Modafinil Treatment for Fatigue in HIV+ Patients: A Pilot Study

Judith G. Rabkin, Ph.D., M.P.H.; Martin C. McElhiney, Ph.D.; Richard Rabkin, M.D.; and Stephen J. Ferrando, M.D.

Background: Fatigue is widespread among human immunodeficiency virus–positive (HIV+) patients, yet few studies have assessed effective treatments. The authors conducted a pilot study to evaluate the efficacy of modafinil for fatigue in this clinical population.

Method: Response was evaluated after a 4-week open-label trial. Data were collected from February 2003 through January 2004. Responders were offered 8 additional weeks of modafinil. Inclusion criteria included written approval from the primary care physician, clinically significant fatigue, current use of antiretroviral medications, and the absence of treatable medical conditions known to cause fatigue. Exclusion criteria included untreated major depression and current substance abuse. Major outcome measures were the Fatigue Severity Scale, Chalder Fatigue Scale, Hamilton Rating Scale for Depression, Beck Depression Inventory, and neuropsychological tests assessing verbal memory, speed of processing, and executive function. Immunologic and virologic measures were performed at baseline and week 4 to assess safety of treatment.

Results: All 30 patients who enrolled completed 4 weeks of treatment; 24 (80%) were rated as responders. Responders showed statistically significant improvement on all measures of fatigue, depressive symptoms, and executive function, while nonresponders did not. Mean values of CD4 cell count and HIV RNA viral load did not change. The most common side effect was headache, followed by irritability and feeling "hyper."

Conclusion: This pilot study shows encouraging results for modafinil in alleviation of fatigue in HIV+ patients. In addition, depressive symptoms were substantially reduced. Improvements on measures of verbal memory and executive function were significant, but in the absence of a placebo control, the magnitude of effect due to practice cannot be determined.

(J Clin Psychiatry 2004;65:1688–1695)

Received March 16, 2004; accepted May 3, 2004. *From the New York State Psychiatric Institute (Drs. J. G. Rabkin, McElhiney, and R. Rabkin); the Department of Psychiatry, Columbia University (Drs. J. G. Rabkin and McElhiney); and the Department of Psychiatry, Weill Medical College of Cornell University (Dr. Ferrando), New York, N.Y.*

The authors report no financial affiliation or other relationship relevant to the subject matter of this article.

The authors thank Deborah Henninger, M.A., for assistance with the conduct of neuropsychological tests.

Corresponding author and reprints: Judith G. Rabkin, Ph.D., New York State Psychiatric Institute, Unit 51, 1051 Riverside Drive, New York, NY 10032 (e-mail: jgr1@Columbia.edu).

Fatigue is a pervasive and clinically significant problem for a substantial number of human immunodeficiency virus–positive (HIV+) adults, secondary to the virus, the antiretroviral medications that today prolong survival and protect health, or associated health problems or treatments for HIV infections. Estimates of fatigue prevalence in HIV+ samples cluster around 40% and rise to over 50%.[1–3] Fatigue in HIV/acquired immunodeficiency syndrome (AIDS) has substantial behavioral impact in terms of reduced capacity for meaningful engagement and restricted activity levels that contribute to social isolation.[4] It is a common reason for leaving work and going on disability as well as an inability to return to work even when medical status is otherwise stabilized. It may also interfere with medication adherence, including doses missed due to falling asleep prematurely or sleeping through a scheduled dose.[5,6] Overall, persistent fatigue in HIV is prevalent and can be disabling.

Medical conditions commonly found in HIV+ patients that often contribute to or directly cause fatigue include anemia, liver pathology and its treatment, and hypogonadism. Medications including most protease inhibitors and efavirenz, a currently recommended first-line treatment medication, list fatigue as a known side effect. Opiates used for pain may also play a causal role.

The considerable overlap between symptoms of fatigue and depression is to some extent circular in that fatigue is one of the criteria for major depressive disorder (DSM-IV) and is also associated with subjective neurocognitive complaints such as poor concentration, which is another DSM-IV criterion for major depressive disorder. There may be a reverse causal effect as well; when fatigue restricts activities and exposure to pleasant events, reduces social interactions, and leads to long days alone at home, depressed mood is a likely consequence. When symptoms of depression and fatigue co-occur, patients often insist that their sadness, loss of interest, and poor concentration are secondary to fatigue.

Both fatigue and mild cognitive impairment are common in HIV+ patients, but the nature of this relationship has been difficult to define. In medically healthy subjects, research has shown that fatigue diminishes cognitive performance.[7,8] Among patients with HIV/AIDS, the evidence is mixed.[9] What is consistently found is that pa-

tients reporting fatigue often cite impaired concentration; inability to sustain attention, which can affect new learning and memory; and a general cognitive haziness.

Previous placebo-controlled clinical trials for fatigue in HIV+ patients evaluated methylphenidate, pemoline, and dextroamphetamine.[10–12] All active drugs were superior to placebo. Testosterone also has been shown useful in treating fatigue in HIV+ men,[13,14] although in these studies fatigue was an ancillary rather than a primary presenting problem among men with hypogonadal symptoms. While these treatments appear to be helpful, they have significant limitations in terms of access, suitability, and concern over abuse liability.

Modafinil is a wake-promoting agent approved for the treatment of narcolepsy, work shift–related sleep disorders, and obstructive sleep apnea. While the exact mechanism of its wake-promoting activity is unknown, it appears to involve different neurochemical and neuroanatomical substrates than either antidepressants or psychostimulants.[15–18] Modafinil's primary metabolic pathway proceeds by way of esterase enzymes. Cytochrome P450 (CYP) is a weak secondary pathway, and modafinil may have weak inducer as well as inhibitory effects in drug interactions.[19] Its advantages over other stimulant treatments include its classification as a Schedule IV rather than Schedule II drug since it has a low addiction potential[20] and reduced likelihood of adverse events.[21] It does not cause euphoria or lead to dose acceleration, tolerance, or rebound sleepiness.[15] Modafinil has been shown to enhance the cognitive dimension of executive function in a variety of populations, including normal volunteers.[16,22]

In other medical conditions, modafinil has been found helpful in treating fatigue in patients with multiple sclerosis,[23] Parkinson's disease,[24] and myotonic dystrophy.[25] A placebo-controlled trial of modafinil as augmentation for patients with major depression and partial response to antidepressant treatment found more rapid improvement among patients randomly assigned to modafinil after 1 week (sleepiness) and 2 weeks (fatigue), but the differences at week 6 were not statistically significant.[26]

The current pilot study was designed to assess the effects of modafinil on (1) fatigue, (2) depressive symptoms, (3) immunologic/virologic status as proxies for assessing drug interactions, and (4) neuropsychological function. The design follows that of other modafinil studies with the exception that the daily starting dose was 50 mg rather than the usual 100 or 200 mg, and the maximum dose was 200 mg/day rather than 400 mg/day to limit the risk of drug interactions.

METHOD

Sample

Eligible patients were HIV+ and aged 21 to 75 years, had clinically significant fatigue as defined by interference with activities of daily living including employment, and gave informed consent, and their primary care providers (PCPs) agreed in writing to their study participation. Exclusion criteria included unstable medical condition, untreated conditions associated with fatigue, change in antiretroviral medications in the past month or initiation of antidepressant medication in the past 2 months, and untreated major depressive disorder. A complete list of exclusion criteria is presented in Table 1.

Table 1. Study Inclusion and Exclusion Criteria

Inclusion criteria
HIV+ and age 21–75
Clinically significant fatigue
Primary medical provider gives written approval for study participation
Able and willing to give informed consent
Exclusion criteria
Unstable medical condition (eg, liver failure, cirrhosis, new onset opportunistic infection in past month)
Untreated hypogonadism (serum testosterone level below the Quest reference range)
Untreated hypothyroidism (TSH > 5 mIU/mL)
Uncontrolled hypertension
Clinically significant anemia (hematocrit < 30%)
Started or changed steroids during the past 3 weeks
Started or changed antiretroviral regimen during the past month
Started antidepressant medication during the past 2 months
Untreated major depressive disorder
Significant insomnia (score of ≥ 4 on 3 HAM-D insomnia items)
Meets criteria for current substance abuse/dependence (past 4 months)
Frequent marijuana use (more than twice per week, regularly)
Current clinically significant suicidal ideation or HAM-D score > 24
Schizophrenia or bipolar disorder
Currently pregnant or breastfeeding
Fecund woman not using barrier methods of contraception

Abbreviations: HAM-D = Hamilton Rating Scale for Depression, HIV = human immunodeficiency virus, TSH = thyroid-stimulating hormone.

Study Design

This was a 4-week open-label pilot study. Patients were initially evaluated, including medical and psychiatric history and current medications; blood work was performed to determine eligibility; and a letter was faxed to the PCP describing the study and requesting signed agreement for participation. This is done routinely in our studies, so that the PCP knows about and approves our treatment. Because of the theoretical risk of drug interactions, the PCP's approval was considered particularly important. Eligible patients were then seen by the study psychiatrist (R.R.) at baseline when neuropsychological tests were administered and at weeks 1, 2, and 4. Medication was dispensed by the physician at each visit, and patients were asked to return unused tablets at the next visit. They were instructed not to start any other treatment for fatigue, including initiating steroids, during the trial. If their HIV medications were changed by their physician, they were asked to inform us at the next study visit.

At the end of 4 weeks, patients completed self-ratings of fatigue and mood, and then the study psychiatrist and patient together determined whether modafinil made a significant difference in fatigue. Neuropsychological tests were again administered. Responders were offered 8 more weeks of treatment with visits every other week. Starting modafinil dose was 50 mg/day for 1 week, increased in the absence of sufficient clinical response and dose-limiting side effects to a maximum of 200 mg/day by the end of week 2. Laboratory tests were performed at study baseline and weeks 4 and 8. Partway through the study, an additional assay for HIV RNA viral load was added at week 12. The protocol was approved by the New York State Psychiatric Institute Institutional Review Board, and all participants gave written informed consent after being informed of the procedures, risks, and alternatives to study participation. Data were collected from February 2003 through January 2004.

Measures

Fatigue. (Note: Higher scores indicate greater fatigue in all cases.) Nearly all modafinil trials have used the 9-term self-rated Fatigue Severity Scale (FSS),[27] which measures the impact of fatigue on everyday functioning. Scores for individual items range from 1 to 7; the final score is the item average. A change in score of 0.5 or greater is considered clinically significant. The Epworth Sleepiness Scale[28] is also widely used in modafinil trials and inquires about the probability of dozing in various settings. Total scores are the sum of item scores and range from 0 to 24. In addition, we used the 7-item physical fatigue subscale of the Chalder Fatigue Scale,[29] which our group has previously found useful for assessing fatigue in HIV+ patients. Likert response options range from 1 to 5, and items are summed for a total score.

The dependent variable in assessing fatigue was a global clinician rating using the Clinical Global Impressions (CGI) scale[30] (described below) based on the patient's report, FSS score decline, and the clinician's judgment.

Depression. The psychotic screen, substance use disorders screen, and depression and bipolar disorder modules of the Structured Clinical Interview for DSM-IV (SCID)[31] were used to determine study eligibility. The Structured Interview Guide for the 21-item Hamilton Rating Scale for Depression (HAM-D)[32] is a clinician-rated scale to assess depressive severity, combining both severity and frequency. The Beck Depression Inventory II (BDI)[33] is a 21-item self-report scale used to provide patient perspective on depressive symptoms. The Clinical Global Impressions-Severity of Illness scale was used at baseline, and the 7-point Clinical Global Impressions of Change scale was used at subsequent visits. The rating of "responder" was defined as a CGI Improvement score of "much improved" or "very much improved" (score of 2 or 1, respectively) at week 4. The clinician judgment of improvement in depression (CGI scores of 1 or 2) was based on clinical interview and HAM-D and BDI scores.

Side effects were measured at every study visit with a checklist modeled on SAFTEE (Systematic Assessment for Treatment Emergent Events),[34] a comprehensive assessment of treatment-emergent side effects. Each item, if present, is scored on a 5-point severity scale. A side effect was considered "treatment emergent" if the score at subsequent study visits was ≥ 2 points higher than at baseline.

Neuropsychological tests. These included the Rey Auditory Verbal Learning Test (RAVLT)[35] assessing verbal memory, the digit symbol coding subtest of the Wechsler Adult Intelligence Scale (WAIS)-III[36] and Color Trails 1[37] to assess processing speed, Color Trails 2[37] and Stroop Color and Word Test[38] to assess executive function, Grooved Pegboard[39] to assess manual dexterity, and CalCap[40] to assess categories of reaction time.

Laboratory tests. These included hematology, serum chemistry, thyroid panel, CD4 cell subsets, and an ultrasensitive HIV RNA viral load assay (detectable range, 50–100,000 copies) performed at baseline and week 4. Clinically significant change was defined as a change of ≥ 100 cells in CD4 cell count or ≥ 0.5 log in viral load copies. While CD4 counts seldom change rapidly, viral load copies can show major changes within days. Since modafinil reaches steady state within 3 weeks, the week 4 assay was expected to capture change, if any, due to drug interactions. Another HIV RNA viral load assay was added to the protocol at week 12 partway through the study. Urine toxicology screens were performed at initial evaluation and at a random study visit.

Statistical Analysis

Responders and nonresponders were compared using χ^2 tests and t tests for categorical and continuous variables, respectively. Change over time was assessed using analysis of covariance with baseline scores as the covariate. All patients were included in analyses since there was no attrition, but there are some missing data for neuropsychological tests: 1 patient was blind, and the CalCap was added after the trial began. Following convention, $\log_{10}$ viral load was used, conservatively entering "1.69" when the result was "under 50 copies (= 1.70 $\log_{10}$ copies)," which is the assay's limit of detectability. All tests were 2-tailed, $\alpha = .05$.

RESULTS

Sample Characteristics

Forty-one patients were evaluated, and 30 entered the study. Among the 11 who did not enter the study, 2 chose not to do so and 9 were ineligible (medically unstable, using drugs, untreated major depression, psychotic symptoms, fatigue not clinically significant). All 30 completed

Table 2. Baseline Demographic, Medical, and Psychiatric Characteristics of HIV+ Patients With Clinically Significant Fatigue

Characteristic	All Patients (N = 30)	Responders (N = 24)	Nonresponders (N = 6)	t or χ^2	p
Demographic					
Age, mean (SD), y	47 (6.7)	46 (7.2)	51 (2.3)	–2.621	.015
Ethnicity, N (%)					
White	16 (53%)	11 (46%)	5 (83%)		
Hispanic	7 (23%)	6 (25%)	1 (17%)		
Black	7 (23%)	7 (29%)	0	3.158	.206
Men, N (%)	28 (93%)	22 (92%)	6 (100%)	0.536	.464
Risk factors, N (%)					
MSM	23 (77%)	17 (71%)	6 (100%)		
IDU	2 (7%)	2 (8%)	0		
Heterosexual	5 (17%)	5 (21%)	0	2.283	.319
Education, N (%)					
Less than high school/GED	3 (10%)	2 (8%)	1 (17%)		
High school graduate	1 (3%)	0	1 (17%)		
Some college	12 (40%)	11 (46%)	1 (17%)		
Finished college or more	14 (47%)	11 (46%)	3 (50%)	6.979	.323
Medical					
Baseline CD4 cell count, mean (SD)	488 (292)	468 (281)	642 (347)	–1.300	.204
CDC AIDS diagnosis, N (%)	22 (73%)	19 (79%)	3 (50%)	2.088	.148
No. of ART medications, mean (range)	3.4 (2–5)	3.5 (3–5)	3.2 (2–4)	1.079	.290
Baseline $\log_{10}$ HIV RNA, mean (SD)	2.26 (.85)	2.32 (.92)	2.02 (.37)	0.767	.449
Psychiatric					
Current Axis I diagnosis, N (%)	21 (70%)	16 (67%)	5 (83%)	0.635	.426
Dysthymia	12 (40%)	9 (38%)	3 (50%)		
MDD	1 (3%)	1 (4%)	0		
MDD in partial remission	2 (7%)	2 (8%)	0		
Minor depressive disorder	6 (20%)	4 (17%)	2 (33%)	2.049	.727

Abbreviations: AIDS = acquired immunodeficiency syndrome, ART = antiretroviral therapy, CDC = Centers for Disease Control and Prevention, HIV = human immunodeficiency virus, IDU = injecting drug use, MDD = major depressive disorder, MSM = men having sex with men.

the 4-week trial. Demographic, medical, and psychiatric characteristics are summarized in Table 2. Patients were in general middle-aged (mean age = 47 years); 23% were Hispanic, 23% black, and 53% white; and 93% were men. All but 4 patients had completed at least some college.

At baseline, mean CD4 cell count was 488 (SD = 292), and 73% of patients had an AIDS diagnosis according to Centers for Disease Control and Prevention (CDC) criteria. They had known their HIV status for an average of nearly 12 years (range, 24–216 months). They had been taking combination antiretrovirals for over 5 years on average (range, 13–120 months). Mean hematocrit was 45% (range, 32%–55%, with high values associated with concurrent steroid use). Five patients (17%) had hepatitis C, but none was currently in treatment. All were taking various combinations of 16 antiretroviral medications (range, 2–5 per patient), and of these regimens, 47% (14) included a protease inhibitor. Seventy percent had a current (past month) depressive disorder including major depression in partial remission, dysthymia, or minor depression. One third were currently taking antidepressants, and 43% (12/28) of the men were currently receiving testosterone (usually the gel preparation).

Responders differed from nonresponders in age; they were slightly younger. Nonresponders were also more likely to be taking antidepressant medication (5/6 vs. 5/24, Fisher exact test [FET] = .018) and testosterone (5/6 vs. 7/24, FET = .051). As determined by the baseline neuropsychological test battery, 28% (8/29) of the whole sample had at least mild cognitive impairment, defined as scoring at least 2 SDs from the mean on 2 or more nonredundant tests (that is, we do not count more than 1 subscale of a given test in this definition).

Final Dose

As noted above, the starting dose of 50 mg/day of modafinil is lower than that indicated in the package insert. The final mean dose for responders was 135 mg/day, and for nonresponders, 158 mg/day. Two patients responded at 50 mg/day, 13 at 100 mg/day, and 9 at 200 mg/day. Among nonresponders, 2 could not tolerate more than 100 mg/day and 4 did not improve at 200 mg/day. For the latter group, dose was not increased to 400 mg/day (as indicated in the package insert) because of concern about possible interactions with antiretroviral medications.

Treatment Outcome: Fatigue

At week 4, 80% (24/30) of patients were responders, based on CGI ratings of 1 or 2 and patient-clinician consensus. Patients were extremely clear about whether or not modafinil was helpful: there was no ambiguity in their

Table 3. Fatigue and Depression Measures at Baseline and Week 4[a,b]

Measure	Responders (N = 24)	Nonresponders (N = 6)	t or F	p
Fatigue				
Fatigue Severity Scale score				
Baseline	6.0 (0.8)	5.5 (0.8)	1.251	.221
Week 4	4.2 (1.5)	5.6 (0.9)	4.279	.048
Chalder Fatigue Scale score				
Baseline	3.7 (0.5)	3.8 (0.7)	–0.298	.768
Week 4	2.4 (0.8)	3.7 (0.6)	11.993	.002
Epworth Sleepiness Scale score				
Baseline	14.8 (4.0)	13.0 (5.0)	0.914	.368
Week 4	7.7 (5.3)	12.3 (4.0)	5.492	.027
Depression				
Beck Depression Inventory score				
Baseline	26 (11)	27 (14)	–0.170	.866
Week 4	10 (7)	26 (16)	14.288	.001
HAM-D score				
Baseline	11 (5)	10 (4)	0.298	.768
Week 4	4 (4)	8 (6)	7.270	.012

[a]All scores are mean (SD).
[b]All week 4 analyses controlled for baseline measure.
Abbreviation: HAM-D = Hamilton Rating Scale for Depression.

reports. Responders had higher baseline fatigue scores and showed both statistically and clinically significant improvement on the FSS, while the mean score for nonresponders actually increased (more fatigued). Controlling for baseline scores, responders showed more improvement than nonresponders on all 3 fatigue measures (Table 3). Eight (89%) of 9 patients without a depression diagnosis and 16 (76%) of 21 patients with a depression diagnosis were responders. Of the 24 responders at week 4, 20 completed 12 weeks of treatment and all but 1 maintained their response. At study termination, they were referred back to their PCP for maintenance treatment as insurance permitted. The others ended the study at week 4 for one of the following reasons: started working full-time, intercurrent illness, probable drug relapse, or to start another treatment.

Treatment Outcome: Depression

Patients who were responders in terms of fatigue showed significantly more improvement on measures of depression than did fatigue nonresponders (Table 3). Among responders, mean self-report BDI scores declined from 26 to 10, while for nonresponders, BDI scores went from a mean of 27 to a mean of 26 at week 4. HAM-D scores also showed clinically and statistically significant declines for responders but not nonresponders. These analyses were repeated after deleting the fatigue items from both measures, with the same results (data not shown). When we examined change scores on the BDI and HAM-D only for the 20 patients who had a current depression diagnosis at study baseline, responders had greater declines on both the full and adjusted HAM-D ($F = 5.97$, $df = 1$, $p = .026$ and $F = 3.74$, $df = 1$, $p = .07$, respectively) and full and adjusted BDI ($F = 13.33$, $df = 1$, $p = .002$ and $F = 11.73$, $df = 1$, $p = .003$, respectively).

Relationship Between Fatigue and Depression

Excluding 6 patients with HAM-D scores in the "not depressed" range (< 8) at baseline, 17/24 (71%) of fatigue responders were also "depression responders," while 2 fatigue nonresponders reported improved mood (FET = .08). Two patients whose mood improved continued to have fatigue, and 3 patients remained unimproved in either category.

Treatment Outcome: Neuropsychological Function

As shown in Table 4, statistically significant improvement was observed on measures of memory (RAVLT), speed of processing (WAIS-III digit symbol-coding), and executive function (Stroop Color and Word Test and Color Trails 2). On a computerized task of reaction time (CalCap), 1 of 4 measures showed significant improvement. No change was observed on the Grooved Pegboard Test. Overall, modafinil appears to improve cognitive function, but the magnitude of effect cannot be determined in the absence of placebo controls.

Effect of Modafinil on CD4 Cell Count and HIV RNA Log Viral Load

As shown in Table 5, mean baseline CD4 count did not change between baseline and week 4. Mean $\log_{10}$ viral load copies were calculated excluding 1 patient whose viral load was above the upper limit of the assay of 100,000 copies at both baseline and week 4. For the remaining patients, mean change over time was not significant. With respect to individual changes in viral load copies, 5 patients showed a clinically significant decline (defined as at least 0.5 log change), signifying reduced viral burden, while 2 patients had a clinically significant increase and the remainder did not change.

Table 4. Neuropsychological Test Results at Baseline and Week 4: Paired t Tests[a]

Test	Baseline	Week 4	t	df	p
Rey Auditory Verbal Learning Test					
Total trials 1–5	46 (8)	53 (10)	–4.815	25	< .001
WAIS-III					
Digit symbol-coding	67 (17)	74 (15)	–5.020	25	< .001
Digit span	16 (4)	16 (4)	–0.632	22	.534
Color Trails Test					
Color Trails 1	39 (18)	40 (19)	–0.374	25	.711
Color Trails 2	95 (34)	86 (30)	2.138	25	.043
Stroop Color and Word Test					
Words	96 (19)	103 (18)	–4.038	25	< .001
Colors	65 (14)	70 (13)	–3.670	25	.001
Color-Words	39 (8)	44 (10)	–3.628	25	.001
Interference	0.7 (5.7)	2.0 (6.8)	–0.885	25	.385
Grooved Pegboard					
Dominant hand	68 (13)	68 (13)	–0.140	24	.890
Nondominant hand	78 (22)	74 (20)	1.534	24	.138
CalCap					
Simple reaction time	463 (245)	378 (59)	1.649	21	.114
Choice reaction time	436 (43)	425 (42)	1.303	21	.207
Sequential reaction time 1	565 (90)	530 (82)	2.633	21	.016
Sequential reaction time 2	654 (101)	660 (103)	–0.249	21	.806

[a]All baseline and week 4 values are mean (SD).
Abbreviation: WAIS-III = Wechsler Adult Intelligence Scale-III.

Table 5. CD4 Cell Count and HIV RNA Viral Load at Baseline and Week 4[a]

Measurement	Baseline	Week 4	t	p
CD4	488 (292)	473 (227)	0.616	.543
HIV RNA viral load[b]	754 (1953)	728 (2262)	0.151	.881
Log_{10} HIV RNA viral load[b]	2.16 (0.68)	2.12 (0.65)	0.760	.454

[a]All baseline and week 4 values are mean (SD).
[b]Excluding 1 patient with baseline and week 4 viral load > 100,000 copies (upper limit of assay).
Abbreviation: HIV = human immunodeficiency virus.

Thirteen patients had week 12 viral load assays performed. Mean baseline was 2.13 log_{10} copies, and 2.01 log_{10} copies at week 12. Change from baseline was not significant (paired t test = –1.6, df = 12, p = .13). One patient showed a clinically significant decrease in number of viral copies, 2 showed an increase, and 10 did not change.

Treatment-Emergent Side Effects

Five adverse events were reported during the first 4 weeks: headache (6/30), irritability and insomnia (4/30 each), nervousness or feeling "hyper" (3/30), and nausea (2/30). Only irritability was reported between weeks 5 and 12, and that was 1 patient on a single occasion. The maximum number of consecutive study visits that occurred was 3 visits for nervousness and irritability, 2 visits for headaches and insomnia, and 1 visit for nausea.

DISCUSSION

In this open-label trial of modafinil for HIV+ patients with clinically significant fatigue, often accompanied by non–major depression, response rate was 80%. All 30 patients completed the 4-week trial, and of the responders, 83% completed 12 weeks. Typically, the outcome was decisive: patients reported either no apparent effect or an immense impact. By the end of the 12-week trial, 5 patients started working again, 2 others increased their hours of work, and 2 enrolled in vocational training programs. This is noteworthy given the rarity of return to work by HIV+ patients who have stopped or significantly reduced their hours of employment.[41]

The association between fatigue and depressive symptoms is strong but not universal. Two patients reported improved energy but remained depressed. More typically, dramatic changes in energy level were accompanied by remission of depressive symptoms. An extreme example is that of a pharmacist who had stopped working and was being treated with sertraline for depression by his primary care provider. With modafinil, he returned to work, and his BDI score declined from 49 to 0. So what were we treating? Overall, 70% of the patients had depression as well as fatigue. Since in the aggregate both improved, perhaps modafinil is acting as an antidepressant. However, among the 9 euthymic patients, 8 (89%) were responders compared with 16 (76%) of 21 of those with depression. These are small numbers but suggest an independent effect of modafinil on fatigue.

In this pilot study, there is no evidence of clinically or statistically significant increase in HIV RNA viral copies, which would occur if modafinil had a potent inducer effect on antiretrovirals. In fact, 5 patients showed a clinically significant decrease in viral load, which conceivably may reflect improved medication adherence, an issue that warrants further study. Of these 5, 2 were fatigue nonresponders.

We could find no additional common characteristics among the 6 nonresponders apart from being slightly older, less severely fatigued, and more likely to be getting adjunctive testosterone and antidepressants. They did not have more baseline anxiety symptoms, were not more often currently depressed, were not taking a distinctive combination of antiretrovirals, and did not more often have protease inhibitors as part of their regimens.

While it may be premature to draw clinical implications from a pilot study, the findings tentatively suggest that fatigue in the context of HIV infection is treatable, that untreated fatigue seriously restricts employment, and that patients are forthright about reporting fatigue when asked. We recommend that clinicians treating HIV+ patients inquire directly about fatigue severe enough to interfere with daily activities or plans to return to work, and if it is identified, offer treatment. One may think of a continuum of treatment options ranging from the mild steroid dehydroepiandrosterone (DHEA) (which in our ongoing clinical trial using 200–400 mg/day shows promise for alleviation of fatigue in the presence of depression), to testosterone gel and then injection for men without prostate problems, to modafinil. Patients with insufficient response to modafinil may respond with augmentation (atomoxetine, testosterone, or bupropion for its activating effect) or switch to methylphenidate or dextroamphetamine. There are no studies of drug interactions between HIV medications and the latter compounds, however.

Study limitations include the absence of a placebo comparison group and relatively small sample size. In addition, this is a sample of predominantly middle-aged, educated men (87% had at least some college) who were infected many years ago and who have been taking antiretroviral medications for several years. Whether fatigue is as much of a problem in younger, more recently infected men and women, and whether modafinil would be as effective for them, or would have such a strong behavioral or vocational impact, cannot be determined from the current results. A larger double-blind, randomized, placebo-controlled trial is indicated. However, the ease of recruitment and these preliminary results suggest that fatigue is a common problem among people with HIV/AIDS, or at least those taking antiretroviral medications, and that modafinil appears to be effective in its amelioration.

Drug names: atomoxetine (Strattera), bupropion (Wellbutrin and others), dextroamphetamine (Dexedrine, Dextrostat, and others), efavirenz (Sustiva), methylphenidate (Metadate, Ritalin, and others), modafinil (Provigil), pemoline (Cylert and others), sertraline (Zoloft), testosterone (Testim, Delatestryl, and others).

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