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ORIGINAL INVESTIGATION

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Effect of modafinil on fatigue, mood, and health-related quality of life in patients with narcolepsy

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Abstract *Introduction:* In addition to excessive sleepiness, patients with narcolepsy often have significant fatigue, depressed mood, and decreased quality of life. *Objective:* To determine whether treatment with modafinil for excessive sleepiness improves fatigue, mood, and health-related quality of life (HRQOL) in patients with narcolepsy. *Materials and methods:* Outpatients with narcolepsy underwent a 14-day washout of psychostimulants and then were enrolled in this 6-week, open-label, multicenter study. Patients received modafinil starting at 200 mg once daily for week 1, and then 200 or 400 mg daily for weeks 2 through 6. Efficacy was evaluated using the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) and the Profile of Mood States (POMS). Safety was assessed by monitoring adverse events (AE). *Results:* At baseline, 151 patients had moderate to severe excessive sleepiness (mean Epworth Sleepiness Scale score= 17.8±4.4). Most patients (≥70% of 123 who completed the study) received 400 mg modafinil once daily during weeks 2 through 6. Modafinil significantly improved HRQOL, based on SF-36 measures of mental and physical component summary scores and subdomain scores of role-physical, social functioning, and vitality (each $P<0.001$). Modafinil treatment was also associated with significantly reduced fatigue and significantly improved vigor and cognition as assessed by the POMS (each $P<0.001$) from weeks 1 through 6. The most frequent AE with modafinil treatment were headache, nausea, and insomnia; most AE were mild or moderate in nature. Only seven patients (5%) withdrew from the study because of AE. *Conclusion:* In narcolepsy patients who were switched from psychostimulants, modafinil therapy improved HRQOL and subjective feelings of vigor and cognitive functioning and reduced fatigue.

Keywords Narcolepsy · Quality of life · Fatigue · Cognition · Mood · Modafinil

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Introduction

Narcolepsy is a sleep disorder that affects 0.03–0.06% of the population in North America and Western Europe (Hublin et al. 1994). Recent research implicates the absence of hypocretin-containing neurons in the etiopathology of narcolepsy (Lin et al. 2001; Mignot et al. 2002). Narcolepsy is primarily characterized by chronic excessive sleepiness that significantly impairs daily life. Narcoleptic symptoms, such as chronic sleepiness, sleep attacks, and poor concentration, interfere with participation in interpersonal and social activities and decrease professional attainment and earnings (Roy 1976; Broughton et al. 1981; Beusterien et al. 1999). Moreover, people with narcolepsy have a greater likelihood of accidents attributable to excessive sleepiness at home, on the job, and while driving (Broughton et al. 1981).

Previous research also indicates that, in addition to or perhaps associated with these difficulties, narcolepsy patients have an increased vulnerability to psychiatric disorders when compared with patients without narcolepsy. Many narcolepsy patients exhibit major depression, altered personality, and other psychiatric difficulties (Roy

1976; Broughton et al. 1981; Krishnan et al. 1984; Mosko et al. 1989). In a study from Broughton and colleagues, nearly half of the patients with narcolepsy reported "personality changes" in association with onset of the condition (Broughton et al. 1981). Results of a more recent survey indicate that, despite treatment for excessive sleepiness, narcolepsy patients remain at significant risk for psychiatric and psychosocial limitations (Goswami 1998).

Amphetamines and other psychostimulants have long been a mainstay of treatment for excessive sleepiness associated with narcolepsy. However, it has been argued that psychostimulants may compound some psychiatric and interpersonal problems of patients with narcolepsy (Douglas 1998). Well-documented side effects of psychostimulants include increased feelings of anxiety and agitation, erectile dysfunction, insomnia, decreased libido, and, in some cases, mania (Palfai and Jankiewicz 1991). All of these side effects might exacerbate existing or underlying psychiatric conditions and thereby worsen interpersonal relationships (Horrigan and Barnhill 2000).

Modafinil is a novel wake-promoting agent that is chemically and pharmacologically distinct from the psychostimulants. The effects of modafinil on health-related quality of life (HRQOL) have recently been examined in an analysis of data pooled from two large, well-controlled, randomized clinical trials of modafinil for the treatment of excessive sleepiness in patients with narcolepsy (Beusterien et al. 1999). After 9 weeks of modafinil therapy, patients receiving modafinil 400 mg exhibited significantly improved wakefulness, using both objective and subjective measures, as well as improvements on ten of 17 HRQOL scales using the Medical Outcomes Study 36-item Short-Form Health Survey (SF-36) (Ware and Sherbourne 1992; Beusterien et al. 1999). Importantly, HRQOL improvements with modafinil were seen not only in physical functioning and productivity but also in aspects of psychiatric well-being: enhanced social functioning, attention/concentration, and self-esteem. Decreased limitations due to emotional problems were also observed. These findings suggest that modafinil may improve HRQOL, including those aspects of QOL associated with psychiatric well-being.

Several extensive investigations have shown that the 65-item Profile of Mood States (POMS) questionnaire is a valid measure of six transient mood states, sensitive to change in treatment in the psychiatric outpatient population (Lorr et al. 1964; Holland et al. 1986; McNair et al. 1992). Concomitant use of the SF-36 and the POMS allows for examination not only of HRQOL but also subjective mood and functioning, based on patient ratings of six different categories of mood states with the POMS: vigor-activity, fatigue-inertia, confusion-bewilderment, tension-anxiety, depression-dejection, and anger-hostility.

Results showing that modafinil significantly improved wakefulness, as indicated by a reduction in Epworth Sleepiness Scale (ESS) scores in this patient population have been reported elsewhere (Schwartz et al. 2003). The objective of the present study was to further examine and clarify the effects of modafinil on subjective HRQOL, mood, and fatigue. This paper presents the findings of the effect of modafinil on the SF-36 and POMS responses in outpatients with narcolepsy.

Material and methods

Study design

This was a flexible-dose, open-label investigation of modafinil conducted by 19 investigators at 20 centers in the United States. The protocol was approved by local ethics committees and abided by the guidelines of the Declaration of Helsinki and its amendments. Patients meeting eligibility provided written, informed consent before entry into the study.

Patient selection

Outpatients between 18 and 68 years of age participated in the study if they had a current diagnosis of narcolepsy according to International Classification of Sleep Disorders criteria (American Sleep Disorders Association 1997) and if they or their physicians reported dissatisfaction with psychostimulants (i.e. dextroamphetamine, methylphenidate, or pemoline) taken to alleviate excessive sleepiness. Psychostimulant treatment was considered to be unsatisfactory for one or more of the following reasons: low tolerability; concern about reducing efficacy, dependence, or abuse potential; the need for occasional interruption of treatment to maintain efficacy ("drug holidays"); or unspecified reasons. Prior to receiving study medication, patients received a urine drug toxicology test to ensure that they had not been taking unauthorized medications.

Patients with a history of therapeutic failure for excessive sleepiness were excluded from study participation, as were patients with any active, clinically significant medical disorders. Patients with concomitant severe obstructive sleep apnea syndrome and periodic limb movement disorder were also excluded. Additional exclusion criteria included uncontrolled hypertension, obstructive respiratory disease, glaucoma, insulin-dependent diabetes, drug sensitivity or drug allergy to stimulant medications, or any prior experience with modafinil.

Study procedure

The investigation included a prestudy evaluation followed by a 2-week psychostimulant washout period, then a 6-week period of open-label, flexible-dose treatment with modafinil. Patients were scheduled to visit the clinic 5 times: at screening (day −14), at baseline after the 2-week washout period (day 0), at the end of the first and second weeks of treatment (weeks 1 and 2, respectively), and at the end of the study (week 6 or at the termination visit). Alcoholic and caffeinated beverages were limited to two of each class per day. Other medications, including anticataplectic therapy, were maintained at stable dosages.

Prestudy assessments

For the prestudy assessment, eligible outpatients underwent a complete physical examination, measurement of vital signs (including sitting and standing blood pressure and pulse rates), and collection of blood and urine samples for hematology, blood chemistry, and urinalysis. Patients who satisfied the study criteria then entered the 2-week washout period, which included 5 days to taper off psychostimulants followed by 7–9 days without stimulants. Patients with a negative urine drug toxicology screen for excluded agents (stimulants, decongestants, antihistamines, unau-

thorized psychoactive agents, and sedative/hypnotic agents) at the baseline clinic visit were eligible to begin modafinil treatment.

Dosing regimen

Patients met with the same investigator at all visits. During the first week of treatment, all patients received 200 mg modafinil, supplied as two 100-mg tablets, to be taken orally as a single dose 1 h before or after the morning meal. At the end of week 1, the dose of modafinil could be increased to 400 mg at the discretion of the investigator, depending on efficacy and tolerability, and was to be taken in the same manner as the 200-mg dose. At the end of the second week of treatment, the investigator determined the optimal daily dose of modafinil (either 200 or 400 mg), which was taken for the remainder of the study (weeks 3–6).

Safety and adverse events monitoring

All observed and spontaneously reported adverse events (AE) were recorded by type and day of onset. Adverse events that were reported or observed during open-label treatment with modafinil, but not during the washout period, were considered to be treatment emergent. For each AE, investigators assigned a severity rating and assessed the relationship to study medication as not related, unlikely to be related, possibly related, probably related, or definitely related. Physical examinations were conducted at the screening visit and at the end of the study. Blood and urine samples were collected at the screening visit, the baseline visit, and at the end of the study. Vital signs (including sitting and standing blood pressure and pulse rates) were monitored at each clinic visit.

Outcome measures

The efficacy of modafinil for improving wakefulness (reported elsewhere) (Schwartz et al. 2003) was assessed using the ESS, a validated measure of subjective sleepiness (Johns 1991), and the Clinical Global Impression of Change (CGI-C), a measure to assess the change in overall clinical condition over time (Guy 1976). We report here the results of secondary outcome measures using the SF-36 and POMS, which are widely accepted subjective measures of HRQOL, mood, and fatigue.

The SF-36, a widely used and validated HRQOL questionnaire, is an instrument that has been demonstrated to be applicable to a wide variety of general and medical populations and interventions (McHorney et al. 1993, 1994). Patients were assessed with the SF-36 at baseline and week 6. Physical and mental component summary scores were calculated from the eight multi-item scales of the SF-36 (general health, mental health, physical functioning, role-emotional, role-physical, social functioning, vitality, and bodily pain). Additionally, mental and physical summary scales were calculated from scores of the eight SF-36 scales (Ware et al. 1995). The scaling assumptions of the SF-36 have been documented, and the reliability and validity of the eight-scale profile and two summary scales have been extensively studied in the general population and patient populations (McHorney et al. 1993, 1994; Ware et al. 1995). Scores for the eight SF-36 scales range from 0 to 100, with higher scores reflecting higher quality of life (i.e. better health). The two summary scales are scored to have a mean of 50 and a standard deviation of 10 in the general US population (Ware et al. 1995).

The POMS, a widely used measure of transient mood states, is a general psychological assessment tool which has six subscales (vigor-activity, fatigue-inertia, confusion-bewilderment, tension-anxiety, depression-dejection, and anger-hostility) that can be administered and scored collectively or individually (McNair et al. 1992). Specific validation of the POMS for narcolepsy has not yet been performed, but other instruments in narcoleptic clinical studies have used the POMS as a method of determining convergent validity. In our study, patients' mood and fatigue were assessed at baseline and at weeks 1, 2, and 6, using the POMS. Patients reported how they had been feeling over the past week by rating 65 adjectives relating to mood (e.g. friendly, tense) using a 5-point scale ranging from 0 ("not at all") to 4 ("extremely"). Each of the six POMS subscales, or mood factors, comprised a subset of adjectives; a score for each mood factor was obtained by summing responses in each subset. Total "disturbed mood" scores were calculated by summing the scores for the six primary mood factors, with negative weight assigned to the vigor-activity factor (McNair et al. 1992). Particular scores that were monitored carefully included fatigue (e.g. physical fatigue, mental fatigue), vigor (e.g. energy level, activity level), and cognitive state (e.g. clarity of thinking, concentration).

Statistical analysis

All patients who received at least one dose of modafinil and had one post-washout efficacy evaluation were included in the current analyses. Patients were evaluated as a single population (all patients) and also by subgroup according to the stimulant medication taken most recently before entry into the study. Comparisons of outcome measures between prior-stimulant subgroups were performed based on generalized least-squares means. These analyses showed that these prior-stimulant subgroups did not differ with respect to the effects of modafinil on ESS scores. Furthermore, no such differences were seen based on SF-36 and POMS scores. Consequently, all patients were defined as a single modafinil-treated population for subsequent statistical evaluation of outcome and safety measures. Analyses in this study were not powered for changes in the SF-36 and POMS scores; results reported elsewhere were powered for the mean changes from baseline in ESS and CGI-C data. For all patients, the mean changes from baseline in SF-36 and POMS scores from all relevant time points were analyzed using paired *t*-tests. Each test of treatment effect was two-sided, and significance was set at ≤ 0.05. All analyses presented were originally specified in the statistical analysis plan and all analyses performed are presented here or in the original report (Schwartz et al. 2003). However, because of the open-label design and the exploratory nature of these analyses, we have chosen to use the Bonferroni correction for multiple comparisons. Therefore, the more conservative threshold for statistical reliability will be determined at 0.0025. Data from all patients who received at least one dose of modafinil were included in analysis of safety and AE.

Results

Patient demographics

A total of 151 patients who had been dissatisfied with psychostimulant treatment [dextroamphetamine (n=8), methylphenidate (n=66), or pemoline (n=37)] for excessive sleepiness associated with narcolepsy were enrolled in the study and treated with modafinil. Baseline characteristics of all patients are summarized in Table 1. Of the 150 patients who received a CGI-S baseline rating, 124 patients (82.7%) were considered to be moderately ill, markedly ill, or among the most extremely ill.

A total of 123 patients (81.5%) completed the study. The percentages of patients completing the study were similar among all three prior-treatment subgroups (approximately 80%). Eight patients (5%) discontinued the study because of insufficient efficacy. Of these patients, two had received dextroamphetamine previously, two patients had received methylphenidate, and four had received pemoline. Nine patients (6%) discontinued the

Table 1 Patient demographics and baseline characteristics. *ESS* Epworth Sleepiness Scale; *CGI-S* Clinical Global Impression of Severity; *POMS* Profile of Mood States

Characteristic	Patients (n=151)
Mean age (range), years	39 (18–68)
Male/female (n)	70/81
Mean weight±SD (kg)	81±19
Years since narcolepsy diagnosis (mean±SD)	6.4±9.3
Baseline ESS score (mean±SD)	17.8±4.4
Baseline CGI-S [n (%)]	
Normal/slightly ill	26 (17.3)
Moderately ill	71 (47.3)
Markedly/extremely ill	53 (35.3)
Baseline POMS Mood Factor Score (mean±SEM)	
Total mood disturbance	26.3±2.8
Tension-Anxiety	4.2±0.5
Depression-Dejection	8.5±0.8
Anger-Hostility	5.8±0.6
Vigor-Activity	9.8±0.5
Fatigue-Inertia	13.2±0.6
Confusion-Bewilderment	4.6±0.4

study because of one or more adverse clinical events; in five patients (3%), the adverse events leading to discontinuation were considered by the investigator to be related to treatment. Two of the five patients had received dextroamphetamine previously and three had received methylphenidate. Other reasons for study discontinuation included abnormal laboratory test results (n=1), protocol violation (n=1), withdrawn consent (n=4), noncompliance (n=1), lost to follow up (n=1), and other (n=3).

Modafinil dosing

During the first week of the study, the majority of patients (95%) received 200 mg of modafinil, according to the study protocol. At the end of week 1, 105 patients (69.5%) had an increase in dosage, at the investigator's discretion, to 400 mg daily. At week 6, about three-quarters of patients were receiving 400 mg modafinil and one-quarter were receiving 200 mg. A small number of patients received doses of modafinil other than the 200 or 400 mg specified in the protocol. At the final visit at week 6, one patient received 300 mg and one patient received 800 mg, and at earlier time points four patients received 100 mg (week 1) and three patients received 300 mg (week 2).

Outcomes

Medical Outcomes Study 36-item Short-Form Health Survey

At baseline, the lowest (most impaired) scores for HRQOL on the SF-36 scores were observed in the role-physical and vitality domains; mean (SD) physical and mental component summary scores were 44.5 (6.6) and 41.4 (11.8), respectively (Table 2). After 6 weeks of treatment, modafinil significantly improved HRQOL compared with baseline as shown by the mental (P<0.0001) and physical (P<0.001) component summary scores on the SF-36. Additionally, modafinil treatment significantly improved three of the eight domains (role-physical, social functioning, and vitality) of the SF-36 versus baseline (P<0.0001). Although modafinil also significantly improved scores in the physical functioning and role-emotional domains, these improvements did not meet the adjusted criterion for statistical significance.

Table 2 Medical Outcomes Study 36-item Short Form Health Survey (SF-36): change from baseline to week 6. Domain scores range from 0 (lowest quality of life) to 100 (highest quality of life). Significance levels reflect change from baseline to week 6 by paired t-test. *NS* not significant.

SF-36 domain	Mean score (SD)				
	Baseline		Week 6		P
General health	69.0	(21.0)	68.5	(21.8)	NS
Mental health	68.7	(19.8)	70.1	(19.8)	NS
Physical functioning	76.1	(25.0)	80.1	(22.9)	<0.05
Role-emotional	63.6	(42.2)	73.7	(37.9)	≤0.01
Role-physical	34.3	(36.6)	58.3	(40.6)	<0.0001
Social functioning	57.0	(29.4)	68.9	(28.8)	<0.0001
Vitality	27.9	(20.4)	47.4	(24.9)	<0.0001
Bodily pain	74.2	(24.5)	72.6	(25.6)	NS
Mental component summary score	41.4	(11.8)	45.8	(12.3)	<0.0001
Physical component summary score	44.5	(6.6)	46.8	(11.2)	<0.001

Profile of Mood States

At baseline, the most impaired scores on the POMS were observed in the fatigue-inertia factor (Table 3). Modafinil treatment improved all six of the POMS mood factors, with significant improvements reported as early as week 1 and continuing throughout the 6-week study period (improvement range, 24–43%). The most statistically reliable improvements occurred in the fatigue-inertia, vigor-activity, and confusion-bewilderment factors. Modafinil significantly reduced fatigue by week 1 and this effect was sustained. Modafinil also significantly improved vigor and cognition by week 1 and these improvements were sustained. Improvement in the other three mood factors of the POMS (i.e. tension-anxiety, depression-dejection, and anger-hostility) was also demonstrated at all post-baseline time points; although these improvements did not meet the adjusted criteria for statistical significance. Consistent with overall changes in the POMS scores, modafinil resulted in significantly decreased total mood disturbance from baseline (61.6%), with improvements noted at week 1 maintained throughout the study (P<0.001).

Table 3 Profile of Mood States (POMS): change from baseline to weeks 1, 2, and 6

POMS factor	Score (SD)				
	Baseline	Week 1	Week 2	Week 6	P^a
Vigor-Activity[b]	9.8 (6.0)	13.1 (6.4)	13.7 (7.1)	13.3 (7.7)	<0.001
Fatigue-Inertia	13.2 (7.2)	8.2 (6.2)	6.3 (6.0)	7.5 (6.6)	<0.001
Confusion-Bewilderment	4.6 (4.9)	2.9 (4.7)	2.4 (4.6)	3.0 (5.4)	<0.001
Tension-Anxiety	4.2 (6.2)	3.1 (5.8)	2.1 (4.9)	2.7 (6.0)	<0.05
Depression-Dejection	8.5 (10.2)	6.1 (9.2)	5.3 (8.2)	6.5 (11.0)	<0.05
Anger-Hostility	5.8 (7.7)	4.6 (7.0)	3.3 (5.3)	4.1 (7.4)	<0.05

[a] Weeks 1, 2, and 6 vs baseline score by paired *t*-test
[b] Higher scores represent improvement for the Vigor-Activity item of the POMS; lower scores represent improvement in the other items

Safety and adverse events

Modafinil was well tolerated. With modafinil, mean changes from baseline in laboratory test results and vital signs (including heart rate and sitting and standing systolic and diastolic blood pressure) were generally small and not clinically significant. No serious AE were reported over the course of the study. During the active treatment period, the most common treatment-emergent AE were headache (35%), nausea (10%), and insomnia (9%). The majority (93%) of these were mild or moderate in severity. Eight patients (5%) discontinued modafinil treatment because of insufficient efficacy, and ten patients (7%) discontinued because of one or more AE; in seven patients (5%), the AE were considered by the investigator to be related to treatment. Treatment-related AE leading to discontinuation were headache (*n*=4), abnormal thinking (*n*=2), confusion (*n*=2), and depression (*n*=2).

Discussion

Modafinil significantly reduced fatigue and improved HRQOL, vigor, and cognition in this population of patients with narcolepsy who were switched from treatment with psychostimulants. Improvements occurred rapidly (as early as week 1) and were maintained throughout this 6-week study. The most significant, specific improvements in the SF-36 were seen in the subdomains of vitality, role-physical, and social functioning, and in the mental and physical component summary scores. Similarly, the most substantial improvements on the POMS were seen in the mood factors associated with fatigue, vigor, and cognition. These findings suggest that modafinil treatment may produce improvements in subjective functioning and HRQOL that extend beyond those specifically related to improvements in wakefulness.

Investigational significance

Although primarily characterized by excessive sleepiness, narcolepsy is a disorder associated with other primary symptoms such as cataplexy and hypnagogic hallucinations, and secondary symptoms such as fatigue and cognitive deficits (Roy 1976; Broughton et al. 1981; Krishnan et al. 1984; Mosko et al. 1989; Goswami 1998). The extent to which each of these symptoms contributes to the impairment in overall functioning, HRQOL, and increased likelihood of psychiatric problems is not determined. Despite their potential importance to the patient, relatively few studies have focused on the impact and treatment of these secondary symptoms. For example, analysis of the personal interviews used in a retrospective record review revealed that some patients found hypnagogic hallucinations to be an under-recognized clinical symptom of narcolepsy (Goswami 1998). The results of the retrospective study underscore the importance of eliciting information regarding potential residual symptoms (e.g. hypnagogic hallucinations) in the course of gathering patient history and providing appropriate treatment (Goswami 1998). The lack of standardized, sensitive, reliable, and valid narcolepsy-specific instruments to measure the HRQOL and overall functioning of patients with narcolepsy is a distinct drawback to investigators in this field.

HRQOL is inherently a multidimensional phenomenon, and most useful QOL instruments reflect this. Multidomain instruments, such as the SF-36, are generally preferred for QOL assessment strategies, since an instrument that does not include several dimensions will make it impossible to determine the nature of a score change (Ware and Sherbourne 1992). Although not narcolepsy-specific, the SF-36 has been a useful tool for assessing HRQOL across a wide variety of disease states, such as depression, migraine, epilepsy, and narcolepsy. The SF-36 scores for HRQOL seen in the current investigation at baseline were substantially and appreciably lower than those seen in the general population (Beusterien et al. 1999). The present study suggests that modafinil treatment to improve wakefulness may help to further alleviate the burden of narcolepsy by improving HRQOL. Consistent with the findings of Beusterien et al (1999), modafinil significantly and rapidly improved HRQOL in the present study. The most significant improvements in the SF-36 were found in the subdomains of vitality, role-physical, and social functioning, as well as in the mental component summary scores. The magnitude of the improvements in HRQOL (as assessed by the SF-36 scores) observed in the present study may reflect meaningful improvements in the lives of patients receiving modafinil treatment.

The positive changes in specific POMS factor scores in the present investigation indicate that modafinil treatment significantly reduces fatigue and significantly improves vigor and cognition, consistent with the POMS rating results in a previous study (Pigeau et al. 1995). Modafinil has been shown to preserve various aspects of cognition, such as concentration and sustained attention, in laboratory models of acute sleep loss (Baranski et al. 1998; Stivalet et al. 1998). Further support of modafinil's cognitive enhancing effects in healthy volunteers without sleep deprivation can be drawn from a recently published study using a comprehensive battery of neuropsychological tests (Turner et al. 2003). Notably, modafinil significantly enhanced cognitive performance on tests of digit span, visual pattern recognition memory, spatial planning, and stop-signal reaction time (Turner et al. 2003). Subjects in this study reported feeling more alert, attentive, and energetic after taking modafinil.

The magnitude of improvement in the POMS mood factor scores in the present investigation was moderate, although it did not meet the conservative criterion for statistical significance. Improvements in mood factors like tension-anxiety, depression-dejection, and anger-hostility ranged from 24% to 36%, compared with baseline. The findings on mood are in agreement with those of Pigeau et al (1995), who found that modafinil treatment prevented decrements in mood that were seen with placebo in normal, healthy subjects undergoing sustained sleep deprivation. This and other studies have shown no adverse effects of modafinil treatment on mood (Pigeau et al. 1995; Broughton et al. 1997). The findings of improved vigor are also similar to a previous investigation that evaluated modafinil to prevent sleepiness in healthy volunteers deprived of sleep for a prolonged period (Pigeau et al. 1995) and to treat excessive sleepiness experienced by patients with narcolepsy (Broughton et al. 1997). Furthermore, the findings of improved subjective cognition in our narcoleptic patients dissatisfied with psychostimulants are similar to previous studies of modafinil in healthy volunteers undergoing sustained sleep deprivation (Baranski et al. 1998; Stivalet et al. 1998).

Technical considerations

The open-label design is a limitation of the present findings, as knowledge of receiving active drug may bias investigator and/or patient ratings and self-reports. Similarly, the absence of a placebo control group is another limitation. However, the magnitude of changes in ESS, CGI-S, and HRQOL are similar to those reported in earlier double-blind, placebo-controlled trials (Broughton et al. 1997; US Modafinil in Narcolepsy Multicenter Study Group 1998, 2000; Beusterein et al. 1999). The open-label design also included the absence of an adverse-event checklist and relied only on spontaneously reported AE.

Patients with psychiatric disorders were excluded from this investigation because of its preliminary nature. While improvements in fatigue and mood were seen in the present patient population, the effects of modafinil on mood and HRQOL in narcolepsy patients with comorbid psychiatric disorders remain to be determined.

Conclusions

Modafinil significantly improved subjective fatigue, vigor, cognition, and HRQOL among patients with moderate to severe symptoms of narcolepsy, and was well tolerated. Significant and broad improvements in HRQOL occurred, based on SF-36 measures of the mental and physical component summary scores and the subdomain scores of role-physical, social functioning, and vitality. Although improvements were also seen in all six mood factors defined by the POMS (i.e. vigor-activity, fatigue-inertia, confusion-bewilderment, depression-dejection, tension-anxiety, and anger-hostility), the most reliable improvements were demonstrated in fatigue, vigor, and cognition. Improvements on all of these measures occurred rapidly following initiation of modafinil treatment and persisted throughout the 6-week study. These findings suggest that modafinil treatment for wakefulness may significantly alleviate the other symptoms associated with narcolepsy and may help to reduce the overall burden for these patients. By improving wakefulness, reducing fatigue, and improving vigor and cognition, modafinil may help patients with narcolepsy to improve their overall functioning.

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