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Recommended protocols for the Multiple Sleep Latency Test and Maintenance of Wakefulness Test in children: guidance from the American Academy of Sleep Medicine

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ABSTRACT

The American Academy of Sleep Medicine commissioned a task force of clinical experts in pediatric sleep medicine to review published literature on performing the Multiple Sleep Latency Test (MSLT) and Maintenance of Wakefulness Test (MWT) for diagnosis and management of central disorders of hypersomnolence among children and adolescents. This paper follows a similar format to the paper "Recommended protocols for the Multiple Sleep Latency Test and Maintenance of Wakefulness Test in adults: guidance from the American Academy of Sleep Medicine" that was published in 2021. Since there is insufficient evidence to specify a recommended protocol for the MWT in children and adolescents, this paper focuses only on the MSLT protocol. This protocol paper provides guidance to health care providers who order, sleep specialists who interpret, and technical staff who administer the MSLT to pediatric patients. Similar to the adult protocol paper, this document provides guidance based on pediatric expert consensus and evidence-based data when available. Topics include patient preparation, evaluation of medication and substance use, sleep needs before testing, scheduling considerations, optimal test conditions for youth, and documentation. Specific changes recommended for pediatric MSLT protocols include (1) provision of a minimum of 7 hours of sleep (with a minimum 8-hour recording time) on polysomnography (PSG) the night before the MSLT, ideally meeting age-based needs; (2) use of clinical judgment to guide the need for sleep-disordered breathing treatments before PSG-MSLT testing; and (3) shared patient-health care provider decision-making regarding modifications in the protocol for children and adolescents with neurodevelopmental/ neurological disorders, young age, and/or delayed sleep phase.
Keywords: Multiple Sleep Latency Test; Maintenance of Wakefulness Test; pediatrics

BACKGROUND

The onset of central disorders of hypersomnolence including narcolepsy and idiopathic hypersomnia (IH) often occurs before 21 years of age.[1-3] Thus, it is critical to utilize best practices and standardized sleep study protocols developed for children and adolescents in diagnosing these disorders. Adherence to protocols promotes standardization of sleep lab practices and diagnoses, which is important for clinical management and research. The American Academy of Sleep Medicine (AASM) convened a task force of experts in pediatric sleep disorders to update protocols presented in the 2012 paper "Practice Parameters for the Non-Respiratory Indications for Polysomnography and Multiple Sleep Latency Testing for Children"[4] and modify the 2021 paper "Recommended protocols for the Multiple Sleep Latency Test and Maintenance of Wakefulness Test in adults: guidance from the American Academy of Sleep Medicine"[5] for pediatric patients. This pediatric task force reviewed the literature and used expert consensus in formulating the recommended protocol. Importantly, this protocol considers diagnostic criterion changes in the *International Classification of Sleep Disorders*, third edition, text revision (ICSD-3-TR).[6] The recommended protocol detailed here reflects the needs of patients in most situations, but the protocol may need modification based on the judgment of clinical providers to meet unique patient needs. The AASM Board of Directors reviewed and approved this pediatric protocol paper. All members of the pediatric task force and AASM Board of Directors completed detailed conflict of interest statements listed under the disclosures section.

The peak onset of narcolepsy type 1 (NT1; formerly narcolepsy with cataplexy) is 15 years of age and typically begins between 7-25 years of age.[1,2] Narcolepsy type 2 (NT2, formally narcolepsy without cataplexy) onset is typically reported in adolescence but specific age of onset is not reported in the literature. The mean onset of IH is 16.6-21.2 years across different case series.[7] Symptoms of narcolepsy can present differently in children and adolescents compared to adults. First, daytime sleepiness may be expressed as inattentive, hyperactive, emotionally labile, and/or impulsive behavior in children and adolescents. Second, children and adolescents with NT1 can present initially with cataplectic facies (a static form of cataplexy presenting with ptosis, jaw lowering, tongue protrusion) before more classic emotionally triggered cataplexy develops.[8] Overall, daytime sleepiness and cataplexy may be more observable to people who spend the most time with children and adolescents during the academic year. As a result, teachers and friends of pediatric patients may be the first to be aware of concerning daytime sleepiness and other symptoms such as cataplexy and prompt parents/caregivers to seek medical evaluation.

NT1 is caused by the degeneration of hypothalamic neurons that make orexin, resulting in very low or no evidence of orexin in cerebral spinal fluid (CSF). The ICSD-3-TR permits NT1 diagnosis based on daily sleepiness and at least one of the following (1) CSF orexin levels <110 pg/ml, (2) the presence of a nocturnal sleep onset REM period [SOREMP; REM sleep occurring within 15 minutes from sleep onset on the nocturnal polysomnogram (PSG)] and reporting of typical cataplexy, or (3) two or more sleep onset REM periods on the Multiple Sleep Latency Test (MSLT), mean sleep latency of 8 minutes or less, and reporting of typical cataplexy. The etiology of NT2 is unknown since CSF orexin levels are normal in NT2. ICSD-3-TR diagnostic criterion is based on daily sleepiness and two or more sleep onset REM periods on the MSLT, mean sleep latency of 8 minutes or less, and no reporting of typical cataplexy.

IH is also associated with normal CSF orexin levels and is a heterogeneous condition with symptoms of long sleep duration and excessive daytime sleepiness varying in severity.[3] As a result, the ICSD-3-TR permits different ways to diagnose IH including use of MSLT (diagnostic criterion of mean sleep latency ≤ 8 minutes and less than 2 SOREMPs), 24 hours polysomnogram (diagnostic criterion of ≥ 660 minutes of sleep), and 7-day average sleep duration on actigraphy testing (diagnostic criterion of ≥ 660 minutes of sleep). Diagnostic PSG-MSLT remains the most commonly used clinical method for making diagnoses of these central disorders of hypersomnolence due to limited capability to perform alternative testing methods such as extended PSG, availability of resources such as actigraphy, or willingness of pediatric patients to acquiesce to invasive NT1 testing methods with lumbar puncture.

It can be difficult to discern symptoms of a CNS disorder of hypersomnolence when excessive daytime sleepiness is common in the general population. In a United States survey, 41% of teens aged 13-17 years reported excessive daytime sleepiness and nearly 12% reported hypersomnolence as defined by presence of excessive daytime sleepiness, unrefreshing sleep, difficulty waking in the morning despite normal sleep duration.[9] Excessive daytime sleepiness in the pediatric population commonly results from chronic insufficient sleep due to delayed circadian rhythm sleep-wake disorder coupled with early school start times, insufficient sleep syndrome, irregular weekend/weekday sleep schedules, electronic use at bedtime, and caffeine use.[10,11] Recommended sleep duration varies by age[12] (see **Figure 1**) and may require close monitoring and counseling to ensure optimal sleep needs are being met. In clinical practice, patients often have difficulty differentiating fatigue from daytime sleepiness, with the latter warranting more directed PSG-MSLT when severe. There are surveys specifically validated for children and adolescents to assess sleepiness severity, such as the Epworth Sleepiness Scale for Children and Adolescents (validated ages ≥ 6 years[13]) or Pediatric Daytime Sleepiness Survey (validated ages ≥ 9 years[14]), or to assess more specific symptoms of central disorders of hypersomnolence, such as the Pediatric Hypersomnolence Survey[15] (validated ages ≥8 years), Pediatric Narcolepsy Severity Scale (validated for ages ≥10 years), or Idiopathic Hypersomnia Severity Scale (validated for ≥16 years).[16]

The MSLT is an objective measure of daytime sleepiness performed after a nocturnal PSG. This test typically is performed with 5 nap opportunities during the daytime period with each nap opportunity lasting 20 minutes and with a 2-hour wake period required between naps. The MSLT is indicated in children and adolescents being evaluated for narcolepsy or IH.[6] It is important for health care providers, patients, and their parent/caregiver to understand the limitations of the MSLT. The MSLT was validated and proven reliable for NT1 with sensitivity of 90-95%, specificity of 93-95%, and reliability of 72%.[17–19] Clinical use of PSG-MSLT testing was then expanded for the evaluation of NT2 and IH without formal validation testing in these specific groups. Based on clinical use, the reliability of MSLT testing for NT2 and IH in adults ranges from 18-42% and accuracy is also variable.[17] According to prior pediatric MSLT practice parameters, the MSLT is technically and clinically valid in developmentally normal children ages 5 years and older but normative values differ depending on pubertal Tanner stage (see Appendix A in supplemental material).[20] The accompanying supplemental material also includes a sample MSLT report (see Appendix B) and a checklist for MSLT preparation for the ordering health care provider (see Appendix C).

The Maintenance of Wakefulness Test (MWT) is an objective test of daytime alertness assessing the ability to stay awake in non-stimulating conditions for four periods of 40 minutes across the day. Based on literature review, there are no normative values for people <18 years or data to inform task force protocol development. Nevertheless, some centers report performing the MWT in pediatric patients to clinically assess treatment efficacy.[21]

PROTOCOL FOR MSLT

The protocol for the MSLT is presented in **Box 1** and **Box 2**. **Box 3** contains data acquisition and reporting procedures. A thorough justification of patient MSLT preparation, general testing, data acquisition, reporting procedures and protocol steps can be found in the paper "Recommended protocols for the Multiple Sleep Latency Test and Maintenance of Wakefulness Test in adults: guidance from the American Academy of Sleep Medicine."[5] Further detail relevant to pediatric populations and new changes to the ICSD-3-TR NT1 diagnosis allowing for diagnosis based on a nocturnal SOREMP on PSG and presence of cataplexy is presented hereafter. The intent of this discussion is to guide health care providers and sleep technologists on conducting accurate PSG-MSLT testing in pediatric populations.

Box 1—Multiple Sleep Latency Test (MSLT) clinical guidance and patient preparation.

1. In preparation, the health care provider, patient, and parent/caregiver should define goals for adequate sleep at home with regards to timing and duration. Adequate sleep should be documented by a sleep diary and, ideally, actigraphy.[22]
2. If another sleep disorder that causes daytime sleepiness is present, an MSLT should be pursued after this sleep disorder is treated using evidenced-based treatments or well-established therapies. However, other sleep disorders can be comorbidities to primary central disorders of hypersomnolence and clinical judgement is recommended. (see *Comorbid sleep and other disorders* section). For patients with sleep-disordered breathing treated with positive airway pressure (PAP) therapy, the health care provider should ensure efficacy and adherence based on a review of downloaded data. If the patient is using non-PAP therapy for sleep-disordered breathing, self-report of adequate use and efficacy of therapy should be confirmed prior to the MSLT. If adequate effectiveness is suboptimal, the health care provider should determine if the anticipated impact on the test results warrants rescheduling. The patient should use PAP and/or non-PAP therapy (see **Box 2**, step 3) during the PSG on the night prior to the MSLT.
3. The health care provider should develop a plan regarding use of prescription medication, over-the-counter (OTC) agents, herbal remedies, and other substances. In general, medications with alerting, sedating, and/or REM-modulating properties should be stopped at least two weeks before the MSLT, but this may vary based on the half-life of medications. Clinical judgment should be used regarding the safety of withholding these medications. The patient and their parent/caregiver should be instructed to consult with the health care provider before starting any prescriptions or OTC medications prior to the test.[22]
4. The health care provider should discuss acceptable caffeine consumption with the patient and their parent/caregiver prior to testing to avoid confounding the MSLT results while avoiding caffeine withdrawal symptoms on the day of the test. The goal should be abstinence and, when necessary, preceded by a taper.
5. The health care provider should inform the patient and their parent/caregiver that a urine drug screen will be obtained to ensure adherence to the medication instruction plan.
6. The patient should avoid insufficient sleep (see **Figure 1** for healthy sleep durations by age) or long naps (>1 hour) before the PSG test to ensure habitual nocturnal sleep duration is present during testing.

Box 2—Multiple Sleep Latency Test (MSLT) general testing, conditions and instructions, and data acquisition.

1. Patients being evaluated for central disorders of hypersomnolence should have PSG set-up at least 30 minutes prior to habitual bedtime to avoid missing a diagnostic sleep-onset REM period[6] and ensuring sufficient sleep on the PSG.
2. The MSLT should be performed following an attended PSG which allows at least 8 hours of time in bed with at least 7 hours of total sleep time. The test should not be performed after a night during which PAP pressures were adjusted (split-night or initial PAP titration study).[23-25]
3. Any home PAP/non-PAP therapies for sleep-disordered breathing patients should be used during the PSG and considered for use during MSLT naps based on clinical judgement. The therapeutic modality, PAP settings, and/or mask interface should match those used at home.
4. Electronic devices should be turned off at least 30 minutes before lights out and should not be accessible to the patient after lights out.
5. The patient's clothing should be comfortable, appropriate to the environment, and not interfere with the performance of tests. A change in clothing is not required between the PSG and MSLT.
6. The patient should abstain from caffeine, nicotine, alcohol, marijuana and other sedating or alerting agents on the day of the test.

7. The recording montage for the MSLT should, at a minimum, include three EEG recording leads with at least one each for frontal (F3-M2 or F4-M1), central (C3-M2 or C4-M1), and occipital (O1-M2 or O2-M1) derivations, left and right eye electrooculograms (EOGs), mental/submental electromyogram (EMG), and electrocardiogram (EKG). Other recording devices or sensors used for the PSG are unnecessary and should be removed to promote patient comfort. The use of alternate acceptable montages in the current version of the AASM Scoring Manual are at the discretion of the sleep clinician.
8. Audio-visual recordings must be made during the nap trials and be accessible to interpreting clinicians. The patient must be audio-visually monitored throughout the day, but retention of recordings made between nap trials is discretionary.
9. The MSLT should consist of five nap trials. The initial trial should begin 1.5 to 3 hours after termination of the nocturnal recording. Each subsequent trial should begin two hours after the start of the prior trial. Only when the results are clearly diagnostic of narcolepsy after four naps or unique patient circumstances dictate a 4-nap study, should a shorter 4-nap trial test be considered (see *Performance of nap trials* section).
10. Sleep rooms should be dark, quiet, and at a comfortable temperature during testing. Parents/caregivers should be offered an area outside of the room to wait during the nap trials. If necessary, parents/caregivers may be in the room during the nap trials but should be instructed to not interfere with testing or provide any distraction to the patient and remain quiet.
11. The patient should be lying in bed for all nap trials.
12. Patient bio-calibrations should be conducted prior to starting each nap trial. Standard instructions include: (1) lie quietly with your eyes open for 30 seconds, (2) close both eyes for 30 seconds, (3) without moving your head, look to the right, then left, then right, then left, right and then left, (4) blink eyes slowly 5 times, and (5) clench or grit your teeth tightly together. Instructions should be tailored to the developmental age of the patient. For example (5) "bite down on your teeth" or "pretend like you're chewing gum."
13. At the start of each nap trial, the patient should be instructed as follows: "Please lie quietly, assume a comfortable position, keep your eyes closed and allow yourself to fall asleep." Testing starts immediately after instructions are given, and bedroom lights are turned off.
14. Each nap trial ends if the patient does not fall asleep in 20 minutes. If sleep onset occurs, the trial is continued for an additional 15 minutes, regardless of the amount of intervening sleep or wake. Sleep onset is defined as the start of the first epoch scored as any stage of sleep.[6]
15. Vigorous physical activity and prolonged exposure to sunlight/bright artificial light should be avoided all day.
16. Between nap trials, the patient should be out of bed and not permitted to sleep. Parents/caregivers should participate in keeping the patient awake between the nap trials.
17. A light breakfast at least one hour prior to the first trial and a light lunch immediately after the termination of the second nap trial is recommended.
18. Urine drug screening should be employed when indicated to ensure that the MSLT results are not confounded by inadvertent, intentional, or illicit medication or substance use (see Appendix C in supplemental material).

Box 3—Data acquisition and reporting procedure.

1. Patient demographics (name, date of birth, test date, body mass index, medical record number).
2. Names of referring health care provider, sleep specialist, and sleep technologist.
3. Documentation of the indication for the sleep study (e.g., narcolepsy, IH).
4. Documentation of daily medications that influence sleep or wake and changes to medications used within the last 2 weeks. The type of drug screening should be documented.

5. Documentation of patient symptom severity surveys is encouraged: such as Epworth Sleepiness Scale for Children and Adolescents, Fatigue Score, Idiopathic Hypersomnia Severity Scale, Pediatric Hypersomnolence Survey, and/or momentary sleepiness measures collected between naps.
6. Documentation of review of available pre-study data including habitual sleep time, sleep diary, actigraphy and PAP download is strongly encouraged.
7. Recording parameters including start time, end time, total sleep time, sleep latency, and REM latency of each trial. Sleep latency is defined as the time from lights out until the start of the first epoch of any stage of sleep (an epoch of N1, N2, N3, or R). REM latency is defined as the time from the start of the first epoch of sleep until the start of the first epoch of stage R (REM sleep)
8. Mean sleep latency, number of SOREMPs during naps and whether SOREMP occurred on the PSG. If no sleep occurs in a trial, 20 minutes is used for the sleep latency value and in the calculation of the mean sleep latency.
9. Deviations from ideal testing times and conditions (e.g., caffeine, nicotine, napping, cell phone, fire alarms, or other stimulating activities) documented by the sleep technologist.
10. Interpretation of study findings with signature of board-certified sleep medicine specialist. Other data collected by the sleep technologist should be included in the report if relevant to interpretation to the study results (see Appendix C in supplemental material).

Considerations for the MSLT

Planning before the MSLT

Age considerations: MSLT may not be appropriate in children < 5 years of age due to lack of normative data in this age group. However, consideration may be given to performing MSLT in children < 5 years of age in special circumstances such as classic symptoms of narcolepsy with cataplexy, and/or inability to obtain CSF orexin testing. Additional consideration should be given when interpreting MSLT results in pre-pubertal children, as pre-pubertal children are less likely to fall asleep during the day than older adolescents.[26] Habitual naps are common in younger children[24] and should be taken into account when interpreting MSLT data. Furthermore, mean sleep latencies tend to decrease with advancing Tanner stages in pubescent children.[20,27] Normative mean sleep latency data for Tanner stage are presented in Appendix A in the supplemental material.

Sleep-wake scheduling before testing: Documentation of sleep-wake schedules through sleep diaries and ideally for 2 weeks before testing is advised to ensure a consistent and sufficient amount of sleep leading up to the MSLT. Optimal sleep times by age as recommended by the AASM[12] should be ensured. In one adult study, 52% of patients with Insufficient Sleep Syndrome had MSLT findings necessary for narcolepsy diagnosis suggesting adequate sleep duration is important for avoidance of false positive results.[28] Likewise, for patients with circadian phase delay, it is important to take steps to gradually advance bedtime and rise time on a schedule that aligns with school or social requirements prior to testing. Researchers have reported the presence of multiple SOREMPs on the daytime MSLT in 16% of healthy adolescent 10th graders with delayed circadian phase and experiencing early school start times.[29] Furthermore, correction of irregular sleep timing on weekdays and weekends is advised. Testing should be conducted in line with the patient's habitual sleep-wake schedule. Guidance for shift workers can be found in the recommended protocols for MSLT and MWT for adults.[5] Daytime naps ideally should be avoided prior to overnight PSG but if needed, a nap < 1 hour duration and before 3 pm is suggested so not to interfere with the patient's ability to sleep through the night.

Comorbid sleep and other disorders: Patients with central disorders of hypersomnolence can have comorbid sleep disorders. In narcolepsy, co-existing obstructive sleep apnea (OSA), periodic limb movement of sleep, REM sleep behavior disorder, and restless legs syndrome are well-described.[30,31] In

addition, obesity is present in up to 50% of pediatric narcolepsy patients and may contribute to OSA development.[32,33] On the other hand, daytime sleepiness can accompany a number of sleep disorders making it difficult to discern the true cause of patients' complaints. The severity of symptoms and presence of other symptoms associated with narcolepsy and IH can guide health care providers.

Excessive daytime sleepiness is typically mild in children and adolescents with OSA with average reported Epworth Sleepiness Scale (ESS) scores of 7.2 in children with untreated OSA compared to 5.1 in treated OSA.[34] More severe OSA is associated with more severe daytime sleepiness. In a study of 54 pediatric OSA patients, only 7 (13%) had mean sleep latencies of <10 minutes.[35] All 7 patients had AHI >10 events/h and shorter sleep latencies on MSLT were associated with obesity and oxygen desaturation nadirs <92%.[35] In another study of adults and children with OSA or suspected OSA (age range 6-85 years), 5% of patients were reported to have two or more SOREMPs on MSLT.[36] Factors associated with increased odds of two or more SOREMPS included low minimum oxygen saturation (model change with 15% point decrease) and severely elevated AHI (model change with 30 unit increase). Thus, clinical judgement is required in determining if OSA severity warrants treatment prior to the evaluation of severe daytime sleepiness. Based on these data, moderate to severe OSA should be treated prior to PSG-MSLT evaluation for central disorders of hypersomnolence. It is worth noting that disrupted nighttime sleep is common in narcolepsy,[37] and caution should be taken not to misattribute cortical arousals to respiratory events, particularly given the low AHI threshold (AHI >1 event/h) for OSA diagnosis in children.

Periodic limb movements of sleep are common in people with narcolepsy. A large meta-analysis showed a mean periodic limb movement index of 15.4 events/h in people with narcolepsy versus 2.8 events/h in controls.[38] PLMS are thought to be intrinsic to the sleep architecture of NT1 and may not require directed treatment unless associated with RLS. It is also important to recognize that PLMS may be associated with, or exacerbated by, medications used to treat narcolepsy and other central disorders of hypersomnolence, particularly selective serotonin reuptake inhibitors (SSRIs).[39,40]

Many patients with central disorders of hypersomnolence have comorbid mood disorders. In adults with depression, short REM latency, increased REM sleep duration and increased REM density (i.e., the frequency of rapid eye movements per REM period) have been reported in the literature and considered as biological markers that might predict relapse and recurrence.[41] Although subjective sleep disturbances are commonly reported in children with depression, there is not consistent polysomnographic evidence for sleep architectural disturbance paralleling that seen in adult depression.[42] However, many medications such as SSRI/serotonin noradrenergic reuptake inhibitors (SNRIs) used to treat depression are understood to affect PSG and MSLT results, particularly via suppression of REM sleep. Consideration should be given to tapering of such medications prior to MSLT, when safe to do so, as outlined in the section on Medications and **Table 1**.

Medications: Certain medications may impact sleep architecture and thus confound results of sleep testing. In particular, medications that suppress REM sleep may inhibit SOREMPs on the PSG and MSLT, and their discontinuation may result in REM rebound in the short-term. The task force recommends that medications listed in **Table 1** be discontinued prior to MSLT to minimize the impact of such medications on sleep architecture in general and REM sleep in particular. A sufficient period of time for observation after discontinuation should be established and will depend on the pharmacokinetics of each medication. A two-week washout period is generally considered adequate for most REM-suppressing medications, although medications with longer half-lives may require a longer period. A recent study showed that 13.2% of patients weaned off REM-suppressing medications ≥ 2 weeks prior to MSLT vs. 5.9% of patients with no history of such medication use had a positive MSLT.[43] Such results may suggest that weaning off REM suppressing antidepressant even weeks before testing can still result in REM-rebound and longer tapers may be needed.

Prior to discontinuation, the health care provider should consider an appropriate taper to also minimize withdrawal effects and ensure patient safety. This may require developing a taper plan with the patient's care team prior to testing, and a medication re-initiation plan following testing.

A two-week washout is generally recommended; agents with an asterisk in **Table 1** have long half-lives and longer washout (up to 6 weeks) may be needed. **Table 1** includes commonly encountered medications or those requiring a prolonged washout period, but it is not an exhaustive list.

Caffeine, drugs, and drug screening: Health care providers should screen for recreational and illicit drugs prior to MSLT, as they can affect sleep architecture and either produce or inhibit daytime sleepiness. Methods of drug screening vary from urine tests utilizing immunoassay technology to urine or blood testing using more advanced gas chromatography-mass spectroscopy techniques that can also test for prescription and over-the counter products.

In children, the yield of standard drug testing may be low. A 2014 study of 214 MSLTs performed in children revealed 0 positive screens for drugs of abuse, although further testing using gas chromatography/mass spectrometry showed a 31% test positivity rate for caffeine, 5% positivity rate for SSRIs, and 4% positivity rate for over-the-counter medications.[51] Positive urine toxicology screens may be more likely in older adolescents. In a 2015 study of 383 patients under age 21 undergoing MSLT, no patients under 13 years old had a positive toxicology screen, but 20% of patients above age 13 screened positive for THC.[52] Among the 14 patients with a positive urine drug screen for THC, 71% had multiple SOREMPs on MSLT. Data collection for these studies occurred prior to legalization of marijuana in many states and follow-up studies are needed.

Caffeine is known to affect nighttime sleep quality resulting in shorter sleep duration, increased sleep onset latency, increased wake time after sleep onset, and decreased slow wave activity; increased daytime sleepiness is associated with higher caffeine intake in children as young as 12 years of age.[53–57]

Overall positive drug and substance testing results will require clinical judgement when interpreting PSG and MSLT results.

Special populations

Secondary narcolepsy: Secondary narcolepsy with or without cataplexy can occur in pediatric genetic syndromes including Niemann-Pick type C disease, Angelman syndrome, Norrie disease, Prader-Willi syndrome, DNMTI-complex disorder, and myotonic dystrophy. Orexin loss, as measured by CSF orexin level, is not always found in these conditions suggesting differing etiologies from primary NT1. Additionally, secondary narcolepsy with cataplexy symptoms can occur due to hypothalamic lesion due to stroke, autoimmune or paraneoplastic disorder (e.g., anti-Ma2 or antiaquaporin-4 antibodies), multiple sclerosis, head trauma, or tumors. There has been no systematic study validating ICSD-3 or ICSD-3-TR criterion for the diagnosis of secondary narcolepsy with or without cataplexy in any of these special populations. Thus, health care providers must recognize limitations of PSG-MSLT testing in making diagnosis of secondary narcolepsy with or without cataplexy. Future research is needed to develop and validate clinical criteria as well as diagnostic tests for secondary narcolepsy not associated with orexin deficiency.

Prader-Willi syndrome Excessive daytime sleepiness is very common in Prader-Willi syndrome (PWS), with prevalence approaching 67-95%.[58,59] Patients with PWS may manifest narcolepsy- and cataplexy-like symptoms though the etiology of these symptoms are unclear. In a cohort study of 14 patients with Prader-Willi Syndrome, mean cerebrospinal fluid orexin levels were intermediate [192 (25-75%: 161-234.5) pg/ml] and significantly higher than patients with primary narcolepsy with cataplexy [mean 40 (25-75%: 40-60.5), $p<0.001$]; two Prader-Willi Syndrome patients with cataplexy had CSF orexin levels >200 pg/ml.[60] While a negative correlation between ESS and orexin levels in the cerebrospinal fluid of individuals with Prader-Willi Syndrome has been reported,[61] decreases in the number of orexin neurons do not seem to play a role in the Prader-Willi Syndrome narcolepsy phenotype. PSG-MSLT testing is commonly employed for clinical investigation for secondary narcolepsy with or without cataplexy in Prader-Willi Syndrome when sleep-disordered breathing (80% estimated prevalence

in Prader-Willi Syndrome) is not felt to be solely causal to daytime sleepiness severity or is effectively treated.[62,63] As previously noted, PSG-MSLT testing has yet to be validated for diagnosis of secondary narcolepsy with or without cataplexy in this population. In a study of n=15 patients with Prader-Willi Syndrome [mean age 27.5 years (5.5)], patients had a reduced mean sleep latency [Prader Willi Syndrome: 7.2 minutes (2.9), controls: 15.3 (7.2) minutes] but only 3 people with Prader-Willi Syndrome had sleep onset REM periods during the MSLT. Limitations of this study are that none of the 15 people with Prader Willi Syndrome had cataplexy and mean ESS showed mild subjective daytime sleepiness (mean 11.2 points (0.7).[64] Other abnormal features of REM sleep specific to primary NT1 have been reported on nocturnal PSG in Prader-Willi Syndrome.[19,65] In a study of n=9 patients with Prader-Willi Syndrome ages 3-21 years and excessive daytime sleepiness, 5 participants had nocturnal sleep onset REM periods and authors noted features of REM without atonia in some participants' REM periods.[66] Future research is needed to not only validate PSG-MSLT testing in adults and children with Prader-Willi Syndrome and narcolepsy symptoms but also nocturnal sleep biomarkers available on the PSG alone such as the nocturnal sleep onset REM period that may facilitate diagnosis.

Considerations for patients with intellectual disability, neurodevelopmental disorders, psychiatric conditions: Children and adolescents with behavioral concerns, cognitive impairment, neurodevelopmental disorders, and psychiatric conditions can pose challenges to adhering to standard PSG-MSLT protocols. There is no published data providing guidance on modifications to PSG-MSLT testing in such cases. Based on clinical experience, the following is some guidance on planning for the MSLT and data acquisition in special populations:

1. Health care providers should review the ICSD-3-TR for hypersomnia due to medical conditions which does not require PSG-MSLT testing for diagnosis of hypersomnia associated with medical disorders.[6] Plausibly, PSG-MSLT testing may not be necessary if other validated measures of excessive daytime sleepiness are utilized.
2. Patient/patient families should be explained the protocol in detail to share expectations. Parents/caregivers may need to share the responsibility of explaining the study protocol and providing guidance to optimize protocol adherence for the patient.
3. Lab tours and equipment desensitization (such as having patients apply sample sensors at home prior to testing) may be helpful
4. Additional technologists or staff resources such as child life services, behavior response teams, or nursing staff may be needed for safety and protocol adherence, especially if patients have stopped REM suppressing medications such as anti-psychotics or SSRI/SNRIs.
5. A parent/caregiver may be allowed to stay in the room with the pediatric patient to alleviate separation anxiety and facilitate sleep.
6. Health care providers and sleep technologists may consider minimizing monitoring equipment when possible (e.g., using only 2 EEG leads [Cz, O2] for sleep stage scoring) if patient is anticipated to have or develops intolerance to study equipment.

General testing and data acquisition

PSG before MSLT: The PSG should be set-up at least 30 minutes before patients' habitual bedtimes to provide sufficient time for patients to adjust to monitoring equipment and capture accurate sleep onset latency, REM sleep onset latency, and normal sleep duration for age. Across the literature, people with central disorders of hypersomnolence have quick sleep onset latencies and delaying start time of the study could impact the ability to capture habitual sleep duration. Ideally, habitual sleep duration is consistent with normative values for age (see **Figure 1**). If delayed sleep phase is uncorrected, the sleep study may need to start and end later to prevent false positive MSLT results for narcolepsy. Long sleep duration (>10 hours) is present in 51.3% of adult IH patients and long sleep time may be an early manifestation of pediatric NT1.[3,7,67] Based on clinical experience, curtailing nocturnal sleep duration (specifically waking patients from REM sleep) should be avoided because such actions have the potential to shorten mean

sleep latency and result in daytime SOREMPs (particularly in the first 2 naps) during MSLT testing. Likewise, the sleep technologist should not begin the MSLT prior to the patient's typical awake period.

Accordingly, the timing of PSG testing and daytime MSLT may need to be personalized to the patient which may require changes in sleep study staffing and space allocation as well as coordination with environmental services for bed turnover. Overall, there is recognition that a habitual amount of sleep may not be achieved in the sleep lab setting given unfamiliar surroundings and potentially uncomfortable monitoring equipment. Thus, the task force consensus is that pediatric patients need to obtain a minimum of 7 hours of total sleep time with minimum 8 hours of total recording time to ensure adequate sleep for MSLT interpretation.

To eliminate confounding factors that can cause sleep disruption and daytime sleepiness, children with clinically significant OSA should use their PAP or non-PAP device during the PSG. Non-PAP therapy includes mandibular advancement devices, palatal expanders, or hypoglossal nerve stimulation which are used, although less commonly, in certain pediatric populations with OSA.

Environmental factors: Electronic devices should be shut off and inaccessible to patients for a minimum of 30 minutes before lights out time. Electronic use is known to reduce sleep duration and delay sleep onset latency in children and adolescents.[68] Few studies have directly measured the effects of light from screens on PSG-measured sleep architecture. Young adults exposed to light-emitting devices (a light emitting e-reader) before bedtime had a phase delay of melatonin release, modestly increased time to fall asleep, and reduced REM sleep duration; changes in REM sleep latency were not reported.[69] In a study of adolescents, researchers found no significant changes on PSG NREM and REM sleep stage amounts with evening exposure to light-emitting devices but again, REM sleep onset latency was not reported.[70] Thus, it is unknown how lab procedures and environmental factors may impact the presence of a nocturnal SOREMP, a diagnostic biomarker for NT1.[6]

Efforts should be made to alleviate patient fears or anxiety, including the need for comfort tools such as preferred bedding, a stuffed animal or favorite pillow. Parents/caregivers should step out of the room to avoid distracting the patient when they are using their cell phone, tablets, or laptops. Likewise, if a parent/caregiver is known to snore loudly, an alternative parent/caregiver should be advised to stay with the patient to avoid sleep disturbance. Between naps, however, parents/caregivers should help keep the patient awake.

Performance of nap trials: For both the PSG and MSLT nap trials, bio-calibrations should always be attempted with clear, age-appropriate instructions. Only when the results are clearly diagnostic of narcolepsy after 4 naps (mean sleep latency $\leq$ 8 minutes and 2 or more SOREMPs, one of which may be a PSG SOREMP), does the task force advise a shorter 4-nap trial test be considered. Otherwise, all 5 nap trials should be performed in order to obtain data that may inform overall disease severity and timings of future medications.[71]

PROTOCOL FOR MWT

The protocol for the MWT can be found in the paper "Recommended protocols for the Multiple Sleep Latency Test and Maintenance of Wakefulness Test in adults: guidance from the American Academy of Sleep Medicine."[5] The MWT is not validated in people under 18 years of age and thus its clinical utility in pediatric hypersomnolence evaluation is uncertain.[21] Clinically, the MWT is used by pediatric health care providers to assess treatment efficacy. Research investigators used the MWT to assess treatment outcome in a double blind, randomized, placebo-controlled, multi-site study of pitolisant with people 6-17 years with narcolepsy (with or without cataplexy). In this trial, investigators reported a baseline MWT score in the placebo group of 10.6 (8.3) minutes. More data are needed to determine the normative baseline score for pediatric NT1 patients who are drug naïve, or drug weaned.[72] It should be noted that the MWT may not be reliable to assess driving safety in adolescents with central disorders of

hypersomnolence. The predictive power of MWT for an increased risk of impaired driving was significant but low (area under the curve = 0.27, p = 0.01), and non-significant for the sustained attention to Response Task in a recent study of n=44 adults with central disorders of hypersomnolence.[73]

DISCUSSION

Age, puberty, development, psychological needs, as well as physiology and operational capabilities affect MSLT and MWT protocols and study interpretation. Given that some central disorders of hypersomnolence such as narcolepsy are considered chronic, life-long disorders, thoughtful consideration of pediatric patient needs and adherence to protocols is necessary for accurate diagnostic testing. Diagnosis of a central disorder of hypersomnolence can affect the patients' abilities to access treatments and educational and social/emotional support services, as well as help address safety concerns about pedestrian and driving risks.[74,75] At the same time, misdiagnosis can expose children and adolescents to inappropriate medication risks and adverse side effects, misshape identity with an incorrect disease label, and pose limitations on patient capabilities and job opportunities throughout life. The validity and reliability limitations of the MSLT for NT2, IH, and secondary narcolepsy require explanation to patients and parents/caregivers to optimize preparation for testing, consider alternative diagnostic testing options, and mitigate unrealistic expectations.

The MSLT cannot be relied upon as the sole criterion for diagnosis without clinical context. Information on central disorders of hypersomnolence disease symptoms and severity, habitual sleep amount and timings, medical and psychiatric diagnoses and comorbidities, and medication and substance history must be available to the health care provider making the diagnosis. To facilitate this role, the task force recommends the collection and documentation of validated surveys regarding disease severity, sleep logs/diaries (and ideally other validated sleep tracking device data), protocol deviations or observations about the patient or testing environment that impact study results, and information about medication and substances recently taken or stopped. Communication of this information in the MSLT study report ensures accurate data transfer across health care institutions and providers (see Appendix B in supplemental material).

For the most part, the newly developed protocol for MSLT in pediatrics follows guidance specified in the 2021 recommended protocols for adults,[5,76] which included the following changes from prior adult MSLT recommendations[77]: (1) frontal electrodes for sleep staging scoring based on *The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications*;[78] (2) termination of stimulating activity 30 minutes before naps/trials including the use of all electronic devices for both the MSLT and the MWT; (3) sufficient treatment of OSA using PAP or non-PAP based therapies during PSG and MSLT naps; (4) shared patient-health care provider decision-making concerning the use of medications and caffeine prior/during MSLTs.

Specific changes recommended for pediatric MSLT protocols from the 2021 MSLT protocol in adults paper[5] include (1) provision of a minimum of 7 hours of sleep (with minimum 8 hour recording time) on the PSG the night before the MSLT, ideally meeting age-based needs (see **Figure 1**);[12] (2) use of clinical judgement to guide need for sleep-disordered breathing treatments prior to PSG-MSLT testing; and (3) shared patient-health care provider decision-making regarding any suggested modifications in protocol for children and adolescents with neurodevelopmental/ neurological disorders, young age, and/or delayed sleep phase.

Limitations

The task force identified many limitations in formulating this recommended protocol including:

- Lack of pediatric data regarding normative values for age <5 years on MSLT and for children with neurodevelopmental/neurological conditions
- Lack of normative values for age on MWT and MWT validation in children and adolescents with and without central disorders of hypersomnolence

- Lack of MSLT validity and reliability data in pediatric patients with NT2 and IH
- Unquantified influence of comorbid conditions to narcolepsy and IH such as OSA, attention-deficit/hyperactivity disorder, and depression on mean sleep latency and SOREMPS
- Unknown environmental effects, such as light/electronic exposure on presence of nocturnal SOREMPs among people with NT1
- Lack of validated alternative protocols that account for delayed sleep phase by starting and ending all testing later
- Lack of validated alternative protocols that account for long sleep time for age that may be useful in diagnosis of IH
- Unknown specific medication effects on PSG-MSLT diagnostic measures because existing studies typically group medications by class (e.g., SSRI/SNRI, anti-depressants, or stimulants). The task force encourages health care providers to review the half-life of medications that may influence sleep/wake physiology and ensure they have been stopped at least 5 half-lives of the drug.
- Lack of generalizability testing of alternative pediatric MSLT diagnostic criteria. While MSL of ≤8. minutes or 2 MSLT SOREMPs alone have been shown to be highly accurate for the diagnosis of pediatric NT1 in two European testing sites, the generalizability of these findings at other international clinical sleep centers is needed.

Future directions

To improve diagnostic delays, the accuracy of objective diagnostic testing, and clinical care for pediatric central disorders of hypersomnolence, future research is needed to:

1. Validate sleep-tracking devices beyond actigraphy in children and adolescents to exclude other sleep disorders such as insufficient sleep or circadian rhythm disorders prior to MSLT testing.
2. Validate PSG-MSLT protocol modifications in children and adolescents with a) neurodevelopmental, psychological, or neurological conditions, b) comorbidities such as OSA, and c) altered sleep needs such as long sleep durations or late bedtime/rise times.
3. Provide age-dependent data and validation studies for MSLT protocols with children <6 years.
4. Provide age-dependent data and validation studies for MWT in children and adolescents of all ages.
5. Identify and validate other diagnostic biomarkers or testing methods that may be easier to obtain from children and adolescents and more accurately measure patient symptoms compared to PSG-MSLT.
6. Validate and assess reliability of NT1 diagnostic biomarkers such as nocturnal SOREMP and measures of disrupted nighttime sleep available on the PSG alone to assess generalizability to secondary narcolepsy with cataplexy.[79,80]
7. Identify clinical utility of MSLT and MWT measures for assessment of prognosis, functional capabilities such as driving, and treatment timing.

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Figure 1—American Academy of Sleep Medicine recommendations for health sleep duration.

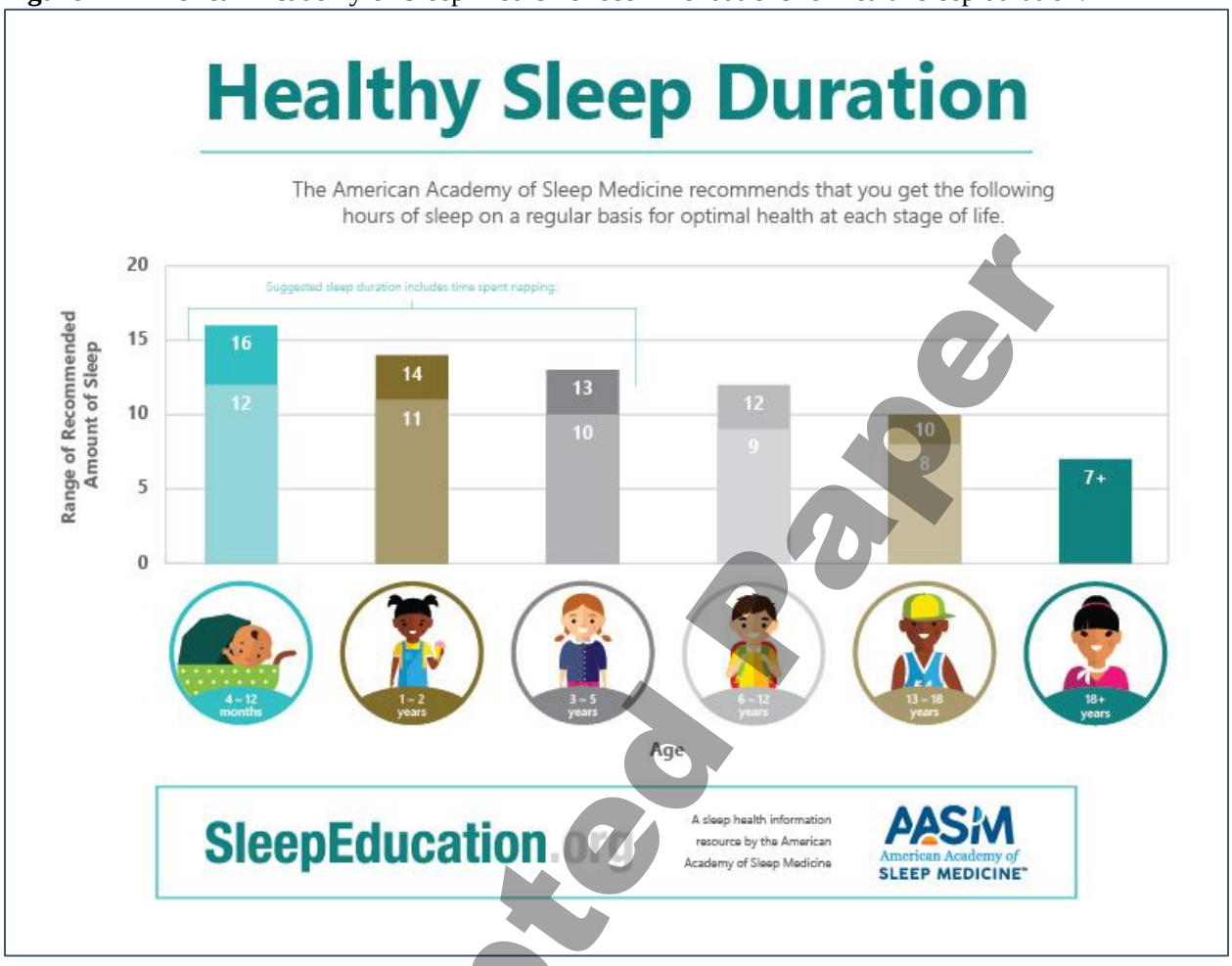

Table 1—Medications that may interfere with sleep architecture.[44]

Drug Class	Example Agents
Adenosine modulators	theophylline, theobromine, caffeine
Alpha-2 delta ligands	gabapentin
Antidepressants	
SSRIs[45]	fluoxetine,* escitalopram, sertraline, paroxetine
SNRIs	venlafaxine, duloxetine
Bupropion	bupropion
Tricyclic antidepressants	nortriptyline, amitriptyline, doxepin
Antihistamine, sedating	diphenhydramine, doxylamine
Antipsychotic agents	quetiapine
Alpha antagonists	prazosin
Benzodiazepines/NBRAs	flurazepam*, clonazepam, lorazepam, zolpidem, eszopiclone, zaleplon
Dopamine agonists	pramipexole, rotigotine, ropinirole[46]
Lithium	lithium
Melatonin agonists	ramelteon, tasimelteon
Opioid agonists	morphine, hydrocodone, methadone,[47] fentanyl[48]
Oxybates	sodium oxybate; calcium, magnesium, potassium, sodium oxybate[49]
Steroids	prednisone[50]
Stimulants	methylphenidates, amphetamines
Wake-promoting agents	armodafinil, modafinil, pitolisant, solriamfetol

*Medication agents with long half-lives and longer washout (up to 6 weeks) may be needed
SSRIs–selective serotonin reuptake inhibitors; SNRIs–serotonin noradrenergic reuptake inhibitors; MAOIs–monoamine oxidase inhibitors; NBRA–non-benzodiazepine receptor agonists, CBG–cannabigerol. This list is not exhaustive and health care providers should consider impacts on sleep architecture with newer/future medications.