Double-Blind, Placebo-Controlled Study of Modafinil for Fatigue and Cognition in Schizophrenia Patients Treated With Psychotropic Medications

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Objective: To assess the effects of modafinil on fatigue, symptoms, attention, working memory, and executive functioning in schizophrenia patients treated with psychotropic medications.

Method: Twenty-four patients with a DSM-IV diagnosis of schizophrenia or schizoaffective disorder (10 men and 14 women) were randomly assigned to modafinil up to 200 mg a day (N = 13) or placebo (N = 11) as an adjunct therapy in an 8-week, double-blind, placebo-controlled study. Data were collected from May 18, 2001 to September 11, 2003.

Results: Four subjects terminated the study early, including one because of worsening of psychosis during the first week taking modafinil. In the modafinil (N = 10) and placebo (N = 10) groups, fatigue improved significantly over time ($p < .01$), but there were no differences between groups on changes in fatigue, positive and negative symptoms, or cognition.

Conclusion: Fatigue improved in both groups, and there were no differences between groups on changes in fatigue, symptoms, attention, working memory, or executive functioning. Lack of differences between groups may be due to small sample size or possible regression to the mean in the placebo group.

(J Clin Psychiatry 2005;66:839–843)

Received Sept. 24, 2004; accepted Dec. 21, 2004. *From The Zucker Hillside Hospital, North Shore-Long Island Jewish Health System, Glen Oaks, N.Y. (Drs. Sevy, Alvir, Gunduz-Bruce, and Schooler and Mss. Meyer and Visweswaraiah); and BMR HealthQuest, San Diego, Calif. (Dr. Rosenthal).*

Supported by a grant for an investigator-initiated study from Cephalon, Inc., West Chester, Pa.

Presented at the 42nd annual meeting of the American College of Neuropsychopharmacology, Dec. 7–11, 2003, San Juan, Puerto Rico.

Dr. Rosenthal has served as a consultant for and on the speakers or advisory boards of Cephalon, Inc. Drs. Sevy, Alvir, Gunduz-Bruce, and Schooler and Mss. Meyer and Visweswaraiah report no financial affiliations relevant to the subject matter of this article.

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Modafinil is a U.S. Food and Drug Administration–approved medication indicated for improving wakefulness in patients with excessive sleepiness associated with narcolepsy,[1] obstructive sleep apnea/hypopnea syndrome,[2] and shift work sleep disorder.[3] The neurobiological mechanisms underlying the effects of modafinil on wakefulness are not fully understood, but may be related to central α_1-adrenergic agonist activity,[4] increase in dopaminergic transmission,[5] decrease in γ-aminobutyric acid–related activity,[6] and increased histamine release.[7] Because of its effect on wakefulness, modafinil may be the drug of choice to reduce fatigue and daytime sleepiness induced by psychotropic medications in patients with schizophrenia. In mice, modafinil decreases the sedation induced by chlorpromazine and haloperidol (data on file, Cephalon, Inc., West Chester, Pa.). In humans, modafinil is safe, has a low level of interactions with other medications,[1,8] and is not potentially addictive.[9] Recently, Rosenthal and Bryant[10] found in a 4-week open-labeled study of 10 patients with schizophrenia that modafinil, up to 200 mg a day, produces significant improvement on global functioning and fatigue. Although modafinil was well tolerated in general, 2 patients reported the emergence of hallucinations.

Besides its effect on fatigue, modafinil may also improve cognition in schizophrenia patients. In a randomized, double-blind, placebo-controlled study in healthy subjects, Turner et al.[11] found an improvement in spatial planning, recognition memory, digit span, and accuracy after 1 dose of 100 mg (N = 20) or 200 mg (N = 20) of modafinil compared with placebo (N = 20). Muller et al.[12] found that 200 mg of modafinil improved working memory in 16 healthy subjects using a double-blind, placebo-controlled, crossover design. A double-blind, placebo-controlled, within-subject–designed study in 18 non–sleep-deprived healthy subjects suggests that a single dose of 300 mg of modafinil improves cognitive functioning, and more specifically, serial reaction time, logical reasoning, and vigilance.[13] However, a double-blind, placebo-controlled, parallel-designed study in 30 non–sleep-deprived healthy subjects failed to find an effect of 100 or 200 mg of modafinil on attention, memory, mental flexibility, planning, or verbal fluency.[14]

In schizophrenia, 200 mg of modafinil improved attentional set shifting and short-term verbal memory span in 20 patients entered into a double-blind, randomized, placebo-controlled, crossover study.[15]

On the basis of these findings, we present a double-blind, randomly assigned, placebo-controlled study of the effects of modafinil on fatigue, attention, working memory, and executive functioning in schizophrenia patients stabilized on psychotropic medications. We also examined the safety of modafinil in these patients and looked at changes in symptoms and side effects during the study.

METHOD

The study was conducted at The Zucker Hillside Hospital (Glen Oaks, N.Y.) and BMR HealthQuest (San Diego, Calif.). Data were collected from May 18, 2001 to September 11, 2003.

Inclusion criteria were (1) DSM-IV criteria for schizophrenia or schizoaffective disorder, confirmed by the Structured Clinical Interview for DSM-IV Axis I Disorders, Patient Edition[16]; (2) age between 18 and 64 years; (3) treatment with antipsychotic medications for more than 3 months; (4) stable dose of psychotropic medication (antipsychotics, antidepressants, anxiolytics) for at least 1 month prior to entering the study; (5) severity score of at least 4 ("moderately ill") on the Clinical Global Impressions (CGI) fatigue component[17]; (6) score of ≤ 7 on the 17-item Hamilton Rating Scale for Depression (HAM-D)[18] after excluding items 7 (work activities), 8 (retardation), and 13 (somatic symptoms); (7) no DSM-IV diagnosis of alcohol or drug dependence in the last 3 months; and (8) no current treatment with psychostimulants, tricyclics, clozapine, diazepam, monoamine oxidase inhibitors, anticoagulants, carbamazepine, phenobarbital, phenytoin, or barbiturates.

After signing an informed consent form approved by the institutional review board of the participating centers, subjects were followed for 2 weeks, then randomly assigned to an 8-week, double-blind, placebo-controlled phase with modafinil or placebo as adjunct therapy. They were seen weekly during the first 4 weeks of the study, then every other week by a psychiatrist for fatigue, symptom, and side effect assessments.

Fatigue was assessed with the CGI-Severity of Illness and CGI-Improvement subscales,[17] the Fatigue Severity Scale (FSS),[19] and a 10-cm visual analogue fatigue scale (VAFS; global rating of fatigue ranging from 0 [worst] to 10 [normal, no fatigue]).

The following instruments were used to assess subjects' symptoms: CGI-Severity of Illness and CGI-Improvement subscales, Brief Psychiatric Rating Scale (BPRS),[20] BPRS-anchored version,[21] Scale for the Assessment of Negative Symptoms (SANS; modified version),[22] and HAM-D. Side effects were assessed with the Abbreviated Treatment Emergent Symptom Scale (TESS),[17] the Modified Simpson dyskinesia scale[23] (assessment of dyskinesia), and the Modified Simpson-Angus Scale[24] (assessment of akathisia).

Neuropsychological assessments at the beginning and end of the double-blind phase included the Continuous Performance Test, Identical Pairs version (CPT-IP)[25,26]; the letter-number span[27]; the Oculomotor Delayed Response Test[28]; the Delayed Match to Sample Task[29]; the Controlled Oral Word Association Test (COWAT)[30,31]; and the Rey Auditory Verbal Learning Test.[31]

CPT-IP is a measure of sustained attention and vigilance. The subject is presented with a series of digit strings at a rate of 1 per second and asked to respond each time the current digit string is identical to the one shown in the prior trial. The letter-number span assesses attention and concentration. The subject is asked to reorder a mixed series of letters and numbers in ascending alphabetical and numerical order. The Oculomotor Delayed Response Test is a computerized version of a classic spatial working memory task[32] in which subjects are required to locate a visual stimulus following brief delays (2 and 6 seconds). The measure of interest is the accuracy of the subject's response (deviation from the actual position). The Delayed Match to Sample Task assesses nonverbal working memory. The subject is presented with a grid of 9-by-9 squares, 40 of which are darkened. Following a delay period, the patient is presented with 2 smaller 9-by-9 grids and asked to identify which one matches the initial stimulus. COWAT is a measure of executive functioning and requires the subject to produce as many words as possible that begin with specific letters in a 60-second period. Two matched sets of letters ("CFL" and "PRW") are used as alternate forms of the test. The score is the sum of all correct words produced during the three 60-second trials, with adjustments for age, sex, and years of education. The Rey Auditory Verbal Learning Test is a 15-word list and assesses immediate and delayed recall. All the above instruments and tests administered for symptom, fatigue, side effect, and cognitive assessments have been previously standardized and used in schizophrenia studies conducted at The Zucker Hillside Hospital and BMR HealthQuest.[10,33]

At the beginning of the randomization phase, 1 tablet of modafinil (100 mg) or placebo was given in the morning. After 2 weeks, if no side effects had a TESS rating > 2 (mild), 2 tablets of modafinil (200 mg) or placebo were given as a single dose in the morning. Hence, the maximum dose of modafinil in this study was 200 mg, which is the dose currently recommended in the treatment of narcolepsy and is well tolerated.[1]

Groups were compared for baseline variables using either t test or χ^2 tests. Repeated-measures analysis of variance (ANOVA) was used to compare clinical outcomes between groups, using measures taken at baseline

and at the end of the double-blind phase. The last available observation was carried forward in cases wherein the post–double-blind phase measurement was unavailable. Repeated-measures ANOVA was used to estimate both overall (both groups) and differential (between groups) change in the outcome measures. The interaction of time by treatment group was tested to assess differential changes between modafinil and placebo groups. These analyses were run using data on the 20 treatment "completers." Intent-to-treat analyses that included all randomized subjects, as well as mixed-models analyses that estimated overall and between-group rates of change by using all available measurements, including the biweekly measurements done during double-blind treatment, were performed to supplement the repeated-measures ANOVA described above. These supplementary analyses provided similar results to the repeated-measures ANOVA, and we will therefore limit our reported results to the repeated-measures ANOVA.

RESULTS

Twenty-four subjects (10 men and 14 women) completed the stabilization phase and were randomly assigned to either modafinil (N = 13) or placebo (N = 11). One subject terminated the study during the first week on modafinil treatment because of worsening of psychosis while taking 100 mg of modafinil. Three subjects dropped out during the first 2 weeks due to loss of contact (N = 1; modafinil), incarceration (N = 1; modafinil), and choice of another treatment (N = 1; placebo). Data from these 4 subjects were not used for analyses. Ten modafinil subjects and 10 placebo subjects completed the trial.

At baseline, there were no differences between groups for sociodemographic characteristics and types of psychotropic medications (Table 1). All were treated with atypical antipsychotics. The distribution of atypical antipsychotics between the modafinil and placebo groups were 5 versus 2 for olanzapine, 2 versus 4 for risperidone, 2 versus 3 for quetiapine, and 3 versus 1 for ziprasidone. In each group, 3 patients were taking more than 1 antipsychotic medication. Concomitant psychotropic medications included typical antipsychotics (N = 5), antidepressants (N = 14), mood stabilizers (N = 10), benzodiazepines (N = 4), anticholinergics (N = 3), zolpidem (N = 3), and buspirone (N = 2).

There were no differences between groups for baseline clinical characteristics except for FSS and VAFS scores ($p < .01$), immediate recall at the Rey Auditory Verbal Learning Test ($p < .05$), and the spatial working memory test with 2-second delay ($p < .05$) (Table 2). In mixed-models analysis that looked at FSS baseline (modafinil group: 39.7 ± 4.6, placebo group: 50.6 ± 7.5) and week 8 (modafinil group: 32.3 ± 7.2, placebo group: 34.9 ± 14.2) scores, there was an overall reduction in fatigue in both groups ($F = 17.4$, $df = 1,18$; $p < .001$). There was, however, no differential reduction by treatment in FSS scores after 8 weeks of treatment. While there were overall improvements in CGI illness and fatigue scores, VAFS scores, and SANS alogia scores, as well as an overall increase in akathisia after 8 weeks of treatment, there were no differences between groups over time for the outcome variables tested, as well as for symptoms and cognitive test scores (Table 2). The most common side effects associated with modafinil were agitation (N = 4), insomnia (N = 3), and dry mouth (N = 2).

Table 1. Baseline Characteristics of Patients With Schizophrenia Who Completed the Study of Modafinil for Fatigue and Cognition

Characteristic	Modafinil (N = 10)	Placebo (N = 10)
Sex, female, %	50	70
Age, mean ± SD, y	35.9 ± 9.4	38.9 ± 10.0
Age at onset of illness, mean ± SD, y	24.3 ± 8.1	26.1 ± 7.2
Length of illness, mean ± SD, y	11.6 ± 9.0	12.8 ± 10.8
Concomitant medications, N		
Atypical antipsychotics	10	10
Typical antipsychotics	3	2
Mood stabilizers	4	6
Antidepressants	9	5
Benzodiazepines	2	2
Anticholinergics	2	1
Buspirone	2	0
Zolpidem	2	1

DISCUSSION

Our results, which suggest that both modafinil and placebo improve fatigue over time, are consistent with previous findings,[10] but suggest more of a placebo rather than a specific medication effect. A recent study[34] reports similar results regarding the effects of modafinil and placebo on fatigue in patients treated with antidepressants. Both studies demonstrate the essential role of double-blind, placebo-controlled design when looking at the effects of a drug on fatigue. In contrast to a previous study of schizophrenia,[15] we did not find an effect of modafinil on attention, working memory, and executive functioning. Our negative findings may be related to different methodologies (single dose vs. daily doses) and time of testing. Turner et al.[15] tested their subjects 2 hours post–drug-administration, which corresponds to the time of peak plasma concentrations of modafinil.[35] Our study did not control for time of testing after modafinil administration.

Our patients tolerated modafinil well and reported few and mild side effects, and there were no differences between groups on measures of positive or negative symptoms. However, 1 patient had a worsening of psychosis and was hospitalized during the first week of treatment with 100 mg of modafinil. It was unclear that the exacer-

Table 2. Comparison of Clinical and Cognitive Variables Within and Between the Modafinil and Placebo Groups at the Beginning and at the End of the Randomization Phase (mean ± SD)

	Modafinil		Placebo	
Variable	Baseline	Week 8	Baseline	Week 8
Illness CGI-Improvement subscale[a]	4.2 ± 0.4	3.9 ± 0.3	4.3 ± 0.5	3.9 ± 0.9
Fatigue CGI-Improvement subscale[b]	4.1 ± 0.3	3.5 ± 0.7	4.1 ± 0.3	3.3 ± 1.2
Fatigue Severity Scale[b,c]	39.7 ± 4.6	32.3 ± 7.2	50.6 ± 7.5	34.9 ± 14.2
Visual analogue fatigue scale[b,c]	5.0 ± 0.7	6.1 ± 1.7	3.0 ± 1.2	5.8 ± 2.8
Brief Psychiatric Rating Scale	26.6 ± 5.9	25.0 ± 4.0	27.1 ± 6.5	23.3 ± 5.6
SANS affective flattening	1.7 ± 0.7	1.3 ± 1.1	1.3 ± 1.3	1.2 ± 1.0
SANS alogia[a]	0.9 ± 1.0	0.4 ± 1.0	1.1 ± 1.0	0.4 ± 1.0
SANS avolition	1.8 ± 1.1	1.4 ± 1.0	1.7 ± 0.1	1.3 ± 1.2
SANS asociality/anhedonia	1.7 ± 0.9	1.6 ± 1.0	1.6 ± 1.1	1.0 ± 1.1
Modified Simpson dyskinesia	0.3 ± 0.5	0.9 ± 1.3	0.1 ± 0.3	0.0 ± 0.0
Modified Simpson-Angus Scale[a]	0.2 ± 0.4	0.3 ± 0.7	0.3 ± 0.7	0.6 ± 1.1
CPT-IP 2-digit	2.3 ± 1.1	2.5 ± 1.3	2.5 ± 0.9	2.6 ± 1.0
CPT-IP 3-digit	1.8 ± 1.0	2.1 ± 1.4	1.7 ± 1.3	1.8 ± 1.1
CPT-IP 4-digit	0.9 ± 0.8	1.2 ± 1.0	1.2 ± 0.9	1.2 ± 0.9
Letter-number span	7.7 ± 2.5	8.7 ± 1.9	10.3 ± 3.3	8.4 ± 4.6
Oculomotor Delayed Response Test				
Direct touch	9.3 ± 5.3	8.2 ± 4.5	8.2 ± 3.6	7.6 ± 2.5
2-Second delay[d]	33.7 ± 13.3	36.9 ± 19.0	47.7 ± 13.5	40.9 ± 10.4
Delayed Match to Sample Task				
No delay total correct	8.9 ± 1.4	7.9 ± 2.9	9.3 ± 0.8	8.7 ± 1.3
4-Second delay total correct	13.6 ± 2.2	12.1 ± 6.2	14.5 ± 3.4	15.1 ± 3.0
COWAT	28.1 ± 10.0	31.7 ± 12.5	33.7 ± 10.3	35.5 ± 12.2
Rey Auditory Verbal Learning Test				
Immediate recall[d]	36.6 ± 7.8	39.7 ± 4.3	46.8 ± 9.5	46.9 ± 11.3
Delayed recall	5.3 ± 2.6	5.6 ± 1.7	7.7 ± 3.8	6.9 ± 3.2

[a]$p < .05$ change from baseline to week 8 for both groups combined.
[b]$p < .01$ change from baseline to week 8 for both groups combined.
[c]$p < .01$ between groups at baseline.
[d]$p < .05$ between groups at baseline.
Abbreviations: CGI = Clinical Global Impressions scale, COWAT = Controlled Oral Word Association Test, CPT-IP = Continuous Performance Test-Identical Pair version, SANS = Scale for the Assessment of Negative Symptoms (modified version).

bation of symptoms was related to modafinil. The patient was taking a low modafinil dose for a short period of time. There have been reports of psychotic episodes associated with modafinil use.[36,37] While a causal relationship has not been determined, modafinil should be used with caution in patients with a history of psychosis, and schizophrenia patients should be monitored closely while being treated with modafinil.

Lack of differences between groups may be related to the limitations of this study. CGI fatigue and VAF scales may be too imprecise to assess the various dimensions encompassed in the concept of fatigue. The FSS includes symptoms that may be classified as physical fatigue, asthenia, or anergia. In a post hoc analysis, we divided the FSS symptoms in physical fatigue and asthenia/anergia dimensions, but did not find any differences between groups. The sample size was small, and the maximum modafinil dose was limited to 200 mg per day. Furthermore, baseline fatigue scores were higher in the placebo group compared with the modafinil group, and the marked improvement in the placebo group may be due to a regression to the mean. It is doubtful that these findings were related to differences in atypical antipsychotics between groups, since the distribution of atypical antipsychotics was similar between groups. Finally, most of the subjects were taking several psychotropic medications. It is possible that modafinil has an antisedative effect on some but not all psychotropic medications. Modafinil may decrease fatigue associated with divalproex[38] or antidepressant medications.[34,39,40] Because of the small number of subjects, we were unable to compare the effects of modafinil between patients taking different classes of psychotropic medications.

In summary, modafinil improved fatigue in schizophrenia patients treated with psychotropic medications, but the effect of modafinil did not differ from the effect of placebo. Contrary to our expectations, modafinil did not improve attention, working memory, or executive functioning. In most patients, modafinil was safe and well tolerated. However, the worsening of psychosis in 1 patient in the present study and as reported in previous case reports[36,37] suggests that schizophrenia patients treated with modafinil should be closely monitored.

Drug names: buspirone (BuSpar and others), carbamazepine (Carbatrol, Tegretol, and others), chlorpromazine (Sonazine, Thorazine, and others), clozapine (Clozaril, FazaClo, and others), diazepam (Valium and others), divalproex (Depakote), haloperidol (Haldol and others), modafinil (Provigil), olanzapine (Zyprexa),

phenytoin (Dilantin, Phenytek, and others), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon), zolpidem (Ambien).

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