Published in final edited form as:
J Clin Exp Neuropsychol. 2013 August ; 35(7): 718–727. doi:10.1080/13803395.2013.823910.

EFFECT OF ARMODAFINIL ON COGNITION IN PATIENTS WITH HIV/AIDS AND FATIGUE

Martin McElhiney, Ph.D.[1,2], **Judith Rabkin, Ph.D.**[1,2], **Wilfred Van Gorp, Ph.D.**[1], and **Richard Rabkin, M.D.**[1,2]

[1]Department of Psychiatry, College of Physicians and Surgeons, Columbia University

[2]New York State Psychiatric Institute

Abstract

Fatigue and cognitive impairment are common in HIV+ adults and may occur independently or be causally linked. This study examined whether alleviation of fatigue with armodafinil in a placebo-controlled double-blind 4-week trial had an effect on cognitive function among those with and without mild neuropsychological impairment at baseline. Sixty-one patients completed a standard battery of neuropsychological tests at study entry and Week 4: 33 were randomized to armodafinil and 28 to placebo. While there was a significant effect of active medication on fatigue, cognitive performance measured by a global change score did not differ between treatment groups, or those on active treatment with or without mild neuropsychological impairment.

Introduction

Fatigue is common in HIV+ adults. Estimates of fatigue prevalence vary between studies, and cluster around 50% (Barroso et al., 2010; Jong et al., 2010). Neuropsychological impairment also is common in HIV. Overall, Durvasala and colleagues cite the estimate that 40-60% of people with HIV/AIDS have some measurable neurocognitive deficits (Durvasula, Norman & Malow, 2009), with or without accompanying behavioral sequelae, while others estimate the overall rate as 15-50% (Schouten, Cinque, Gisslen, Reiss & Portegies, 2011).

We are unaware of studies that have assessed both problems together, but the overlap appears to be significant. The conditions may occur independently, or may be causally linked in that fatigue can interfere with alertness, concentration and maintenance of attention. Thus, HIV+ patients with fatigue are likely to have higher rates of neuropsychological impairment than the total HIV population, although the impairment attributable to fatigue may be reversible when the fatigue is successfully ameliorated with treatment. In addition, both conditions are more common among those with greater immunosuppression, both historical and current (Heaton et al., 2010).

In this study, we ask whether alleviation of fatigue with armodafinil has an effect on cognitive function among those with and without baseline neuropsychologiacl impairment. The current randomized clinical trial of armodafinil (an r-isomer of modafinil), follows our report of modafinil effects on cognitive function (McElhiney, Rabkin, Van Gorp & Rabkin, 2010).

Corresponding Author: Martin C. McElhiney, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, Unit 51, New York, NY 10032, Phone: 212-543-5331, Fax: 212-543-5326, mcelhin@nyspi.columbia.edu.

Asymptomatic Neurocognitive Impairment (ANI) is the mildest of the three categories of cognitive impairment in the current diagnostic nomenclature of HAND (HIV-associated Neurocognitive Disorders) (Antinori et al., 2007). In a recent national study, 33% of participants met criteria for ANI, 12% for mild neurocognitive disorder (MND), and 2% for dementia (Heaton et al., 2010). ANI is defined as impairment on neuropsychological tests in the absence of decline in everyday functioning. The key term here is "absence of decline in everyday functioning," especially for those without any significant cognitive demands in daily life. For people who don't work and spend most of their time at home taking naps or watching television because of fatigue, determination of functional impairment is a major challenge, particularly since there are no validated strategies for identifying mild functional impairment (Valcour, 2011). Consequently, we cannot rule out the possibility that patients we classify as Neuropsychologically imparied might have functional impairment and therefore ANI or in fact might have mild impairment sufficient to be characterized as having MND. We will use the term neuropsychologically impaired (NPI), recognizing this limitation.

The clinical significance of this "sub-syndromal" impairment is not well-established. While identification of ANI may signify risk for progressive cognitive decline, there is tremendous variability in its course, and "a significant proportion of individuals will improve neurocognitively" (Woods, Moore, Weber, & Grant, 2009), especially when treated with antiretroviral medications that have better CNS penetration (Wright, 2011). On the other hand, a meta-analysis of 23 studies of the effect of antiretroviral therapy on HIV-associated cognitive impairment found the effect modest at best (Al-Khindi, Zakzanis & van Gorp, 2012). In a cross-sectional study of 1555 HIV+ adults in 6 geographic areas, 33% of participants without confounding co-morbidities met criteria for ANI (Heaton et al., 2010). Factors reported to be associated with neuropsychological impairment in HIV+ samples include co-morbid hepatitis C, history of substance abuse, detectable HIV RNA viral load, CD4 nadir, and depression (Devlin et al., 2012).

Fatigue also has substantial behavioral impact. In the context of HIV, it is typically persistent and is associated with restricted activity levels, contributing to social isolation and consequent reduction in opportunities for pleasant events and positive mood (Jenkin, Koch & Kralik, 2006). It is a common reason for leaving work and is a barrier to re-employment.

While there are no established treatments for either fatigue or cognitive problems, the modest available data suggest that psychostimulants such as dextroamphetamine and methylphenidate may increase alertness and modify cognitive decline in HIV+ patients (Brown, 1995; Hinkin et al., 2001). More recently, modafinil and armodafinil (the r isomer of modafinil) have been marketed for the treatment of sleep disorders including narcolepsy, obstructive sleep apnea, and shift work related sleep disorders. In off-label use, randomized clinical trials of both modafinil and armodafinil have demonstrated their efficacy in alleviating fatigue in conditions such as cancer (Cooper, Bird & Steinberg, 2009), neurological diseases (Adler, Caviness, Hentz, Lind, & Tiede, 2003; Rammohan et al., 2002; Rabkin et al., 2009) and depression (Abolfazli et al., 2011).

Modafinil and armodafinil are classified as Schedule IV drugs by the FDA. They differ from methylphenidate and amphetamine (Schedule II) in their lower liability of abuse (Volkow et al., 2009), have a different mechanism of action (Ballon & Feifel, 2006) and, according to patients, have a more modulated impact so that they do not cause the extreme stimulation and then crash associated with amphetamines. While the mechanism of action is not firmly established, and several studies have found an association with increased glutaminergic, adrenergic and histaminergic activity (Urbano, Leznik, & Llinas, 2007), recent evidence based on animal studies suggests that modafinil might block the dopamine transporter and

that the dopamine D1 receptor might contribute to its effects (Young & Geyer, 2010). Armodafinil was marketed in 2009. It has a longer half-life than modafinil. Its efficacy in treating fatigue has been established for patients with sleep disorders (Harsh et al., 2006), but less is known about its impact on cognitive function.

Several studies have evaluated the effects of modafinil on cognitive function. Positive effects have been reported for patients with sleep disorders (e.g. Dinges & Weaver, 2003; Hirshkowitz et al., 2007), although other investigators reported mixed or absent effects (Randall, Shneerson, Plaha & File, 2002; DeBattista, Lembke, Solvason, Ghebremichael & Poirer, 2004). Our group evaluated the effect of modafnil on cognitive functioning in HIV+ patients being treated for fatigue in a 4-week double blind placebo controlled trial. We found that patients randomized to modafinil showed greater improvement than placebo patients in terms of global change scores, although the effect was not specific for any cognitive domain (McElhiney et al., 2010). Patients also reported feeling more alert, focused and better able to concentrate. Overall, while positive findings predominate, it is difficult to summarize this literature due to methodological and population differences.

We conducted a randomized, placebo controlled clinical trial of armodafinil to assess its effect on fatigue, using the same study design and neuropsychological tests (leaving out CalCAP) that we used in our modafinil trial. We address the following questions: 1) Do patients randomized to armodafinil compared to those on placebo show greater improvement in global functioning on neuropsychological tests after 4 weeks? Does active treatment have an impact on these scores for patients with and without neuropsychological impairment(NPI)?, 2) Are hepatitis C status, substance use history, baseline depression, CD4 nadir, or detectable HIV RNA viral load associated with baseline (NPI)and, if so, amount of change? 3) Do patients notice and report changes in concentration and decision-making capacity (Beck Depression Inventory items)?

METHOD

Sample

Eligible participants were HIV+, ages 21-75 years, and had clinically significant fatigue defined as interference with at least two daily activities on a 10-itrem Role Function Scale (Albert & Rabkin, 2008) and a score of 41+ on the Fatigue Severity Scale (described below). Patients with untreated major depression, unstable medical conditions, untreated conditions associated with fatigue such as hypothyroidism, hypogonadism and anemia were excluded, as were patients who started antiretroviral medications in the past month or initiated antidepressant medication in the past 2 months.

Measures

(Note: All tests were administered at study baseline and Week 4. Higher scores indicate more of the condition assessed unless otherwise noted.)

Psychiatric eligibility criteria were evaluated with the Structured Clinical Interview for DSM-IV (SCID) modules for depression (Koback, Skodol, & Bender, 2008) to exclude Major Depressive Disorder (MDD), and to identify current MDD in Partial Remission, minor depression and dysthymia, which were permitted. Screens were used to identify (and exclude) patients with past or current psychotic conditions and bipolar disorder.

Fatigue—The 9-item self-rated Fatigue Severity Scale (Krupp, LaRocca, Muir-Nash, & Steinberg, 1989) was used to measure of the impact of fatigue on daily functioning, and results in scores ranging from 9 to 63. The conventional cut-off for “clinically significant”

fatigue is 41+. The Clinical Global Impressions-Severity of Illness scale (Williams, 2008) was used to assess fatigue at baseline, and the 7-point Clinical Global Impressions-Improvement scale was used at all subsequent visits.

Depression—In addition to the SCID modules for diagnosis of depressive disorders (Koback, Skodol & Bender, 2008), we used the structured version of the 21-item Hamilton Rating Scale for Depression (HAM-D), (Yonkers & Samson 2008), a clinician-rated scale to assess depressive severity. The 21-item Beck Depression Inventory II (BDI) (Yonkers & et al, 2008) was used to provide patient perspective on depressive symptoms.

Neuropsychological Tests—A 1-hour battery of 9 neuropsychological (NP) tests represented the domains of verbal memory (WHO UCLA Verbal Learning Test, Maj et al., 1993; Digit Span, Wechsler, 1997), speed of information processing (WAIS-III Digit Symbol, Wechsler, 1997; Color Trails 1, D'Elia, Satz, Uchiyama, & White, 1996; Symbol Search, Wechsler, 1997), executive function (Stroop, Golden, 1978; Color Trails 2, D'Elia et al., 1996), attention/working memory (WAIS III Letter-Number Sequencing, Wechsler, 1997), motor (Grooved Pegboard, Matthews & Klove, 1964), and verbal fluency (Controlled Oral Word Association Test, Spreen & Strauss, 1998).

Fatigue Outcome Measure

The primary endpoint defining fatigue responder vs. non-responder was the Clinical Global Impressions-Improvement Scale (CGI). Scores range from 1 = very much improved to 7 = very much worse. Responders were rated "1" or "2" on energy compared to baseline; non-responders had scores of 3 (minimally improved) or worse. This global assessment was based on all available data including clinician judgment, patient self-reports and ratings

Perceived Cognitive Changes—We extracted and combined scores on 2 BDI items, concerning indecisiveness (item 13: 0 = I make decisions about as well as ever, 1 = I find it more difficult to make decisions than usual, 2 = I have much greater difficulty in making decisions than I used to, 3 = I have difficulty making any decisions) and concentration difficulty (item 19: 0 = I can concentrate as well as ever, 1 = I can't concentrate as well as usual, 2 = It's hard to keep my mind on anything for very long, 3 = I find I can't concentrate on anything), to create a self-report estimate of cognitive changes. Possible scores range from 0 to 6.

Study Design

This was a 4-week randomized double-blind placebo-controlled study. At study entry and Week 4, a 1-hour battery of NP tests was administered. Week 4 responders to armodafinil were offered an additional 8 weeks of open label medication, and placebo non-responders or placebo responders who relapsed were offered open label armodafinil for 12 weeks. The outcome of fatigue treatment with armodafinil has been previously published (Rabkin, McElhiney, & Rabkin, 2011).

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. Neuropsychological data were collected between June 2008 and May 2010. The study was registered with clinicalTrials.gov, identifier: NCT00614926.

Statistical Analyses

T-tests and chi square tests comparing patients randomized to armodafinil or placebo were performed to test for baseline differences in demographic, medical and psychiatric

characteristics between groups. The treatment effects of armodafinil were examined using intention-to-treat analyses, bringing the last CGI rating forward to determine response for those who did not complete the four-week medication trial. We used Heaton et al's (2010) domain classification to identify patients meeting the NP criteria for ANI (defined as scoring >1 SD away from population normative means in 2+ domains), referred to here as neuropsychologically impaired (NPI). We also created our own more rigorous definition of NPI defined as scoring 1 SD away from normative means on 4+ non-redundant tests or 2 SDs on 2+ tests. Published norms from the test manual were used for the 4 subtests of the WAIS-III (Wechsler, 1997), Stroop (Golden, 1978), and Color Trails (D'Elia et al, 1996). Norms for the remaining tests were as follows: verbal fluency (Spreen & Straus, 1998), Grooved Pegboard Test (Mitrushina, Boone, & D'Elia, 1999), and for the WHO AVLT we used our own unpublished data from an N of 127 HIV+ adults.

T-tests were performed to examine for baseline differences in NP scores for each test and subtest between treatment groups. In addition, chi-square tests were used to compare rates of NPI for subgroups with conditions previously associated with NP impairment, including HCV status, depressive disorder, CD4 nadir under 200 cells, history of substance use disorder, and the presence of detectable viral load.

Next, repeated measures ANCOVA (using covariates of age, education and gender) was performed for each neuropsychological test and subtest, comparing patients randomized to armodafinil vs. placebo. The same analyses were conducted using the subset of the sample who met criteria for NPI. In order to examine the overall effects of armodafinil on NP performance, we created a single composite cognitive change score to assess global cognitive functioning using 9 (non-redundant) test scores (WHO AVLT trials 1-5 total, Digit Symbol, Digit Span, Symbol Search, Letter Number Sequencing, Stroop Color-Words, Color Trails 2, Grooved Pegboard non-dominant hand, and Verbal Fluency FAS total). Results of timed tests were reciprocally transformed into speed scores, and differences between baseline and Week 4 scores from all cognitive measures were calculated. These difference scores were then transformed to z-scores and summed into a composite.

Perceived changes in concentration and decision-making capacity were assessed by selecting those patients who scored 3+ at baseline on the combined 6-point, 2-item BDI scale, and comparing baseline and Week 4 ratings for the two treatment groups using general linear modeling.

All tests were two-tailed, alpha = .05. We did not correct for multiple comparisons as this was an exploratory study, but do not report trend significance.

RESULTS

Sample

Seventy patients were randomized, and 64 completed the double blind trial. Of these, 61 completed both neuropsychological assessments, and constitute the sample for this report. As shown on Table 1 mean age was 46, and 87% were men. In terms of risk factor, 91% of the men reported sex with men. Over half the sample had a history of substance abuse. Twenty-eight percent were Black, 48% were non-Hispanic white, 23% were Hispanic, and 2% other. On average, patients had completed 2 years of college, although 11% (7/61) had not completed high school. At study entry, 74% were unemployed. Forty-four percent had an Axis I depression diagnosis (other than major depressive disorder), and 41% were taking antidepressant medication.

At baseline, mean CD4 cell count was 491, mean time since testing HIV+ was 136, and 57% of patients had an AIDS diagnosis according to CDC criteria, usually based on based on past history rather than current conditions. Mean CD4 nadir was 191 cells (SD = 153.52), with a range of 0 to 600, and 56% had a CD4 cell count <200 cells at some point in time. Ninety percent were taking antiretrovirals, 25 had detectable HIV RNA viral load, and 18% had hepatitis C. As shown on Table 1, armodafinil and placebo groups did not differ on any baseline demographic, medical or psychiatric measures.

Treatment Effects of Armodafinil

In an intention to treat analysis of the randomized clinical trial (N = 70), fatigue response to armodafinil was 75%, and to placebo 26%. Armodafinil did not reduce depressive symptoms in the absence of reduced fatigue, but among those patients with an Axis I disorder at study entry whose energy improved, 82% experienced improved mood as well. Responders did not differ from non-responders on any demographic variable. In the subset of 61 patients included here, response rate to armodafinil was 73% (24/33), and to placebo, 29% (8/28).

Neuropsychological Test Performance

Armodafinil vs. placebo groups: Baseline—No differences in individual NP test and subscale scores were observed at baseline between treatment groups with one exception: patients randomized to armodafinil had superior scores on the Digit Symbol Test (M=78, SD=16.3, vs. M=64, SD = 17.4, t (59) =−3.319, p = .002).

Change over time—Using paired t-tests to compare change from baseline to Week 4 separately for the armodafinil and placebo samples, mean scores improved significantly on 6 of the 18 tests and subtests for the armodafinil group, and 8 of 18 in the placebo group. The tests that showed improvement for both groups include subtests of Verbal Learning, Stroop Color Test, verbal fluency and digit symbol. The placebo group showed a significant decline on the Stroop Word subtest (t= 2.242, 1df, p=.033).

In repeated measures ANCOVAs, controlling for age, education and gender (Table 2), the only significant findings differentiating active and placebo groups were on subtests of the Stroop Color Word test. The armodafinil group's performance improved on the Stroop Words subtest, compared to a worse performance by the placebo group. However, the Stroop Interference score, which is a calculation using the three Stroop Color Word subtest scores, suggested significantly greater improvement for the placebo patients at Week 4 compared to the armodafinil group.

Using the composite change score (difference between baseline and Week 4 scores, converted to z scores and summed) as the outcome measure, an ANCOVA comparing treatment groups and controlling for age and baseline depression (BDI) failed to find a treatment effect (SS = 16.225, F = 1.454, p = .233).

Secondary Analyses

Responders vs. Non-Responders—Results of this comparison are similar to those comparing treatment groups, which is not surprising since 24 of the 32 responders had received armodafinil. Repeated measures analyses of the 18 subtests produced results that were essentially the same as those comparing treatment groups. The only dissimilarity being the lack of a significant difference in performance on the Stroop Words subtest score (data not shown).

Using the composite change score to compare responders and non-responders, we again found no significant difference (SS = 1.254, F = .110, p = .742).

Patients with Neuropsychological Impairment at Baseline.

Using the Heaton et al. domain classification and ANI criteria, 59% (n= 36/61) of patients had neuropsychological test scores on 2+ domains of >1 SD away from normative means and thus met the NP criteria for ANI. Of these, a subset of 11 patients (18%), also met our more rigorous definition of scoring at least 1 SD away from normative means on 4+ non-redundant tests or 2 SDs on 2+ tests. However, the latter group was too small to analyze (8 were randomized to placebo, 3 to armodafinil) so they were included in NPI analyses. As a group, the 36 patients with and without NPI did not differ in terms of rates with baseline depression diagnoses (44% in both groups).

The two domains that contributed most frequently to NPI status were Executive Functioning, 57% (n= 35/61) and Learning and Memory, 44% (n=27/61). For the entire sample, the Stroop Color subtest had the most outliers, with 43% (n=26/61) of the sample below 1 SD compared to the normative sample.

We performed the same repeated measures ANCOVA, controlling for age, education and gender (18/36 of NPI patients were in each treatment group). The results were similar to the whole sample outlined above except for two subtests of the WHO AVLT, both favoring the armodafinil group: Trial 1-5 total, (F = 5.243, p = .029) and Short Delay (F = 4.499, p = .042).

Possible Correlates of NPI: HCV status, Substance Abuse History, Depression, CD4 nadir, and Detectable HIV RNA Viral Load

We compared proportion of patients with and without each of these five conditions in terms of proportion meeting NPI criteria at baseline. As shown on Table 3, the presence or absence of each of these factors was unrelated to proportion of patients with NPI.

Subjective Perception of Cognitive Change After Armodafinil Treatment

In addition to NP test performance, we were interested in patient reports of decision-making capacity and concentration at baseline and Week 4 for patients taking armodafinil. On the BDI 2-item scale of cognitive function, 25 patients had scores of 3+ at baseline. We compared change in slope of scores for those on armodafinil (n= 12) vs. placebo patients (n=13), using general linear modeling. Patients on armodafinil reported significantly greater improvement in concentration/decision-making (SS = 4.154, F = 5.069, p = .034). We next controlled for depression by using the BDI total at Time 4, minus these 2 items, as a covariate, which did not alter the finding that armodafinil patients reported greater improvement in concentration/decision-making compared to placebo patients (SS = 1.781, F = 4.653, p = .042).

We then compared these two subgroups (12 on armodafinil vs 13 on placebo) with respect to the NP composite change measure. Despite reported improvements in concentration/ decision-making in the armodafinil subgroup, their composite change scores did not differ from placebo patients (t (23) =−1.613, p = .120).

Discussion

We did not find an ameliorative effect of armodafinil compared to placebo on NP tests for 61 HIV+ patients treated for fatigue. We thus failed to replicate the findings of Hirshkowitz et al. (2007) and Harsh et al. (2006) who observed significant improvements in memory and

attention among patients with obstructive sleep apnea and narcolepsy, respectively, after armodafinil treatment. We also failed to replicate our own findings in an RCT of modafinil, using the same study design and a similar NP test battery in which we observed a differential improvement in terms of NP global change scores among patients randomized to active vs. placebo medication. None of the five conditions identified in other studies as being associated with neuropsychological impairment (CD4 nadir < 200, detectable viral load, hepatitis C, alcohol/substance use history, or baseline depression) was related to NPI classification. Consistent with other recent findings (e.g. Heaton et al., 2010; Devlin et al., 2012), nearly 60% of these medically stable HIV+ patients, 90% of whom were taking antiretroviral medications, exhibited mild or moderate cognitive impairment.

Among patients who reported significant problems with decision-making and/or concentration at baseline, those randomized to armodafinil reported greater improvement than placebo patients after 4 weeks. This finding, in a small sample, is consistent with our findings in our modafinil RCT in which we administered the Cognitive Failures Questionnaire (CFQ) (Broadbent, Cooper, Fitzgerald & Parkes, 1982). In that study, CFQ scores showed significantly greater decline in cognitive difficulties in the modafinil group vs. placebo. However, CFQ scores were not related to NP global change scores either at baseline or Week 4. Similarly, in the current trial, change on the BDI cognitive subscale for the 25 patients who reported perceived problems at baseline did not correlate with the NP composite change score. This finding, in two trials using different measures of subjective reported cognitive function as outcomes, neither of which was correlated with NP outcomes, suggests that self-reported cognitive function taps into a different but meaningful dimension. In other words, these two measures, the CFQ and the BDI cognitive subscale, may not be addressing the areas of cognitive impairment assessed by the NP testsFor example, patients who report experiencing improved concentration may tackle previously deferred tasks of daily living (e.g. reading, attending to lectures in school) whether or not their NP test scores reflect improvement (in the absence of severe cognitive impairment). As such, the patient's perception of change warrants more thorough examination in future trials using validated measures that assess more areas of perceived cognitive function.

To determine if the differing neuropsychological results in the modafinil and armodafinil trials was an issue of sample size, we calculated effect size for each using the NP composite change score from equivalent NP batteries. The higher Cohen's *d* of 0.55 for the modafinil trial versus 0.30 for the armodafinl trial suggests that sample size is not the only explanation. Instead, the differing outcome is more likely due to the frequency of more severe impairment. When the batteries were made equivalent by eliminating the CalCap test from the modafinil trial, we compared rates of neuropsychological impairment. The two samples had a similar proportion of patients meeting criteria for NPI (60% and 59%, respectively), but they differed in proportion of patients meeting our more rigorous definition of scoring at least 1 SD away from normative means on 4+ non-redundant tests or 2 SDs on 2+ tests (35% or 36/103 in the modafinil trial vs. 18% or 11/61 in the armodafijnil trial). Comparison of baseline neuropsychological test scores across the two samples supports this explanation. While the two samples did not differ on any demographic or medical measures, the armodafinil sample performed significantly better than the modafinil sample at baseline on 4 of the 18 neuropsychological tests and subtests, or 3 of the 9 non-redundant tests.

In addition to the limitation of a rather small sample size that included participants who were not selected for baseline cognitive impairment, we did not control for time elapsed between testing and last medication dose, nor did we address the neuropsychological test performance practice effects such as those outlined by Cysique et al. (2011). We also did not measure behavioral difficulties attributable to cognitive impairment, although at study entry it would have been difficult to distinguish between the overlapping effects of cognitive

function and fatigue. Probably the greatest limitation of our sample is the baseline neuropsychological performance was not severely impaired, thus limiting room for improvement. In the future, selection of patients with more significant cognitive impairment may permit identification of armodafinil efficacy in improving cognitive function.

In summary, we found no effect on NP tests results attributable to 4 weeks of armodafinil vs. placebo treatment in an HIV+ sample presenting with fatigue and having a relatively low frequency of severe NP impairment. However, patients on armodafinil who reported problems with decision-making and/or concentration at baseline, showed greater improvement compared to those on placebo. Baseline depression diagnoses, CD4 nadir < 200, detectable viral load, substance use disorder history or hepatitis C infection were unrelated to NP test performance at study entry. Future research might usefully repeat this design with an RCT powered to detect neuropsychological effects of armodafinil in a sample selecting for cognitive impairment, and to use extended measures of subjective reports regarding cognitive function.

Acknowledgments

This work was partially supported by NIMH grant R01 MH072383 (JGR) and by Cephalon, Inc.

The authors report no financial affiliations or other relationships relevant to the subject of this article.

References

Abolfazli R, Hosseini M, Ghanizadeh A, Ghaleiha A, Tabrizi M, Raznahan M, Akhondzadeh S. Double-blind randomized parallel-group clinical trial of efficacy of the combination fluoxetine plus modafinil versus fluoxetine plus placebo in the treatment of major depression. Depression & Anxiety. 2011; 28:297–302. [PubMed: 21456039]

Adler CH, Cavinoss JN, Hentz JG, Lind M, Tiede J. Randomized trial of modafinil for treating subjective daytime sleepiness in patients with Parkinson's disease. Movement Disorders. 2003; 18:287–293. [PubMed: 12621632]

Al-Khindi T, Zakzanis K, van Gorp W. Journal of the International Neuropsychological Society. 2012; 17:956–969. [PubMed: 21813033]

Albert, S.; Rabkin, J.; Rush, A. General health status, functioning and disability measures. In: First, M.; Blacker, D., editors. Handbook of psychiatric measures. American Psychiatric Publishing; Washington, DC: 2008. p. 107-123.

Antinori A, Arendt G, Becker J, Brew B, Byrd D, Cherner M, Wojna VE. Updated research criteria for HIV-associated neurocognitive disorders. Neurology. 2007; 69:1789–1799. [PubMed: 17914061]

Ballon J, Feifel D. A systematic review of modafinil: Potential clinical uses and mechanisms of action. Journal of Clinical Psychiatry. 2006; 67:554–566. [PubMed: 16669720]

Barroso J, Hammill B, Leserman J, Salahuddin N, Harmon J, Pence B. Physiological and psychosocial factors that predict HIV related fatigue. AIDS Behavior. 2010; 14:1415–1427. [PubMed: 20352317]

Broadbent DE, Cooper PF, Fitzgerald P, Parkes K. The Cognitive Failures Questionnaire (CFQ) and its correlates. British Journal of Clinical Psychology. 1982; 21:1016.

Brown GR. The use of methylphenidate for cognitive decline associated with HIV disease: stimulant use in consultation patients. International Journal of Psychiatry in Medicine. 1995; 25:21–37. [PubMed: 7649716]

Cooper M, Bird H, Steinberg M. Efficacy and safety of modafinil in the treatment of cancer-related fatigue. Annals of Pharmacotherapy. 2009; 43:721–725. [PubMed: 19318599]

Cysique LA, Franklin D, Abramson I, Ellis RJ, Letendre S, Collier A, Heaton R. Normative data and validation of a regression based summary score for assessing meaningful neuropsychological change. Journal of Clinical & Experimental Neuropsychology. 2011; 33(5):505–522. [PubMed: 21391011]

DeBattista C, Lembke A, Solvason HB, Ghebremichael LR, Poirer JA. Prospective trial of modafinil as an adjunctive treatment of major depression. Journal of Clinical Psychopharmacology. 2004; 24:87–90. [PubMed: 14709953]

D'Elia, L.; Satz, P.; Uchiyama, C.; White, T. Color Trails Test. Psychological Assessment Resources; Odessa, FL: 1996.

Devlin K, Gongvatana A, Clark U, Chasman J, Westbrook M, Tashima K, Cohen R. Neurocognitive effects of HIV, hepatitis C, and substance use history. Journal of the International Neuropsychological Society. 2012; 18:68–78. [PubMed: 22132928]

Dinges DF, Weaver T. Effects of modafinil on sustained attention performance and quality of life in OSA patients with residual sleepiness while being treated with nCPAP. Sleep Medicine. 2003; 4:393–402. [PubMed: 14592280]

Durvasula, R.; Norman, L.; Malow, R.; Pope, C. Current perspectives on the neuropsychology of HIV. In: White, R.; Malow, R., editors. HIV/AIDS: Global frontiers in prevention/intervention. Routledge; New York, NY: 2009. p. 177-190.

Golden, CJ. Stroop Word and Color Test: A Manual for clinical and experimental uses. Stoetling Co; Chicago, IL: 1978.

Harsh JR, Hayduk R, Rosenberg R, Wesnes K, Walsh J, Arora S, Roth T. The efficacy and safety of armodafinil as treatment for adults with excessive sleepiness associated with narcolepsy. Current Medical Research and Opinions. 2006; 22(4):761–774.

Heaton RK, Clifford DB, Franklin D Jr. Woods SP, Ake C, Vaida F, Grant I. HIV-Associated neurocognitive disorders persist in the era of potent antiretroviral therapy: Charter Study. Neurology. 2010; 75:2087–2096. [PubMed: 21135382]

Hinkin C, Castellon S, Hardy DF, Farinpour R, Newton T, Singer E. Methylphenidate improves HIV-associated cognitive slowing. Journal of Neuropsychiatry & Clinical Neuroscience. 2001; 13:248–254.

Hirshkowitz M, Black J, Wesnes K, Niebler G, Arora S, Roth T. Adjunct armodafinil improves wakefulness and memory in obstructive sleep apnea/hypopnea syndrome. Respiratory Medicine. 2007; 101:616–627. [PubMed: 16908126]

Jenkin P, Koch T, Kralik D. The experience of fatigue for adults living with HIV. Journal of Clinical Nursing. 2006; 15:1123–1131. [PubMed: 16911053]

Jong E, Oudhoff L, Epskamp C, Wagener M, Van Duijn M, Fischer S, Van Gorp E. Predictors and treatment strategies of HIV-related fatigue in the combined antiretroviral era. AIDS. 2010; 24:1387–1405. [PubMed: 20523204]

Koback, K.; Skodol, A.; Bender, D. Diagnostic measures for adults. In: Rush, A.; First, M.; Blacker, D., editors. Handbook of psychiatric measures. American Psychiatric Publishing; Washington, DC: 2008. p. 35-60.

Krupp L, LaRocca N, Muir-Nash J, Steinberg A. The Fatigue Severity Scale. Archives of Neurology. 1989; 46:1121–1123. [PubMed: 2803071]

Maj M, D'Elia L, Satz P, Janssen R, Zaudig M, Uchiyama C. Evaluation of two new neuropsychological tests designed to minimize cultural bias in the assessment of HIV-1 seropositive persons: The WHO Study. Archives of Clinical Neuropsychology. 1993; 8:123–135. [PubMed: 14589670]

Matthews, C.; Klove, H. Instruction Manual for the Adult Neuropsychology Test Battery. University of Wisconsin Medical School; Madison, WI: 1964.

McElhiney M, Rabkin J, van Gorp W, Rabkin R. Modafinil effects on cognitive function in HIV+ patients treated for fatigue: A placebo controlled study. Journal of Clinical & Experimental Neuropsychology. 2010; 32:474–480. [PubMed: 19937504]

Mitrushina, MN.; Boone, KB.; D'Elia, LF. Handbook of Normative Data for Neuropsychological Assessment. Oxford University Press; New York, NY: 1999. p. 433

Rabkin J, Gordon P, McElhiney M, Rabkin R, Chew S, Mitsumoto H. Modafinil treatment of fatigue in patients with ALS: A placebo controlled study. Muscle & Nerve. 2009; 39:297–303. [PubMed: 19208404]

Rabkin J, McElhiney M, Rabkin R. Treatment of HIV-related fatigue with armodafinil: A placebo controlled randomized trial. Psychosomatics. 2011; 52(4):328–336. [PubMed: 21777715]

Rammohan K, Rosenberg J, Lynn D, Blumenfeld A, Pollak C, Nagaraja H. Efficacy and safety of modafinil (Provigil) for the treatment of fatigue in multiple sclerosis: A two-centre Phase 2 study. Journal of Neurology, Neurosurgery & Psychiatry. 2002; 72:179–183.

Randall DC, Shneerson J, Plaha K, File S. Modafinil affects mood, but not cognitive function, in healthy young volunteers. Human Psychopharmacology. 2002; 18:163–173. [PubMed: 12672167]

Schouten J, Cinque P, Gisslen M, Reiss P, Portegies P. HIV-1 and cognitive impairment in the cART era: A review. AIDS. 2011; 25:561–575. [PubMed: 21160410]

Spreen, O.; Strauss. A Compendium of Neuropsychological Tests. 2nd ed. Oxford University Press; New York, NY: 1998. p. 453-457.

Urbano F, Leznik E, Llinas R. Modafinil enhances thalamocortical activity by increasing neuronal electronic coupling. PNAS. 2007; 104:12554–12559. [PubMed: 17640897]

Valcour V. Evaluating cognitive impairment in the clinical setting: Practical screening and assessment tools. Topics in Antiviral Medicine. 2011; 19:175–180. [PubMed: 22298886]

Volkow N, Fowler J, Logan J, Alexoff D, Zhu W, Telang F, Apelskog-Torres K. Effects of modafinil on dopamine and dopamine transporters in the male human brain: Clinical implications. Journal of the American Medical Association. 2009; 301:1148–1154. [PubMed: 19293415]

Wechsler, D. Wechsler Adult Intelligence Scale-Third Edition (WAIS-III). The Psychological Corp; San Antonio, TX: 1997.

Williams, JBW. Mental health status, functioning and disabilities measures. In: Rush, A.; First, M.; Blacker, D., editors. Handbook of psychiatric measures. American Psychiatric Publishing; Washington, DC: 2008. p. 83-105.

Woods SP, Moore DJ, Weber E, Grant I. Cognitive neuropsychology of HIV-associated neurocognitive disorders. Neuropsychological Review. 2009; 19:152–168.

Wright E. Neurocognitive impairment and neuroCART. Current Opinions in HIV and AIDS. 2011; 6(4):303–308.

Yonkers, K.; Samson, J. Mood disorders measures. In: Rush, A.; First, M.; Blacker, D., editors. Handbook of psychiatric measures. American Psychiatric Publishing; Washington, DC: 2008. p. 499-528.

Young J, Geyer M. Action of modafinil-increased motivation via the dopamine transporter inhibition and D1 receptors? Biological Psychiatry. 2010; 67:784–787. [PubMed: 20132929]

Table 1
Baseline Demographic, Psychiatric and Medical Characteristics of Study Patients (N = 61)

	All Patients N = 61	Armodafinil Group N = 33	Placebo Group N = 28	t or χ^2	*p*
Demographic					
Age, mean (SD)	46 (8.1)	45 (8.9)	47 (7.2)	0.814	.419
Ethnicity, number (%)					
Black	17 (28%)	10 (30%)	7 (25%)		
White (non-Hispanic)	29 (48%)	16 (49%)	13 (46%)	1.727	.631
Hispanic	14 (23%)	6 (18%)	8 (29%)		
Other	1 (2%)	1 (3%)	0		
Gender, number (%)					
Men	53 (87%)	28 (85%)	25 (89%)	0.262	.609
Women	8 (13%)	5 (15%)	3 (11%)		
MSM, number (%)	48 (79%)	28 (85%)	20 (71%)	1.627	.202
Years Education, mean (SD)	14.5 (2.7)	15 (2.6)	14 (2.9)	−1.009	.317
Work Status, number (%)					
Full time	7 (12%)	5 (15%)	2 (7%)		
Part time	9 (15%)	6 (18%)	3 (11%)	1.911	.385
Unemployed	45 (74%)	22 (67%)	23 (82%)		
Psychiatric					
DSM-IV depression diagnosis[1], number, (%)	27 (44%)	14 (42%)	13 (46%)	0.098	.754
Taking antidepressant medication, number (%)	25 (41%)	13 (39%)	12 (43%)	0.075	.784
Past Alcohol/Substance Use Disorder, number, (%)	35 (57%)	18 (55%)	17 (61%)	0.236	0.627
Beck Depression Inventory-II, mean (SD)	21 (9.1)	21 (9.1)	20 (9.3)	−0.289	.773
Fatigue Severity Scale, mean (SD)	53 (6.1)	53 (6.0)	53 (6.4)	0.022	.982
Neuropsychologically Impaired, number (%)	36 (59%)	18 (55%)	18 (64%)	0.594	.441
Medical					
Months since testing HIV+, mean (SD)	136 (81)	124 (86)	150 (73)	1.271	.209
AIDS Diagnosis, number, (%)	35 (57%)	17 (52%)	18 (64%)	1.010	.315
Taking antiretroviral therapy, number, (%)	55 (90%)	30 (91%)	25 (89%)	0.045	.832
Hepatitis C, number, (%)	11 (18%)	4 (12%)	7 (25%)	1.700	.192
CD4 cell count, mean (SD)	491 (232)	520 (217)	456 (247)	−1.081	.284
Undetectable HIV RNA Viral Load, Number, (%)	25 (41%)	13 (39%)	12 (43%)	0.075	.784

[1] DSM-IV depression diagnosis of major depressive disorder in partial remission, minor depression, or dysthymia

Table 2

Armodafinil neuropsychological test data summary using repeated measures ANCOVAs by treatment group

	Armodafinil group (N=33)		*Placebo group (N= 28)*		*Interaction term time by group*	
Test	***Baseline***	***Week 4***	***Baseline***	***Week 4***	***F***	***P***
WHO AVLT						
1-5 Total	49 (11)	55 (12)	45 (10)	49 (8)	1.655	.204
Delay 1	9.3 (2.9)	11.3(3.1)	9.0 (2.6)	10.1 (2.1)	2.219	.142
Delay 2	9.9 (3.2)	11.3 (3.0)	9.0 (2.3)	10.7 (2.4)	0.001	.970
Recognition	14.1 (1.1)	14.4 (0.9)	13.4 (1.9)	13.9 (1.3)	0.602	.441
WAIS-III Digit Symbol	78 (16.3)	82 (18.3)	64 (17.4)	67 (16.9)	0.467	.497
WAIS-III Digit Span	17 (4.0)	17 (3.5)	17 (3.5)	17 (3.5)	0.099	.754
WAIS-III Symbol Search	35 (9.2)	35 (10.5)	30 (7.1)	30 (7.2)	0.033	.857
WAIS-III L-N Sequencing	10 (2.5)	11 (3.1)	10 (2.7)	10 (2.7)	0.367	.547
Stroop						
Words	104 (16.7)	105 (15.3)	102 (15.4)	98 (16.4)	4.099	.048*
Colors	71 (12.2)	75 (13.0)	66 (12.0)	70 (12.1)	0.029	.866
C-W	44 (8.1)	46 (9.0)	40 (10.5)	44 (10.7)	2.532	.117
Interference	2.0 (7.0)	1.3 (6.3)	−0.5 (8.8)	3.2 (7.1)	7.184	.010*
Color Trails: 1	38 (17.4)	35 (20.7)	42 (19.8)	39 (17)	0.002	.965
2	85 (35.4)	80 (32.9)	91 (28.9)	85 (28.7)	0.035	.852
Grooved Peg						
Dominant	66 (13.1)	64 (12.8)	68 (11.8)	65 (7.6)	0.225	.637
Non-Dominant	72 (12.8)	71 (15.4)	73 (11.7)	73 (12.4)	0.154	.696
Verbal Fluency						
FAS Letters total	44 (11.2)	47 (12.0)	43 (8.6)	45 (12.3)	0.038	.847
Animals	22 (4.8)	22 (6.2)	19 (5.0)	20 (5.4)	0.001	.980

Note: All scores are raw scores; Statistics are repeated measure ANCOVAs with age, education, gender as covariates

* $p < .05$.

Table 3

Comparison of possible correlates of NP impairment for Patients meeting criteria for Neuropsychological Impairment (NPI)

	NPI N (%)	χ^2	p
DSM Depression Diagnosis			
Present (N = 27)	16 (59%)	.001	.973
Absent (N= 34)	20 (59%)		
Past Alcohol/Substance Use Disorder			
Present (N = 35)	24 (69%)	3.100	.078
Absent (N = 26)	12 (46%)		
HCV+			
Present (N = 11)	5 (46%)	1.020	.312
Absent (N= 50)	31 (62%)		
CD4 Nadir Below 200			
Present (N = 34)	20 (59%)	.001	.973
Absent (N = 27)	16 (59%)		
HIV RNA Viral Load Detectable			
Present (N = 25)	15 (60%)	.017	.896
Absent (N = 36)	21 (58%)		