Modafinil reduces excessive somnolence and enhances mood in patients with myotonic dystrophy

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Abstract—*Objective:* To evaluate the potential of modafinil in reducing excessive daytime somnolence (EDS) and enhancing indexes of quality of life and mood in patients with myotonic dystrophy (DM). *Methods:* Forty patients with DM were randomized to receive modafinil and placebo for 14 days each, using a double-blind, cross-over design. Before and after each trial, subjects completed handgrip strength testing, spirometry, and quality-of-life measures (RAND). On days 7 and 14, each subject completed the Epworth Sleepiness Scale (ESS), the Stanford Sleepiness Scale (SSS), and the Profile of Mood States (POMS). *Results:* ESS scores were lower while taking modafinil (mean 248 mm; 95% confidence limit 220 to 276 mm) as compared with placebo (309 mm; 281 to 336 mm) ($p < 0.001$). Mean SSS scores were also lower during the modafinil trial (3.05; 2.77 to 3.33) than during the placebo trial (3.45; 3.18 to 3.71) ($p < 0.05$). The POMS indicated that modafinil decreased fatigue–inertia ($p < 0.001$) and increased vigor–activity and tension–anxiety ($p < 0.001$) indexes. The total mood disturbance score was also decreased during the modafinil trial as compared with placebo ($p < 0.05$). The RAND quality-of-life measures of energy ($p < 0.001$) and health change ($p < 0.05$) were both significantly enhanced during the modafinil treatment phase. No changes in maximal grip strength or forced expired volume in 1 second were detected over the course of the study. Headache was the most frequently reported adverse event. Four patients withdrew from the study, three because of side effects (two during modafinil ingestion and one during placebo ingestion). *Conclusion:* Modafinil reduces somnolence and improves mood in patients with DM.

NEUROLOGY 2002;59:1876–1880

Myotonic dystrophy (DM) is a multisystem disorder characterized by myotonia, endocrine dysfunction, cataract formation, cardiac conduction defects, muscle weakness, and hypersomnolence. The predominant form of DM, DM-1, results from an expanded CTG trinucleotide repeat in the 3'-untranslated region of the myotonin protein kinase gene of chromosome 19 and is the most common form of muscular dystrophy in adults.[1]

Hypersomnolence is one of the more frequently reported symptoms in patients with DM, and recent studies have confirmed higher levels of daytime somnolence in this population,[2] not related to sleep apnea per se.[3] Somnolence can ultimately lead to handicaps such as cessation of employment and withdrawal from social activities and eventually impair activities of daily living. Several proposed treatments for hypersomnolence in DM patients either have shown a lack of efficacy[4,5] or have an addictive potential and/or poorly tolerated side effects.[6] Modafinil is a newly available CNS stimulant that has been shown to be efficacious in the treatment of narcolepsy and hypersomnia.[7-12] The mechanism of action of modafinil is still not completely understood, but it is associated with an activation of the tuberomamillary nucleus and orexin-containing neurons,[13] though not via direct orexin receptor binding.[14] Although modafinil is currently approved for use only in patients diagnosed with narcolepsy, a recent small, open, pilot study in DM patients indicated decreased somnolence.[15]

The current investigation represents the first prospective, double-blind, randomized, placebo-controlled study designed to evaluate the potential efficacy of modafinil in decreasing excessive daytime somnolence (EDS) and improving measurements of mood, quality of life, and daily function in those with DM. Additional objectives of the current study were to evaluate any dose–response relationship and to determine the side effect profile of modafinil in this group of patients.

Methods. The planned population for this study comprised patients aged 18 to 60 years with DM and subjective complaints of daytime hypersomnolence. Women of childbearing age were required to undergo a β-human chorionic gonadotropin test to confirm that they were not pregnant and to use an effective birth-control method.

Patients were excluded if they met any one of the following criteria: known hypersensitivity to modafinil; preg-

nant or lactating; agitated or severely anxious; coronary artery disease, recent history of myocardial infarction or unstable angina, mitral valve prolapse, or left ventricular hypertrophy; uncontrolled hypertension; moderate liver disease, renal insufficiency, or cognitive impairment. A patient was deemed to have "cognitive impairment" if, at the baseline visit, it was the investigator's opinion that the patient had a cognitive deficit that could substantially limit the patient's ability to understand and complete any of the rating forms.

The primary efficacy variable was the Epworth Sleepiness Scale[16] (ESS). We modified the ESS from a 4-point ordinal scale to a 10-cm visual analogue scale, with the four descriptors (no chance of dozing, slight chance of dozing, moderate chance of dozing, high chance of dozing) centered at 0.5, 3.5, 6.5, and 9.5 cm. Patients made a single mark across the scale at the point corresponding to their perceived chance of falling asleep. Secondary endpoints were the Stanford Sleepiness Scale[17] (SSS), the vigor–activity and fatigue–inertia factors of the Profile of Mood States[18] (POMS), and the energy–fatigue scale from the RAND 36-Item Health Survey.[19] Peak grip strength and forced expired volume in 1 second (FEV_1) were recorded as measurements of changes in voluntary strength.

Two 14-day treatment periods were separated by at least a 7-day washout period. At baseline, the end of the washout period, and the end of each of the two treatment periods, subjects completed handgrip strength testing, spirometry, and the RAND 36-Item Health Survey.[19] On days 7 and 14 of each 2-week treatment period, subjects completed the SSS[20] at 9:00 AM, 3:00 PM, and 9:00 PM. Also at 9:00 PM, they completed the ESS[20] and the POMS.[18] The SSS asked patients to assess "how you are feeling now." The ESS, RAND, and the POMS required patients to respond based on "the last 7 days."

Modafinil (100-mg tablets) and matching placebo (identical in taste, texture, and size) were supplied in labeled prescription vials of 50 tablets for each 14-day treatment period. Patients were instructed as follows: "Take one tablet at breakfast and one tablet at noon for 1 week; then take two at breakfast and two at noon for another week." Patients were randomized to one or the other treatment sequence in blocks of four using a computerized randomization program (Microsoft Excel's RAND; Microsoft, Redmond, WA). The randomization schedule was kept off-site. Sealed code-break envelopes were available at the investigational site, in case of emergency.

At each follow-up visit, patients were questioned regarding the incidence and nature of any adverse clinical events. Space was provided in a patient diary to record the onset, severity, and duration of any adverse events.

Ethics. The study was conducted in accordance with the Helsinki Declaration of 1975, as revised in 1983, and with ICH Guidelines for Good Clinical Practice, including the archiving of essential documents. The study protocol was approved by the McMaster University Research Ethics Board, and all patients provided written, informed consent prior to beginning the protocol.

Statistics. Data from the POMS and RAND were scored according to established guidelines.[18,19] Data from the ESS and POMS were assessed by analysis of variance for a two-treatment, two-period, two-sequence design.[21] The model included terms for sequence, period, day within period, treatment, and treatment-by-day interaction. Data from the SSS were similarly analyzed but included an additional term for time within day and a treatment-by-time interaction term rather than a treatment-by-day term. Voluntary strength, respiratory strength, and RAND scores were assessed by analysis of variance for a two-period, two-treatment, two-sequence crossover study with baseline and washout periods.[21]

If patients, for either period, had neither a day 7 nor a day 14 ESS, SSS, or POMS or a pre- and postperiod RAND value, they were excluded from that data set. For this reason, four patients were excluded from the ESS data set, five from the SSS data set, five from the POMS data set, and four from the RAND data set. If only the day 7 data were available, then the day 7 data were substituted for the missing day 14 data. This occurred in three patients for the ESS, two patients for the SSS, and one patient for the POMS. When an individual question was unanswered in any one of the questionnaires, the average score of the remaining questions (for that factor) was substituted for the missing data. This occurred six times (of 1,152 questions) for the ESS, three times (of 4,200) for the POMS, and nine times (of 5,184) for the RAND.

Based on the results in narcoleptic patients,[9] and assuming the ESS would be equally sensitive in DM patients, a 40-patient study was calculated to be sufficient to have an 80% chance of detecting a difference of 2 U on a 32-point total ESS or an estimated 50 mm on an 800 mm total ESS visual analogue scale score (two-tailed $\alpha = 0.05$, $\beta = 0.20$). Results are presented with 95% CI or 95% confidence limits.

Results. Forty patients, with a mean $\pm$ SD age of 40.7 $\pm$ 11.6 years, were enrolled in the study. Patients were recruited from the Neuromuscular Disease Clinic at McMaster University Medical Center and through the Canadian Muscular Dystrophy Association. Of the 27 women and 13 men, 33 had genetically confirmed DM-1. The mean $\pm$ SD number of CTG repeats of the genetically confirmed DM-1 patients was 680 $\pm$ 350. Of the remaining seven patients with DM, five had an autosomal dominant family history of cataracts, distal muscle weakness, atrophy, and myotonia with dystrophic changes on muscle biopsy and myotonia by electromyography (genetic classification into DM-1 or DM-2 was not available for these patients at the time of testing). Two patients were classified with DM-2 with genetic confirmation of a large CCTG repeat expansion in intron 1 of the ZNF9 gene. On average, patients had had complaints of EDS for 10 years.

Thirty-nine patients ingested 100 mg of modafinil at breakfast and noon for 7 days (one patient withdrew from the study during the placebo trial in period 1 for personal reasons and thus was not exposed to modafinil). Thirty-six patients ingested 200 mg of modafinil as above for an additional 7 days, and these 36 subjects completed both arms of the study. Three patients withdrew from the study owing to adverse events. One patient described headache, nausea, and dyspepsia on placebo. A second patient had nausea and headache on modafinil. A third patient reported nausea, anxiety, headache, palpitations, nervousness, tachycardia, hypertension, and dry mouth on modafinil. These last two patients withdrew from the study when the dose of modafinil was increased from 100 to 200 mg bid. The final analysis was completed on all of
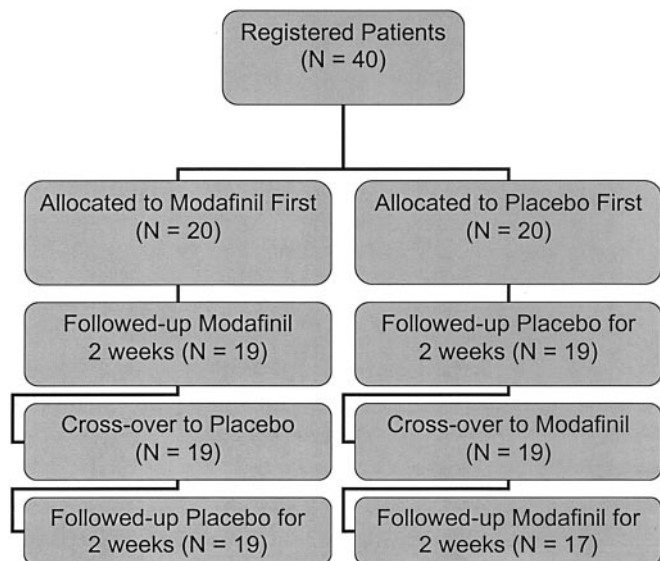
Figure 1. Flow diagram of patient enrollment and participation.

Figure 3. The mean Stanford Sleepiness Scale scores were lower on modafinil (3.05 ± 0.28) than on placebo (3.45 ± 0.26) (p < 0.05). The scores are the means of days 7 and 14 and time (9:00 AM, 3:00 PM, and 9:00 PM) hours are indicated. Open columns = modafinil; shaded columns = placebo.

the 36 patients who completed both arms of the study; however, with an intention-to-treat analysis, there were no significant differences in the conclusions (figure 1).

The mean total ESS score was 20% lower on modafinil (mean 248 mm; 95% confidence limit 220 to 276 mm) than on placebo (309 mm; 281 to 336 mm) ($p < 0.001$). The corresponding values, when converted to the traditional ESS ordinal scale, were 9.9 (8.8 to 11) for modafinil and 12.4 (11.3 to 13.5) for placebo. The mean total ESS score was 15% lower on modafinil than on placebo on day 7 and 25% lower on day 14 (figure 2). Overall, there was no difference between day 7 and day 14 ($p > 0.05$). In addition, there were no sequence, period, or treatment-by-day effects (see figure 2).

Mean SSS scores were also lower on modafinil (3.05; 2.78 to 3.32) than on placebo (3.45; 3.16 to 3.73) ($p < 0.05$). With the exception of day 14 at 9:00 AM, scores were lower on modafinil at all of the individual time points (figure 3).
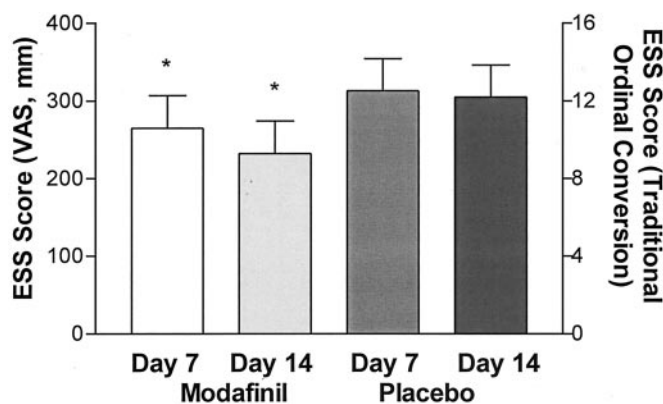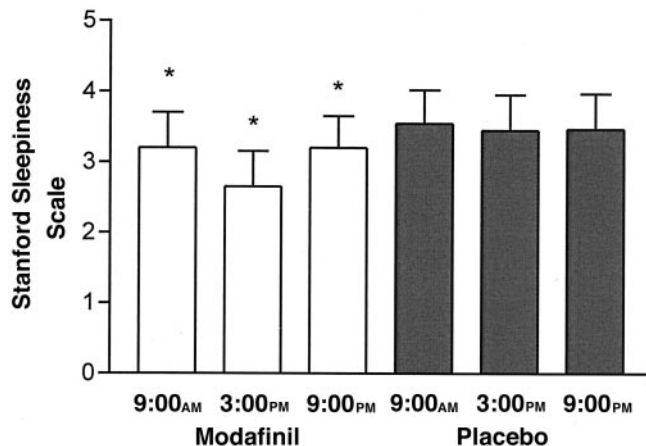

Figure 2. The mean (95% CI) Epworth Sleepiness Scale score was lower on modafinil (248 ± 28 mm) than on placebo (309 ± 28 mm) (p < 0.001). The individual values for days 7 and 14 are indicated for each treatment (left two bars = modafinil; right two bars = placebo). There was no difference between days (p = 0.076).

Although the lowest SSS score was at 3:00 PM for both modafinil periods and for one of the two placebo periods, the analysis did not find the time of day to be a significant factor. There were no period or sequence effects, no difference between days 7 and 14, and no treatment-by-time interactions.

On the POMS rating scale, modafinil improved total mood disturbance ($p < 0.05$), decreased fatigue–inertia ($p < 0.001$), increased vigor–activity ($p < 0.001$), but also increased tension–anxiety ($p < 0.001$), although the score (3.6 ± 1.0) remained well below the normalized score for this factor (6.6).[18] Modafinil had no effect on the other factors. Total mood disturbance, fatigue–inertia, depression–dejection, and anger–hostility factor scores were all higher on day 7 than on day 14 ($p \leq 0.05$), regardless of treatment and of period. A period effect was detected for vigor–activity (period 1 > period 2; $p < 0.05$) but not for any other factor. No sequence effects were detected (figure 4).

With use of the RAND 36-Item Health Survey, patients scored significantly higher on the energy–health concept ($p < 0.001$) and reported a positive health change ($p < 0.05$) while taking modafinil. No treatment effects were detected for physical function, role limitation due to physical health, role limitation due to emotional problems, emotional well-being, social functioning, pain, or general health.

No changes in grip strength or FEV_1 were detected over the course of the study. Of the 36 patients who completed the study, 29 (81%) blindly expressed a preference for modafinil and 7 for placebo ($p < 0.001$). In those who blindly preferred modafinil, their self-rated improvement was "marked" in 61%, "moderate" in 15%, and "mild" in 25% of cases (in two patients, the preference was stated but not rated). The corresponding numbers for placebo were 67% marked, 17% moderate, and 17% mild.

Including patient comments in the diary and at follow-up visits, 30 patients reported a total of 83 adverse events: 65 on modafinil and 18 on placebo. Nearly two-thirds of the complaints were reported during the first 7-day period. Of the adverse events for which severity was
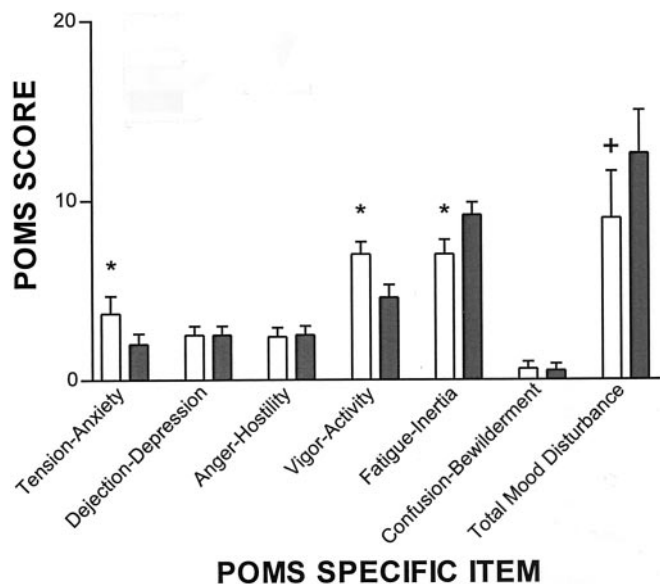
Figure 4. Profile of mood states (POMS). Modafinil increased tension–anxiety (p < 0.001) and vigor–activity (p < 0.001) and decreased fatigue-inertia (p < 0.001). Total mood disturbance score was lower on modafinil than on placebo (p < 0.05). Open columns = modafinil; shaded columns = placebo.

reported, most were mild (32%) or moderate (52%). Adverse events reported more than once consisted of headache (15), anorexia (6), nausea (6), insomnia (5), anxiety (4), dry mouth (4), dyspepsia (4), dizziness (3), nervousness (3), and tachycardia (2).

All of the reported adverse events have been documented in previous studies and are included in the current product labeling. In this sense, none of the reported adverse events was "unexpected." The study medication was discontinued in two patients, but otherwise no interventions or treatments were required, the adverse events subsided with continued use of modafinil, and there were no sequelae. None of the adverse events was considered "serious."

Discussion. EDS is a frequent report of patients with DM. Hypersomnolence may lead to impairments such as a decrease in motivation and voluntary ambulation that can ultimately have a negative impact on employment and social interaction. This double-blind, placebo-controlled clinical trial has demonstrated the effectiveness of modafinil in reducing the perception of EDS in patients with DM. The evidence for this clinical benefit was statistically strong and was consistent across a number of rating scales and with the subjective evaluations of patient preference. A beneficial effect was also evident on nonspecific scales; specifically, a decrease in total mood disturbance (POMS) and a positive health change (RAND).

The ESS has been shown to be somewhat correlated with electroencephalographically measured sleep latencies,[20] and published data support the validity and reliability of the ESS as a subjective measurement of sleep propensity. A recent open study of modafinil in the treatment of somnolence in DM found that the ESS scores and the Multiple Sleep Latency Test (MSLT) both showed significant improvements in subjective and objective somnolence indicators, respectively.[15] Many clinicians use the ESS as a subjective measurement of sleepiness. In the current study, patients reported a 20% decrease in mean ESS scores while taking modafinil. These results are in agreement with those from a recent, small, open trial of modafinil in a similar cohort of patients with DM.[15] In that study, mean ESS scores decreased by 42% compared with baseline, and sleep latencies from the MSLT were increased threefold by modafinil at doses ranging from 200 to 400 mg/day. The discrepancy in the magnitude of the mean EES measurements between studies may be explained by our conversion of the ESS from a 4-point ordinal scale to a 10-cm visual analogue scale. The conversion of the ESS to a visual analogue scale allowed for more degrees of freedom and therefore precision. The decrease in EDS in the current study was also very similar to that reported by Rammohan et al.[22] in a study of modafinil for the treatment of fatigue in MS where ESS scores decreased by 25%. The three major studies supporting the currently approved indication for modafinil, EDS in narcolepsy, all used the ESS as a secondary endpoint. Changes in the total ESS scores in these studies for 200- and 400-mg daily doses were 10 and 15%,[9] 16 and 25%,[11] and 18 and 23%,[12] respectively. With the dose escalation from 200 to 400 mg/day after the first week of treatment, there was no statistically significant further reduction in the ESS scores on the modafinil treatment in the current study. However, from a clinical standpoint, the slight trend in the current study toward lower ESS scores (i.e., less sleep propensity) on the 400- vs 200-mg dose, in combination with those results reported above for narcolepsy, indicates that there may be some patients who may benefit from a 400-mg total daily dose.

The lower ESS scores were also paralleled with the significant reductions in daytime sleep propensity as measured by the SSS. The SSS has also been found to correlate with other established measures of subjective sleepiness.[20] The study did not demonstrate a significant difference in subjective sleepiness between the different times of the day using the SSS. However, the somnolence scores tended to reveal the expected results from the breakfast-and-noon dosing schedule: modest drug effects at 9:00 AM and 9:00 PM and a peak effect at 3:00 PM, coinciding with the time of expected peak somnolence.

It was also encouraging to note that, in addition to decreasing daytime sleep propensity, modafinil also led to enhanced mood, as evidenced by increases in vigor–activity, decreases in fatigue–inertia, and improved total mood disturbance scores using the POMS. In concordance with these results, a previous study of narcoleptic patients also found vigor–activity scores to be increased significantly with modafinil, using the POMS scale.[9] The POMS also indicated

a modest increase in tension–anxiety. This was in agreement with a previous study in narcoleptic individuals.[9] However, anxiety levels were still well below the normalized score[18] and thus pose little concern. No patients in the current or previous narcoleptic study withdrew from only anxiety-related complaints.

The improvements in the energy–health concept and a positive health change measured by the RAND suggested a positive impact upon health-related quality of life in our population of DM patients. Others have also shown improvements in quality-of-life measurements in narcoleptic patients.[23] Whether these results will have an impact on long-term disability and handicap remains to be evaluated.

One of the limitations of the current study was the fact that an objective measure of somnolence such as the MSLT was not employed. However, there are several factors that strengthen the conclusion that modafinil has clinical utility in the treatment of excessive somnolence in patients with DM, including the following: 1) It is the subjective perception of somnolence that is bothersome to patients with DM, and both the ESS and the SSS indicated directionally similar benefits; 2) several indicators of mood that would be deemed beneficial and consistent with a reduction in somnolence showed improvements with only a minor increase in anxiety symptoms; 3) our conclusions are similar to those from the first open study using modafinil in DM, where the MSLT and the ESS both showed improvements following drug treatment; and 4) two indicators of quality of life showed improvements for the modafinil treatment.

The incidence of adverse events in this study was higher than reported in other populations using modafinil.[9,11] This may be a reflection of the conservative approach taken in defining adverse events in this study, or perhaps the nature of this multisystem disease makes patients more susceptible to the adverse effects of modafinil. Most adverse events were transient and disappeared with continued treatment, in spite of dose escalation. For all but two patients, the benefit of treatment with modafinil outweighed the inconvenience of the adverse events.

Although narcolepsy is currently the only clinically approved indication for modafinil, off-label studies have suggested it to be efficacious in a variety of conditions including closed-head brain injury,[24] depression,[25] fibromyalgia,[26] MS,[22] DM,[15] and PD.[27] In spite of the fact that the pathogenesis of hypersomnolence may differ across these various disorders, the results of this and other studies suggest that modafinil may have the potential for widespread use in numerous neurologic disorders in which EDS is a bothersome symptom.

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