https://doi.org/10.5664/jcsm.8470

JCSM | Journal of Clinical Sleep Medicine

SCIENTIFIC INVESTIGATIONS

Multimodal assessment increases objective identification of hypersomnolence in patients referred for multiple sleep latency testing

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Study Objectives: The multiple sleep latency test (MSLT) has limitations when evaluating disorders of hypersomnolence with unknown etiology. Alternative measures of hypersomnolence may objectively identify pathology in patients with complaints of daytime sleepiness that may not be captured by the MSLT alone. This study evaluated the impact of a multimodal hypersomnolence assessment relative to MSLT in patients with unexplained hypersomnolence.

Methods: Seventy-five patients with unexplained hypersomnolence were included in the analyzed sample. Polysomnography was performed without prescribed wake time, and the psychomotor vigilance task and pupillographic sleepiness test were completed between MSLT nap opportunities. Presence or absence of hypersomnolence for each assessment was defined using a priori cutpoints. Proportions of patients identified as hypersomnolent using the multimodal assessment relative to MSLT alone were evaluated, as well as the sensitivity and specificity of ancillary hypersomnolence measures relative to MSLT as a gold standard.

Results: The multimodal assessment more than doubled the proportion of patients identified as having objective deficits relative to MSLT ≤ 8 minutes alone. The combination of excessive sleep duration, lapses on the psychomotor vigilance task, and impairments on the pupillographic sleepiness test also had perfect sensitivity in identifying all patients identified as sleepy by the MSLT across 3 different MSLT cutpoints (5, 8, and 10 minutes).

Conclusions: These data demonstrate the insufficiency of the MSLT as a singular tool to identify objective pathology in persons with unexplained hypersomnolence. Further efforts to refine and standardize multimodal assessments will likely improve diagnostic acumen and research into the causes of these disorders.

Keywords: hypersomnolence, sleepiness, multiple sleep latency test, psychomotor vigilance test, pupillography

Citation: Plante DT, Cook JD, Prairie ML. Multimodal assessment increases objective identification of hypersomnolence in patients referred for multiple sleep latency testing. *J Clin Sleep Med.* 2020;16(8):1241–1248.

BRIEF SUMMARY

Current Knowledge/Study Rationale: The multiple sleep latency test has shortcomings in identifying pathology in noncataplectic disorders of central hypersomnolence. Alternative measures of hypersomnolence may improve objective identification of pathology, advance clinical care, and improve scientific rigor.

Study Impact: Results demonstrate standard care using the multiple sleep latency test likely misses a large number of persons with objective impairments. Efforts to develop alternative techniques and standardized diagnostic strategies beyond the multiple sleep latency test are warranted.

INTRODUCTION

Hypersomnolence, defined as excessive daytime sleepiness often with additional associated features of prolonged sleep duration and/or excessive sleep inertia, is a very common problem in the general population and is frequently encountered in the clinical practice of sleep medicine.[1] The current gold standard for quantifying the severity of hypersomnolence is the multiple sleep latency test (MSLT), which measures the ability to fall asleep during repeated daytime nap opportunities.[2] Since its development nearly 35 years ago as a measure to quantify somnolence in sleep-deprivation paradigms,[3] the MSLT has evolved and is now crucial in the evaluation and diagnosis of central nervous system disorders of hypersomnolence. Current sleep medicine nosology relies heavily on MSLT findings to identify and delineate different disorders, including narcolepsy and idiopathic hypersomnia (IH).

Although the MSLT remains a very useful test for confirming suspected type 1 narcolepsy, its utility in noncataplectic disorders of hypersomnolence has been recently called into question. MSLT test-retest reliability in type 2 narcolepsy and IH has significant limitations, with some, although not all, studies demonstrating low repeatability in these disorders.[4–7] Additionally, both mean sleep latency (MSL) and sleep-onset rapid eye movement periods (SOREMPs) have been shown to have low repeatability in the general population as measured in the Wisconsin Sleep Cohort Study.[8] These factors, coupled with the wide range of normative values for the MSLT,[2] provide an impetus to develop and validate alternative assessments to diagnose disorders characterized by excessive daytime sleepiness.[9]

Hypersomnolence has many facets, and it is unlikely that any single measure will ever be able to fully quantify the self-reported complaint.[10,11] The MSLT and maintenance of

wakefulness test, both statistically correlate with self-report of excessive sleepiness, but MSLT and maintenance of wakefulness test results only marginally explain the variance of one another and can be discordant within individual patients.[12,13] Infrared pupillometry, which quantifies the spontaneous constriction and dilation of the pupil under constant conditions, has been used as a measure of drowsiness in several paradigms/disorders including sleep deprivation, narcolepsy, and obstructive sleep apnea, with limited relationships to the MSLT.[14–16] Other objective measures that significantly correlate with self-reported complaints of daytime somnolence, such as the psychomotor vigilance task (PVT), a measure of neurobehavioral alertness, do not or only marginally correlate with the MSLT.[17–19] Patients with IH with long sleep duration frequently have normal MSLT findings,[20] with both the MSLT and extended duration sleep recordings considered separate objective means for confirming the diagnosis of IH in the current *International Classification of Sleep Disorders* (ICSD-3).[21] In this context, it is highly plausible that patients with noncataplectic and unexplained hypersomnolence may have varying patterns of abnormalities across different objective measures of hypersomnolence and that the MSLT alone is not sufficient to identify a pathologic condition. Therefore, this investigation was performed to determine the degree to which a multimodal assessment that incorporates ancillary measures of hypersomnolence is able to objectively identify abnormalities in patients with unexplained daytime sleepiness referred for MSLT.

METHODS

Participants

All participants were patients at Wisconsin Sleep, the sleep medicine clinic and laboratory affiliated with the University of Wisconsin-Madison, who were referred by their treating clinician for polysomnography (PSG) followed by MSLT to evaluate complaints of daytime sleepiness and suspected central nervous system hypersomnolence disorder. A board-certified sleep medicine practitioner completed a comprehensive history and physical examination before referral for PSG/MSLT in all instances. The decision regarding the safety of tapering psychotropic medications before in-laboratory testing was made as part of collaborative treatment planning between patient and provider and was not influenced by study participation. Patients were recruited consecutively and provided written informed consent on the evening before the start of overnight sleep testing. All experimental procedures were performed in tandem with usual clinical care. The results of additional sleepiness measures (eg, pupillographic sleepiness test and PVT) were not provided to the treating clinician to inform final diagnosis, nor did experimental procedures enter the medical record. Primary diagnoses for all patients were determined by post hoc chart review. All participants provided written informed consent, and the University of Wisconsin-Madison Health Sciences Institutional Review Board approved all procedures.

PSG and MSLT

PSG was performed and scored following American Academy of Sleep Medicine standards (using Alice Sleepware; Phillips Respironics, Murrysville, PA).[22] Participants arrived at the sleep laboratory at approximately 1900–2000 hours. After PSG setup, participants were allowed to determine their bedtime and after sleep onset were minimally disturbed by technicians who entered the room only if technical issues arose that would inhibit sleep staging/scoring. Lights on was determined by the patient informing the technician that they were ready to get up for the day rather than a universally applied standard wake time. The MSLT was then performed unless cancelled based on laboratory protocols (eg, split-night PSG performed because of apnea-hypopnea index $\geq$ 15 events/h). Sleep latency was defined as the time from lights out to the first 30-second epoch scored as any stage of sleep. The nap opportunity was terminated after 20 minutes (if no sleep was achieved) or 15 minutes after the first epoch of scored sleep. SOREMPs were defined as any epoch of rapid eye movement sleep occurring within 15 minutes of sleep onset (for both overnight PSG and MSLT). The primary outcome measure of interest for the MSLT was the MSL across all MSLT nap opportunities. Additionally, total sleep time (TST), summed across overnight PSG and MSLT naps, was used as an additional measure of hypersomnia.[21]

PVT

The PVT is a well-validated measure of neurobehavioral alertness used in sleep research that was originally developed as a neurocognitive assay to quantify the response to sleep loss, measuring the ability to sustain attention and respond in a timely manner to salient signals.[23] The PVT requires responses to a stimulus (digital counter) by pressing a button as soon as the stimulus appears, which stops the stimulus counter and displays the reaction time in milliseconds for a 1-second period. Participants completed the 10-minute version and were instructed to press the button as soon as the stimulus appeared, to keep reaction time as minimal as possible, and not to press the button too soon. The number of lapses (failure to respond within 500 ms of stimulus; Tukey transformed) was considered the primary outcome measure of interest in this investigation. The PVT was administered twice during the testing day (after the first and third MSLT nap), with the average number of lapses between the 2 administrations used for analyses.

Pupillographic sleepiness test

The pupillographic sleepiness test (PST) is an assessment of drowsiness that records oscillations of the pupil diameter in darkness via a computer-based infrared video technique.[24] These oscillations result from progressive reduction of noradrenergic central activation from the locus coeruleus, which promotes arousal, resulting in disinhibition of the parasympathetic Edinger-Westphal nucleus.[24] The fluctuations in the size of the pupil diameter are used to calculate the pupillary unrest index (PUI), defined by absolute values of cumulative changes in pupil size based on the mean values of consecutive data sequences,[25] with increasing values suggestive of increased drowsiness. Both reproducibility/reliability and normative values for the PUI have been established for adults, including middle-aged to older individuals.[24,26–28]

The PST was performed for this investigation using the PSTEco system (AMTech, Dossenheim, Germany), following

established protocols.[25] The PST recording length is 11 minutes, with additional time to accommodate to darkness. During the task, the participant looks straight ahead while their pupil diameter is continuously recorded in darkness using an infrared camera with a sampling frequency of 25 Hz. The PST was administered twice during the testing day (after the first and third MSLT nap), with the mean PUI between the 2 administrations used for analyses. For our protocol, the PST was performed before the PVT, with a brief break (eg, ~5 minutes) used between measures to allow the participant time to use the bathroom, drink water, etc. The PST was performed first because the task requires no specific effort on the part of the participant and was thus theorized to have minimal impact on tasks conducted after its collection. Conversely, the PVT requires active participant input, and thus time-on-task related impairment/fatigue would theoretically be more likely to influence the PST if it was completed after the PVT.

Statistics

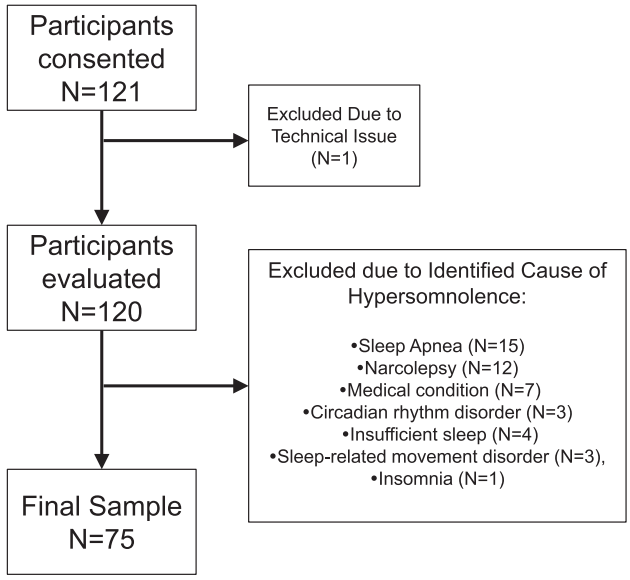
Pearson correlations were conducted to quantify the relationship between hypersomnolence measures and test for statistical significance of the associations.

The presence or absence of hypersomnolence was ascertained using the following dichotomous cutpoints: MSL on MSLT ≤ 8 minutes,[21] TST (nocturnal PSG plus MSLT naps) ≥ 660 minutes,[21] mean PUI > 9.8 on PST,[26] and mean PVT lapses > 4.8.[19] The proportion of patients categorized as excessively sleepy using standard assessment (MSL on MSLT ≤ 8 minutes) was compared with the proportion deemed excessively sleepy by expanded hypersomnolence testing (MSL ≤ 8 minutes or TST ≥ 660 minutes or PUI > 9.8 on PST or PVT lapse > 4.8) using McNemar's test. Proportions of patients deemed objectively hypersomnolent using individual hypersomnolence measures in addition to standard MSLT testing, as well as across alternative MSL cutpoints (eg, 5 and 10 minutes) were examined on an exploratory basis. Findings were also examined and stratified by the presence or absence of moderate or worse depressive symptoms (Inventory of Depressive Symptomatology-Self Report [IDS-SR] ≥ 26) and use of concurrent psychotropic medication on the day of PSG/MSLT procedures.[29] Test characteristics (eg, sensitivity and specificity) of individual and combined hypersomnolence measures (PST, PVT, and TST) were also examined against MSLT, which was considered a gold standard measure of hypersomnolence.

RESULTS

One-hundred twenty-one participants enrolled in the study. The inclusion/exclusion of the sample is outlined in **Figure 1**. One participant enrolled but was not able to complete MSLT recordings because of laboratory closure (inclement weather) on the day of MSLT and thus was not included in final analysis because of absence of data. Among study participants, 45 were excluded from the final analysis because of a condition thought to cause and/or contribute to their complaints of sleepiness (sleep-disordered breathing [apnea-hypopnea index > 5 events/h]; n = 15); narcolepsy (n = 12; n = 5 with cataplexy), medical condition (n = 7); circadian rhythm disorder (n = 3); insufficient sleep (n = 4); sleep-related movement disorder (n = 3); and insomnia (n = 1). The final sample of patients with unexplained daytime sleepiness consisted of 75 participants (**Table 1**). Within this sample, 39 were taking psychotropic medications, whereas 36 were not taking psychotropic medications (predominantly antidepressant medications) at the time of testing. Also, 33 participants had current moderate or worse depressive symptoms (IDS-SR ≥ 26), whereas 42 did not have active depression. Among participants included in final analyses, 2 demonstrated a nocturnal SOREMP without daytime SOREMPs on MSLT; 1 participant had a single daytime SOREMP during their first nap, without nocturnal SOREMP.

Figure 1—Study flow diagram.



Recruitment of consecutive patients referred for polysomnography/multiple sleep latency test with delineated reasons for exclusion from final sample.

The correlation matrix for all hypersomnolence measures is displayed in **Table 2**. Across all measures, only a modestly significant correlation was observed between MSL on MSLT and PUI on PST ($r = -.26$, $P = .03$). All other measures demonstrated no significant association.

In the primary analysis using MSL on MSLT ≤ 8 minutes as the standard measure of hypersomnolence, each additional measure resulted in a significantly elevated proportion of patients identified as objectively impaired (**Figure 2**). When combined, the use of multimodal assessment that included all 4 hypersomnolence measures more than doubled the diagnostic yield relative to MSLT alone (25.3% vs. 56.0%). Very similar patterns were observed using different MSLT cutpoints (ie, 5 and 10 minutes); however, higher MSL cutpoints were associated with reductions in the relative magnitude of differential diagnostic yields and vice versa (**Figure 2**). For example, using a more conservative MSL cutpoint of 5 minutes resulted in the multimodal assessment more than quadrupling diagnostic yield (10.7% vs. 48.0%) relative to MSLT alone, whereas an MSL

Table 1—Descriptive characteristics of the sample (N = 75).

Characteristic	Total
Age in years	31.2 (9.8)
Female sex, n (%)	67 (89.3)
BMI in kg/m^2	26.9 (5.6)
ESS	14.0 (4.4)
HSI	22.8 (6.2)
FOSQ-10	12.4 (3.25)
SIQ	65.1 (16.8)
PSQI	7.5 (3.3)
IDS-SR	25.5 (12.8)
PUI	7.8 (4.6)
Lapses	3.5 (6.2)
MSLT MSL in minutes	11.8 (4.93)
TST in minutes	570.9 (103.7)

Reported in mean (SD) except where indicated. ESS = Epworth Sleepiness Scale,[45] FOSQ-10 = Functional Outcomes of Sleep Questionnaire-10 item,[46] HSI = hypersomnia severity index,[47] IDS-SR = Inventory of Depressive Symptomatology-Self Report,[29] Lapses = mean lapses (Tukey transformed) on psychomotor vigilance task, MSLT MSL = mean sleep latency on multiple sleep latency test, PUI = mean pupillary unrest index from pupillographic sleepiness test, PSQI = Pittsburgh sleep quality index,[48] SIQ = Sleep Inertia Questionniare,[49] TST = total sleep time (overnight ad libitum polysomnography plus MSLT naps).

Table 2—Correlation coefficient matrix for hypersomnolence measures.

Measure	MSL	TST	PUI	PVT
MSL	—	−.08	−.26*	−.10
TST	−.08	—	.06	.20
PUI	−.26*	.06	—	.04
PVT	−.10	.20	.04	—

*P < .05. MSL = mean sleep latency on MSLT, MSLT = multiple sleep latency test, PUI = pupillary unrest index, PVT = lapses on psychomotor vigilance task, TST = total sleep time from polysomnography and MSLT.

cutpoint of 10 minutes less than doubled the number identified as objectively hypersomnolent (38.7% vs. 62.7%).

In exploratory analyses, similar patterns were observed when analyses were stratified by the presence/absence of psychotropic medications, as well as presence/absence of depressive symptoms (**Figures S1** and **S2** in the supplemental material). Also, results were very similar when analyzed using the 72 participants who did not have any SOREMs on either PSG or MSLT (**Figure S3**).

Additional post hoc analyses were conducted with the full sample stratified by those who would meet current ICSD-3 objective criteria for idiopathic hypersomnia (MSL on MSLT ≤ 8 minutes and/or TST ≥ 660 minutes) versus those who would not. Fourteen of the 47 participants (29.8%) who did not meet objective ICSD-3 criteria for the diagnosis of idiopathic hypersomnia had an abnormal PST and/or PVT, which was not significantly different compared with the 12 of 28 participants (42.6%) who did meet objective ICSD-3 criteria for IH (z = 1.2; P = .25).

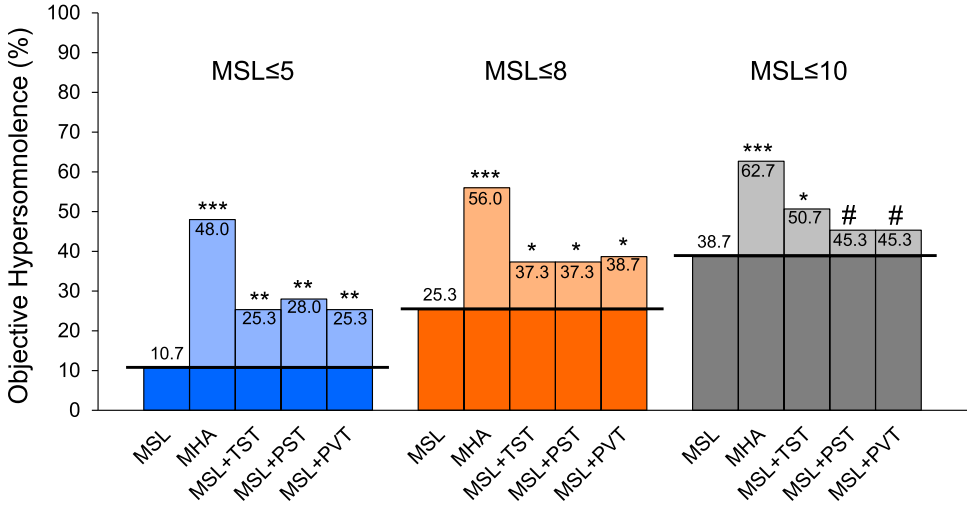
Test characteristics for PST, PVT, and TST were compared individually and in aggregate against MSLT as a gold standard (**Table 3**). Although no individual measure demonstrated high sensitivity, the combination of PST PUI > 9.8, PVT lapses > 4.8, and TST ≥ 660 minutes captured all participants with MSL ≤5, ≤8, or ≤10 minutes (sensitivity = 1.0 for all MSLT cutpoints).

DISCUSSION

This investigation demonstrates that the use of ancillary measures of hypersomnolence objectively identifies a substantially greater proportion of patients with unexplained hypersomnolence relative to the MSLT alone. Specifically, the addition of 3 measures of hypersomnolence (excessive sleep time on ad libitum recordings, elevated numbers of PVT lapses, and increased pupillary unrest indices on infrared pupillography), increases the demonstration of objective deficits by orders of magnitude above the MSLT alone for all MSLT cutpoints that have been historically used to define abnormalities.[21,30,31] These results have several important implications for research and clinical practice related to central nervous system disorders of hypersomnolence.

First, this investigation underscores that standard clinical practice that relies on the MSLT to identify hypersomnolence in noncataplectic disorders of central hypersomnolence is

Figure 2—Multimodal hypersomnolence assessment.



Proportion of sample (n = 75) identified with objective deficits at MSLT mean sleep latency ≤ 5, 8, and 10 minutes. Area below horizontal bars (dark shading) denote proportion of participants identified as sleepy by the MSLT at each MSL threshold. Area above horizontal bars (light shading) denote additional proportion identified by each ancillary hypersomnolence measure. Total proportion identified for each given combination listed for comparison. Cutpoints to define positive test are as follows: TST ≥ 660 minutes; PST pupillary unrest index > 9.8; PVT lapses > 4.8. ***P < .0001; **P < .001; *P < .01; #P < .05. MHA = multimodal hypersomnolence assessment, MSL = mean sleep latency on MSLT, MSLT = multiple sleep latency test, PST = pupillographic sleepiness test, PVT = psychomotor vigilance task, TST = total sleep time (nocturnal polysomnogram plus MSLT naps).

Table 3—Sensitivity and specificity compared with standard multiple sleep latency test.

	MSL ≤ min		MSL ≤ 8 min		MSL ≤ 10 min	
	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
TST + PST + PVT	1.00	.51	1.00	.61	1.00	.74
TST	.38	.84	.26	.82	.17	.80
PST	.50	.81	.42	.82	.41	.89
PVT	.50	.84	.26	.81	.21	.80

Cutpoints to define a positive test are as follows: TST ≥ 660 minutes; PST pupillary unrest index > 9.8; and PVT lapses > 4.8. MSL = mean sleep latency on MSLT, MSLT = multiple sleep latency test, PST = pupillographic sleepiness test, PVT = lapses on psychomotor vigilance task, TST = total sleep time from polysomnography and MSLT.

insufficient. The MSLT's wide range of normative values that have resulted in varying thresholds to define sleepiness over time,[2,21,30,31] as well as both its failure to identify many patients with pathologic hypersomnolence but also inappropriately categorize nonsleepy persons as pathologic, are well described.[20,32,33] In addition, several recent studies have demonstrated limited test-retest reliability for the MSLT in the general population and central nervous system hypersomnias other than type 1 narcolepsy.[4–6,8] This investigation extends these findings by quantifying the impact these shortcomings may have on clinical care. Our data suggest there are likely many patients with hypersomnolence for whom the standard tools applied in sleep medicine are not sufficient to objectively capture their self-reported experience. In this context, it is particularly problematic that a large number of patients with complaints of hypersomnolence may thus be prevented from access to treatment if abnormal objective findings are required by sleep medicine practitioners to justify therapy.

In a related vein, these data underscore the need for sleep medicine to advance beyond the MSLT in its assessment of hypersomnolence. Because hypersomnolence is a multifaceted symptom constellation, for which no singular measure is able to fully quantify the self-reported complaint,[10,11] multimodal assessment methods, as applied here, may not only help identify more patients with objective impairment but may also advance personalized medicine approaches for hypersomnolence disorders. Improved mutlifaceted phenotyping of hypersomnolence using a combination of standardized measures may help categorize this heterogeneous group of patients into subclasses with more distinct biological underpinnings.[34] By focusing on the biology related to specific phenotypic traits that may cut across the current nosologic boundaries that define non-cataplectic central disorders of hypersomnolence, research may be better able to identify the causes of these disorders, which could guide the development of more focused therapies and outcome measures than currently exist.

Although contemporary nosology in sleep medicine relies heavily on the MSLT to make specific diagnoses, it is quite noteworthy that the combination of TST captured using ad

libitum recordings, PVT, and the PST also captured every participant who had MSLT sleep latencies below all MSLT thresholds tested (eg, 100% sensitivity at 5-, 8-, and 10-minute cutpoints). Thus, despite the limited statistical associations between these hypersomnolence measures and the limited individual sensitivity of these tests to identify those with MSLT-defined sleepiness, this investigation suggests that these 3 measures in combination could theoretically be performed instead of the MSLT and would not miss an objectively hypersomnolent individual who would otherwise have been identified as excessively sleepy by the MSLT. Although this finding clearly requires replication in other samples, it suggests alternate diagnostic strategies in lieu of the MSLT may be more useful in patients with unexplained hypersomnolence, with the MSLT itself having little to no added value in this subset of patients.

The field has already begun to incorporate other measures beyond the MSLT in its assessment of noncataplectic central disorders of hypersomnolence. The ICSD-3 allows for excessive sleep duration (≥11 hours) measured by unrestricted electroencelphalogram recordings or actigraphy to serve as an objective finding consistent with a diagnosis of idiopathic hypersomnia. However, there is no singular practice parameter under which such studies are to be conducted, with multiple protocols currently used/proposed, some of which require multiple days/nights in the sleep laboratory for execution.[20,35,36] Particularly in the United States, payer restrictions will severely limit the ability to perform such prolonged recordings in the sleep laboratory. Although the method used here to utilize ad libitum overnight polysomnography coupled with MSLT is not a full 24-hour recording, in theory, all participants who slept greater than 11 hours in this protocol would also sleep at least this amount on a longer-duration recording. However, performing the MSLT after ad libitum overnight PSG is technically challenging and requires coordination of technicians and night/day/evening staff that may not be universally viable across sleep centers. However, it is notable that the guidelines for the MSLT do not specify a prescribed wake time for patients, only that "the MSLT must be performed immediately following polysomnography recorded during the individual's major sleep period."[37] It remains an unresolved question about how much sleep is adequate on overnight PSG before MSLT[38] and whether it is better to wake a patient at a prescribed time to more fully standardize the timing of MSLT naps or allow the patient to sleep until they more naturally awaken, particularly for those with long sleep duration. With the rise of out-of-center testing for many sleep disorders, future efforts to determine pragmatic ways to quantify excessive sleep time outside of the laboratory may help resolve some of these issues.

There are limitations of this study that are meritorious of discussion. First, because all participants in this study had self-reported hypersomnolence complaints warranting clinical evaluation, only the ability of the procedures to objectively identify those with hypersomnolence can be assessed in this investigation. However, based on the sizeable increase in diagnostic yields demonstrated using a multimodal approach, further research is warranted that incorporates the use of healthy sleeper controls completing the same procedures to verify the utility of multimodal assessments. It is noteworthy that the thresholds used to define abnormal PUI and PVT lapses are 2 standard deviations outside of reported means in persons without sleep disorders,[19,26] which is conservative and far less likely to contribute to false-positive results among healthy sleepers than altering the MSL threshold on the MSLT.[2] The collection of PST and PVT data interleaved with MSLT naps may have potentially reduced both the PUI and number of PVT lapses if brief sleep intervals were refreshing to participants and/or reduced homeostatic sleep drive. However, this would have biased results toward a null finding, and thus this is unlikely to have altered the primary results of the investigation. The choice to repeat both PST and PVT twice, in the morning and afternoon, was based on the fact that normative data on which cutpoints for each measure were delineated were similarly derived using a morning and afternoon measurement.[19,26] Values for each might have differed if collected more frequently, in a different sequence, or at different times. However, the choice to perform the PST and PVT after the first and third MSLT nap opportunities was made largely for practical reasons as it allows sufficient time for a light breakfast before the first MSLT nap and a light lunch after the termination of the second trial, as recommended in the current practice parameters.[37] The selection of lapses rather than some other PVT measure (eg, reciprocal response time) as a primary outcome of interest was based on its association with self-reported sleepiness, the absence of an effect of sex on this measure, and the fact that response times greater than 500 ms fall well outside the normal range for mean reaction times across all adult age groups.[19] The PVT itself was selected as the primary measure of neurobehavioral performance as it is (1) indicative of a fundamental aspect of waking cognitive function, (2) easily performed and administered, (3) minimally affected by learning/aptitude, (4) brief, (5) valid and reliable, (6) sensitive, (7) able to provide meaningful outcome variables for interpretation, and (8) has been used in recent studies examining response to novel therapeutics in idiopathic hypersomnia.[39–41] However, our study design is not able to clarify whether the PVT is the optimal vigilance measure to apply in clinical settings, because other measures such as the sustained attention to response task have also demonstrated utility in central nervous system hypersomnias, including ability to quantify treatment effects in narcolepsy.[42] Related to the ability to rule out identifiable causes of somnolence, actigraphic data preceding study procedures were ordered by referring clinicians in roughly half of the participants in this study, and thus the ability to rule out hypersomnolence related to sleep restriction relied on self-report/sleep logs in many cases. Also, concurrent psychotropic medication use may have impacted findings, particularly use of rapid eye movement–suppressing antidepressants that may have suppressed SOREMPs and thus impacted final diagnosis.[43] Finally, there are other potential measures that capture aspects of hypersomnolence that were not measured here but may also be highly relevant to clinical care. For example, event-related potentials have been used to identify patients with excessive sleep inertia[44] and may further be of use in multimodal hypersomnolence assessments. Future work that develops more comprehensive testing procedures for patients with

hypersomnolence are likely to significantly advance the science and practice of sleep medicine. This initial investigation only highlights the vital need for the field to develop and standardize these procedures.

In summary, this investigation demonstrates that use of the MSLT as a singular means of identifying pathologic sleepiness in unexplained hypersomnolence disorders is clearly problematic. Given the multifaceted nature of hypersomnolence, it is logical that multimodal approaches, such as those used in this study, may improve objective identification and diagnosis in these patients, as well as advance research into the biological bases of a likely heterogeneous group of disorders. These approaches will require further evaluation to determine optimal protocols and combinations of assays before they can be applied outside of research settings. However, they offer the possibility of greatly advancing clinical and scientific approaches in noncataplectic hypersomnolence disorders than the current standard of care.

ABBREVIATIONS

ESS, Epworth Sleepiness Scale
FOSQ-10, Functional Outcomes of Sleep Questionnaire-10 item
HSI, hypersomnia severity index
ICSD, International Classification of Sleep Disorders
IDS-SR, Inventory of Depressive Symptomatology-Self Report
IH, idiopathic hypersomnia
MSL, mean sleep latency
MSLT, multiple sleep latency test
PSG, polysomnography
PSQI, Pittsburgh sleep quality index
PST, pupillographic sleepiness test
PVT, psychomotor vigilance task
PUI, pupillary unrest index
SIQ, Sleep Inertia Questionnaire
SOREMP, sleep-onset rapid eye movement period
TST, total sleep time

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ACKNOWLEDGMENTS

The authors thank Sahand Eftekari, Erika Dallman, Megan Sippy, Sara Khan, and Sam Boroumand for assistance with data collection; the patients who participated in this study; and the faculty and staff at Wisconsin Sleep for cooperation and assistance with the protocol.

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication January 31, 2020
Submitted in final revised form March 26, 2020
Accepted for publication March 27, 2020
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DISCLOSURE STATEMENT

All authors have seen and approved the manuscript. This study was funded by American Sleep Medicine Foundation Grant 138-SR-16 to Dr. Plante. Declarations of interest: Dr. Plante has received research support from the American Sleep Medicine Foundation, National Institute of Mental Health, National Institute on Aging, National Institute of Nursing Research, the Madison Educational Partnership, and the University of Illinois at Chicago Occupational and Environmental Health and Safety Education and Research Center (funded by the National Institute for Occupational Safety and Health). Dr. Plante has also served as a consultant for Teva Pharmaceuticals Australia and consultant/medical advisory board member for Jazz Pharmaceuticals. Mr. Cook has served as a consultant to Bodymatter, Inc. Mr. Prairie declares no conflicts of interest.