medications and therefore would need higher dosages to achieve the same level of symptom relief, or even show a resurgence of fatigue despite continued treatment. Alternatively, the possibility of long-term adverse effects from these medications could not be assessed in this study, given the 6-week treatment period. Systematic long-term studies of these medications are necessary to evaluate the long-term effects of these medications.

A second limitation of this study concerns the ambulatory status of study participants. Since all subjects were living independently at the time of participation, we had limited ability to monitor subject compliance with the treatment regimen. Although our weekly pill counts demonstrated a high degree of adherence to the protocol, it is nevertheless possible that unacknowledged missed doses or refusal to titrate the medications despite recommendations from study personnel might have resulted in somewhat more modest benefits from treatment than would be observed in a more structured setting (eg, an inpatient unit or long-term care facility). Of course, although imperfect as a method of determining treatment efficacy, our study method accurately mimics the real-world conditions for most potential treatment subjects. Patients living at home or outside of institutions are likely to be faced with daily dilemmas regarding whether they wish to take an additional medication to combat yet another symptom of the illness. Although not analyzed systematically, a number of subjects expressed reluctance to continue taking study medications once the trial had ended, despite reporting substantial improvement. These impediments to adequate symptom control are often neglected, yet may exert considerable influence on which symptoms are addressed and which are not. Further research into patient attitudes toward fatigue and the barriers to adequate treatment may help elucidate these issues.

A final limitation in this study concerns the sample size and rate of dropout. Our modest sample size (n=109) may have failed to detect meaningful differences between the 2 active treatments. Although some differences in treatment response were evident (Table 2) and may have been statistically significant with a larger sample, the magnitude of these group differences was quite modest (ie, a small-effect size). In addition, because a substantial number of patients terminated the study prematurely (Figure 1), it is unknown whether these patients biased the outcome in any meaningful way.

Despite the limitations described above, this study reflects the first empirical demonstration of the effectiveness of psychostimulants for the treatment of HIV-related fatigue. This common and distressing symptom responded quickly and substantially for most subjects, with relatively few troublesome side effects. Thus, it appears that fatigue cannot only be treated safely and effectively in patients with HIV, but that adequate treatment has a dramatic impact on QOL and psychological well-being. Given the overwhelming number of stressors faced by patients with HIV and AIDS, the ability to adequately resolve even one common and distressing symptom appears worthwhile and necessary.

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