Disorders of Excessive Sleepiness*

Treatment Improves Ability to Stay Awake But Does Not Reduce Sleepiness

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A total of 47 patients with sleep disorder (36 male and 11 female) with a mean age of 47.5 ± 15 years were evaluated for daytime symptoms with a Multiple Sleep Latency Test (MSLT) and a Maintenance of Wakefulness Test (MWT) given on the same day—once at the time of their diagnostic evaluation and again after one to six months of treatment. The MSLT and MWT data are consistent with the notion that sleep tendency, as measured by the MSLT and ability to remain awake, as measured by the MWT, represent different physiologic processes. Data show a marked treatment-related improvement in ability to stay awake as measured by the MWT and no treatment-related improvement in sleepiness as measured by the MSLT. We conclude that there is a heterogeneous subpopulation of patients with sleep disorders whose symptoms of daytime sleepiness will show no treatment-related improvement in daytime symptoms if they are evaluated only by the MSLT. We suggest that, since ability to stay awake (and not ability to fall asleep) is a requisite for all job-related duties, an objective, physiologically based test such as the MWT should be used to assess the impact of sleep disorders in cases where there is a clinical concern about fitness to drive or work.

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MSLT = Multiple Sleep Latency Test; MWT = Maintenance of Wakefulness Test; REI = respiratory event index; UPPP = uvulopalatopharyngoplasty

Situated comfortably in a quiet, dark bedroom, how quickly could you fall asleep? How long could you stay awake? For years the Multiple Sleep Latency Test (MSLT) was used in clinical and research studies to quantify physiologic sleep tendency. After a night’s sleep, subjects are asked to get into bed four or five times throughout the day and try to sleep. Measuring the EEG to mark the onset of sleep and hence the time it takes to fall asleep (Sleep Latency), the MSLT is the standard tool for determining pathologic sleepiness that is associated with sleep apnea, narcolepsy, chronic sleep loss, and a host of other conditions that predispose people to fall asleep. In addition to being an objective, physiologically based test, the MSLT has obvious validity: If someone is sleepy, they should fall asleep quickly, but how does sleepiness relate to alertness? Are sleepiness and alertness opposites? Or, can some sleepy people stay awake and others not? Which sleepy people should drive cars, direct aircraft landings, or operate trains? Physicians who diagnose and treat patients with sleep apnea, narcolepsy, and other disorders associated with the symptom of excessive somnolence must frequently confront these questions.

The MSLT is a standard procedure used to assess and diagnose disorders of excessive somnolence.1 The Maintenance of Wakefulness Test (MWT) employs a variation on the protocol used in the MSLT and was designed by Mitler et al2 to assess daytime function when there are clinical questions concerning treatment efficacy or concerning patient safety.

In a previous report 3 on 258 consecutive patients given the MSLT and MWT on the same day, we showed that the two tests measure different abilities. Some patients with abnormally low MSLT scores were able to stay awake when asked to do so on the MWT and, conversely, some patients who failed to stay awake when asked to do so on the MWT were unable to fall asleep quickly on the MSLT. The MSLT seems to measure ease of falling asleep and the MWT seems to measure ability to stay awake.

The present study was performed to determine how the MSLT and the MWT compare in their ability to measure change in daytime sleepiness with treatment. We administered a standard four-nap MSLT and a four-trial MWT consecutively on the same day to a group of patients with the initial complaint of daytime sleepiness. After treatment, we administered MSLT and MWT consecutively again on the same day to measure objective change in sleepiness. We now report that only the MWT changed in the expected therapeutic direction. The MSLT showed no treatment-related change.

Methods

We studied a total of 47 patients (36 male and 11 female) with a mean age of 47.5 ± 15 years that included patients with the following diagnosis: 27 with obstructive sleep apnea, seven with narcolepsy,
seven with idiopathic hypersomnia, one with head trauma, four with depression, and one with periodic leg movement during sleep. Diagnostic criteria were as described by the Association of Sleep Disorders Centers. All patients were free of medications that significantly affected the central nervous system for at least one week before their pretreatment testing. All patients had symptoms of daytime sleepiness or sleep apnea. We first administered a nocturnal polysomnogram with a monitoring montage consisting of central and occipital electroencephalogram, submental electromyogram, and eye movement electrodes. Respiratory parameters were also studied. The next morning, they were administered a standard diagnostic MSLT that entailed four 20-min long opportunities to fall asleep while lying in bed, which were offered at approximately 1 AM, 12 noon, 2 pm, and 4 pm. Each MSLT was followed within 20 to 60 min by an MWT trial. For MWT trials, patients were seated upright in bed and asked to remain awake for 40 min as described by Poets et al. As in our previous report using this protocol, neither sleep latencies on the MWT nor other diagnostic findings were statistically influenced by the duration of the interval between the end of each MSLT nap and the start of each MWT trial. We also concluded from this lack of effect of the length of interval between each MSLT and MWT trial that the order effect of an MSLT trial preceding each MWT trial was not a major factor in our results. Each MWT test was terminated as soon as the patient was clearly asleep. Sleep onset was defined as three continuous epochs of stage 1 sleep or any epoch of stage 2 to 4 or rapid eye movement (REM) sleep. Sleep latency was then calculated from the beginning of each test to the first epoch of sleep. The lights were then turned on, and patients were awakened and instructed to stay awake until the next sleep latency test. If no sleep occurred, the test was terminated after 40 min. Four tests were administered during the day, one after each sleep latency nap. Scoring of both MSLT and MWT trials was done in the standard way for the MSLT. The initial test results for these patients were included in our earlier report on 258 consecutive patients given both the MSLT and the MWT.

Patients were then treated based on the final diagnosis: 15 were treated with nasal continuous positive airway pressure (CPAP); 11, with uvulopalatopharyngoplasty (UPPP) or jaw advancement surgery; 16, with other therapy including pemoline or methylphenidate; four, with tricyclic antidepressant; and one patient with periodic leg movement during sleep was treated with alprazolam. One to six months after treatment, a polysomnogram was repeated followed by MSLT and MWT as described earlier.

Since we were dealing with truncated, and possibly nonnormal distributions for both MSLT and MWT data, we evaluated treatment-related changes in MSLT and MWT sleep latencies with a nonparametric test, the Mann-Whitney U test, as well as the Student's t test for correlated means (matched pairs t test). In this particular application, we expected the Mann-Whitney U test to produce lower levels of significance than the t test. However, since we are comparing the relative sensitivities of the MSLT and the MWT, we have reported results for both statistical tests throughout the present article.

**Results**

Figure 1 shows box plots that summarize the distributions for the MSLT tests administered before and after treatment. Box plots are useful ways to present truncated data sets such as those resulting when individual scores frequently reach a protocol-dependent maximum such as 20 min for the MSLT and 40 min for the MWT. Each box encompasses the middle 50 percent of the distribution and the horizontal line within the box represents the median. The notches about the horizontal line denote the 95 percent confidence band about the median. The vertical lines above and below denote the extent of the middle 80 percent of the distribution. Outliers above and below the middle 80 percent are denoted by individual dots. The mean ± standard deviation for each condition is printed within the box.

The pretreatment average MSLT sleep latency was 6.27 and the median MSLT sleep latency was 4.89 and a large proportion of these patients had average MSLT sleep latencies between 5 and 10 min. In our experience, the distribution of MSLT scores that we obtained is typical of patients who present to the sleep disorders center with a clinical history that necessitates daytime testing for disorder of excessive somnolence. Using the most recent classification of sleep disorders, the degree of somnolence of the central 50 percent of the present series qualifies as moderate to severe. Statistical tests for differences between pretreatment and posttreatment were done. The Mann-Whitney U test (z = -1.183; p = ns) did not detect a treatment-related change. A matched pairs t test on the pretreatment vs posttreatment means (6.33 ± 4.3 vs 7.28 ± 4.6) was also nonsignificant.

![Figure 1](http://journal.publications.chestnet.org/pdfaccess.ashx?url=data/journals/chest/21654/ on 04/19/2017)
Figure 2 summarizes in box plot format the results for the MWT tests administered before and after treatment.

The Mann-Whitney U test (z = -2.21; p<0.03) indicated a statistically significant treatment-related change. A matched pairs t test on the pretreatment vs posttreatment means (23.4±14.0 vs 30.00±12.0) was also significant (p<0.001).

A detailed analysis was done on a relatively homogeneous subgroup of 26 patients (mean age, 54.6±10 years; 24 male and 2 female) who had the diagnosis of obstructive sleep apnea and who were treated with nasal CPAP and/or UPPP and no central nervous system (CNS) active medications. Their average pretreatment respiratory event index (REI) was 49.58±26.9 and their posttreatment REI was 23.39±30.4. We consider the degree of sleep apnea in this subsample to range from moderate to severe and the amount of posttreatment improvement in REI to be typical, although not at all ideal, for apneics after their first treatment trial. The overall treatment-related reduction in REI was statistically significant (t = 5.20; p<0.0001), but considerable apnea remained in the subsample at the time of posttreatment evaluation.

The pretreatment and posttreatment results for the mean sleep latency on the MSLT and the MWT are summarized in Figure 3.

Note the obvious trend for steeper slopes in the MWT data. Note also that there were discordancies in pretreatment MSLT and MWT sleep latencies. A number of patients at the pretreatment stage were in the bottom half of the range in MSLT sleep latencies and the top half of the range in MWT sleep latencies.

Table 1—The Number of 26 Sleep Apneics Who Showed Improvement on the MSLT and the MWT after Treatment

<table>
<thead>
<tr>
<th>MWT</th>
<th>No</th>
<th>Yes</th>
<th>Totals</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSLT No</td>
<td>6</td>
<td>9</td>
<td>15</td>
</tr>
<tr>
<td>MSLT Yes</td>
<td>4</td>
<td>7</td>
<td>11</td>
</tr>
<tr>
<td>Totals</td>
<td>10</td>
<td>16</td>
<td>26</td>
</tr>
</tbody>
</table>

Conversely, a few patients at the pretreatment stage were in the top half of the range in MSLT sleep latencies and the bottom half of the range in MWT sleep latencies. Such MSLT-MWT discordancies have been described and discussed elsewhere. In these 26 patients, as with the 47 subject parent group, the Mann-Whitney U test did not detect a treatment-related change in the MSLT (z = -1.56; p=ns). The pretreatment vs posttreatment MSLT means (7.00±5.2 vs 6.29±4.2) changed in the wrong direction, but the Student’s t test was nonsignificant. However, the Mann-Whitney U test disclosed a large treatment-related change in the MWT (z = -1.93; p<0.05). The pretreatment vs posttreatment MWT means (24.29±14.3 vs 32.01±11.7) also changed significantly (p<0.007).

A frequency of improvement analysis, based on whether there was any posttreatment increase in sleep latency for either the MSLT or the MWT, is summarized in Table 1.

As can be seen in Table 1, 11 showed improvement in the mean MSLT, whereas 16 showed improvement in the MWT. The χ² did not reach statistical significance, however.

There was a weak, but apparent, trend (r = .23,
p = ns) toward greater improvement in REI and greater change in MWT sleep latency as is summarized in Figure 4.

We examined this weak REI-MWT relationship separately for the 15 patients treated with CPAP and the 11 patients treated with surgery. The patients with CPAP had a significant improvement in REI (44.8 to 7.38; p < 0.001); the patients who had surgery did not have a significant improvement in REI (56.0 to 45.0; p = ns). For MWT sleep latency, the patients with CPAP also had a significant improvement (23.9 to 31.6; p < 0.05); the improvement for patients who had surgery was less pronounced and only approached statistical significance (25.0 to 32.37; p < 0.09).

**DISCUSSION**

Our data clearly indicate that for a heterogeneous sample of patients with the clinical question of excessive daytime sleepiness and for a homogeneous subsample of patients with obstructive sleep apnea, the MWT is sensitive to changes in ability to remain awake that result from therapeutic maneuvers. The MSLT, however, did not change with therapy. The treatment-related changes in MWT sleep latencies are comparable in magnitude to those observed by Poceta et al. in 322 patients with sleep apnea treated with nasal CPAP. However, our treatment-related changes in MSLT sleep latencies are not in agreement with the CPAP results of Sangal and Thomas or with Wittig et al. Not all investigators, however, have found normalization of MSLT sleep latencies after effective treatment of sleep apnea. Gaddy and Doghramji reported 63 apneic subjects before and after treatment with CPAP. The RDI in this study went from 59.3 to 10.2, but the mean MSLT sleep latency only went from 6.9 to 9.0. Some 60 percent of the treated patients of Gaddy and Doghramji remained sleepy by MSLT criteria. By contrast, after treatment, only four of our 26 sleep apneic subjects remained below an MWT sleep latency of 15 min—the level suggested by Poceta et al. as a criterion for restricting driving privileges.

We do not believe that the greater sensitivity and selectivity of the MWT vs the MSLT is an artifact of our protocol. In an earlier article, we showed that the combined MWT and MSLT protocol produced internally consistent results for both the MWT and the MSLT. The individual MWT trials correlated about 0.6 with one another. Also, the individual MSLT trials correlated about 0.6 with one another. Furthermore, there was no trend for MWT trials late in the day to be longer in association with sleep accumulated on MSLT trials. The most likely explanation for the discrepancy in the present data and previous work is that Zorick et al. studied 12 patients with severe obstructive sleep apnea (pretreatment mean REI = 55.1 ± 28.4, posttreatment REI = 6.0 ± 6.1) and Wittig et al. studied ten patients with severe obstructive sleep apnea (pretreatment mean REI = 79.0 ± 26.5, posttreatment REI = 8.2 ± 10.0). By contrast, the 26 apneics in our present series had somewhat less severe sleep apnea (pretreatment REI = 49.6 ± 26.9) and were less completely treated at the time of our second evaluation (posttreatment REI = 23.39 ± 30.4). Moreover, some of our sleep apneic subjects were treated with surgery, rather than nasal CPAP. Those patients who received surgical treatment had less improvement in REI and less improvement in MWT sleep latencies. Thus, it may be that less than maximal reduction in the number of sleep apnea episodes accrued via surgery reduced the likelihood of the MSLT detecting treatment related change in sleep tendency. Such an explanation is consistent with the findings of Zorick et al. of less dramatic improvement in sleep apneas after UPPP than after nasal CPAP and with the data of Gaddy and Doghramji.

Thus, the present data, when viewed in perspective of previous work, suggest that the MSLT can detect large treatment-related changes in sleep tendency provided the pretreatment and posttreatment measurements are done at points representing very different severities of disease. The MWT, on the other hand, seems to be more sensitive to treatment-related changes. As we have described elsewhere, it is unlikely that the MWT is simply a more powerful tool to measure the same ability that the MSLT measures. It is more likely that the MWT and the MSLT measure different abilities (eg, alertness and sleepiness, respectively). If this is so, then a sleep disorder giving rise to the symptom of daytime sleepiness may actually impair both alertness and sleepiness. Also, treatment of such disorders brings about a greater change in alertness than in sleepiness. More generally, we suggest that sleepiness (or lack of alertness) is a complaint...
that probably has many components. These components include but are not limited to the following: (1) ability to fall asleep rapidly as measured by MSLT; (2) inability to stay awake as measured by MWT; (3) reduced attention as measured by cognitive (long-latency) evoked potentials;13,14 and (4) fatigue that may be a separate component or a complex composite of the other components. A patient complaining of sleepiness may have abnormal test results reflecting some or all of these components. We have shown previously that patients may fall asleep rapidly on the MSLT and be able to stay awake on the MWT, or they may fall asleep on the MWT but not on the MSLT. We are planning further studies to compare the MSLT with cognitive (long-latency) evoked potentials. Evaluating a patient with a complaint of sleepiness or lack of alertness may ultimately require a battery of tests, not just an MSLT measuring only one component of sleepiness. To state that a patient has no objective findings based on only the MSLT may be a disservice to the patient.

Whether our line of thinking ultimately proves to be correct, the present MSLT and MWT data are consistent with the notion that sleep tendency, as measured by the MSLT and ability to remain awake, as measured by the MWT, sublend different physiologic processes. At the very least, these findings indicate that there is a heterogeneous subpopulation of patients with sleep disorders with the symptoms of daytime sleepiness who will show no treatment-related improvement in daytime symptoms if they are evaluated only by the MSLT. We suggest that, since ability to stay awake (and not ability to fall asleep) is required for all job-related duties, an objective, physiologically based test such as the MWT should be used to assess the impact of sleep disorders on clinical questions concerning fitness to drive or work. Poceta et al15 have suggested that clinicians might recommend that patients with a MWT mean of less than 15 min do not drive or, presumably, engage in other activity where sustained attention is required for safety. The 15-min level was approximately 1 SD below the mean for their series of 322 sleep apneic patients. Nothing in our data would argue against the use of a 15-min cutoff. About 30 percent of our 48 patients were below the 15-min level on their pretreatment MWT and less than 15 percent were below the 15 min level on their posttreatment MWT. Clearly, however, the clinician should follow all applicable local laws, standards of practice, and institutional policies when deliberating these issues.

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