The Multiple Sleep Latency Test: Guidelines and Pitfalls

Jennifer Liebenthal, MD

Clinical Assistant Professor

Medical Director, Neurology Sleep Lab

The University of Kansas Medical Center

Excessive Daytime Sleepiness

Inability to stay awake and alert during the major wake period of the day

Irrepressible need for sleep or unintentional lapses into drowsiness or sleep

16% of adults experience sleepiness impacting daily functioning (Young, 2004)

Dangers of Excessive Daytime Sleepiness

- Cognition, memory, inattention, focus
- Occupational errors
- Medical errors
- Motor vehicle accidents
- Fatalities

The Multiple Sleep Latency Test

- Provides objective measure of sleepiness
- Measures physiologic tendency to fall asleep in quiet situations
- Used in diagnosis of narcolepsy, idiopathic hypersomnia
- Not routinely indicated for evaluation of sleepiness in medical and other neurologic disorders, insomnia, circadian rhythm disorders
- Not routinely indicated for initial evaluation of obstructive sleep apnea or to assess change following treatment with CPAP

History of the MSLT

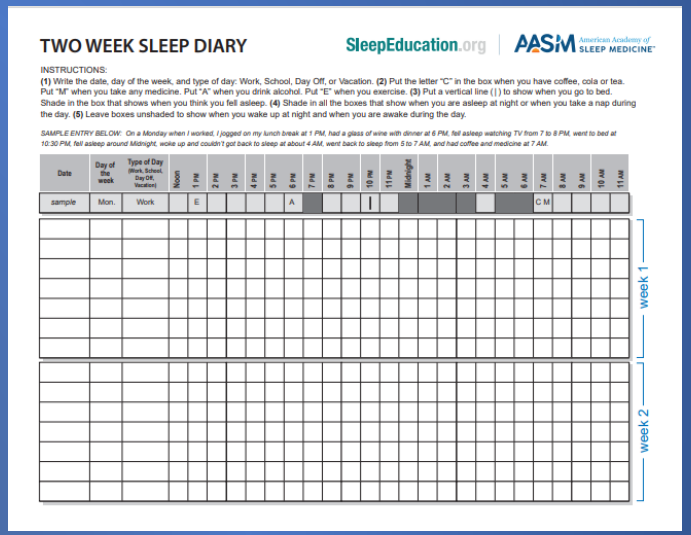
Dr. Mary Carskadon and Dr. William Dement, 1979

- Measured sleep tendency before, during, and after 2 nights of sleep loss in 6 adult volunteers
  - 2 hour intervals during all waking periods
- Sleep latency decreased to 1 minute at 06:00 after 1 night sleep loss and remained low
- Scores remained below baseline levels until after second recovery night

MSLT Guidelines and Patient Preparations

- Adequate sleep documentation for 2 weeks prior to testing, ideally ≥ 7 hours
  - Sleep diary
  - Actigraphy, when available

- Patients with persistent sleepiness despite treatment of OSA or other sleep disorder- Conduct MSLT WHEN
  - Clinically stable
  - Treatment of sleep disordered well-established and effective


TWO WEEK SLEEP DIARY

SleepEducation.org | AASM American Academy of SLEEP MEDICINE

INSTRUCTIONS:
(1) Write the date, day of the week, and type of day: Work, School, Day Off, or Vacation. (2) Put the letter "C" in the box when you have coffee, cola or tea. Put "M" when you take any medicine. Put "A" when you drink alcohol. Put "E" when you exercise. (3) Put a vertical line (|) to show when you go to bed. Shade in the box that shows when you think you fell asleep. (4) Shade in all the boxes that show when you are asleep at night or when you take a nap during the day. (5) Leave boxes unshaded to show when you wake up at night and when you are awake during the day.

SAMPLE ENTRY BELOW: On a Monday when I worked, I jogged on my lunch break at 1 PM, had a glass of wine with dinner at 6 PM, fell asleep watching TV from 7 to 8 PM, went to bed at 10:30 PM, fell asleep around Midnight, woke up and couldn't get back to sleep at about 4 AM, went back to sleep from 5 to 7 AM, and had coffee and medicine at 7 AM.

Date	Day of the week	Type of Day (Work, School, Day Off, Vacation)	Noon	1 PM	2 PM	3 PM	4 PM	5 PM	6 PM	7 PM	8 PM	9 PM	10 PM	11 PM	Midnight	1 AM	2 AM	3 AM	4 AM	5 AM	6 AM	7 AM	8 AM	9 AM	10 AM	11 AM
sample	Mon.	Work		E					A				|								C M				

week 1

week 2

Krahn et al., 2021

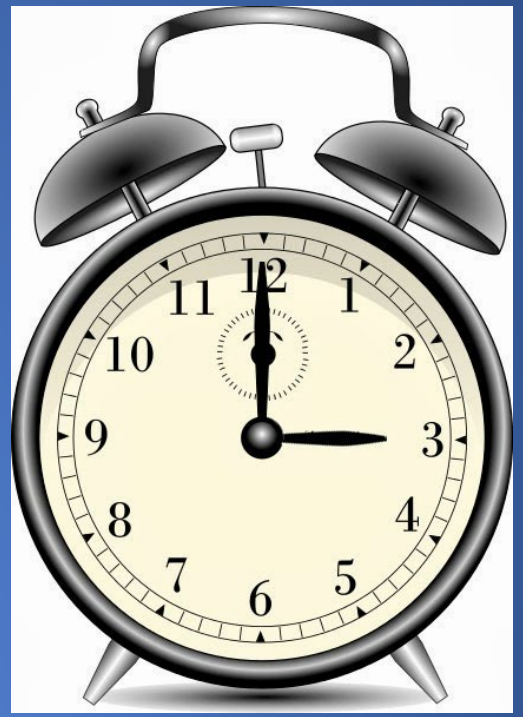
MSLT & Comorbid OSA

- SOREMPs reported in severe, untreated OSA (Chervin, 2000)
- Confirm PAP adherence/treatment efficacy prior to MSLT
  - ≥ 6 hours/night
- Most patients should use OSA treatments to avoid sleep fragmentation during naps
- Patients intolerant to therapy with very mild OSA (AHI< 10/hr) ?

MSLT & Circadian Rhythm Disorders

Timing of study is critical!

- Shift workers MSL ≤ 8 min + ≥ 2 SOREMPs, clinically unlikely to have narcolepsy (Goldbart, et al. 2014)
- Avoid terminating PSG too early in DSPS- SOREMPs in early naps
- Complete study when patient maintains consistent sleep-wake schedule
- May require later PSG and MSLT start time to accommodate delayed/long sleeper



MSLT Guidelines and Patient Preparations

- Clinician develop medication plan with patient
  - Use of prescription medication, OTC, herbal and other substances
  - Ideally discontinue medications/substances with alerting, sedating, REM-modulating properties 2 weeks prior to MSLT
  - Medications or metabolites with longer half-lives (> 1 day), longer washout up to 6 weeks may be needed
  - Medications with very short half-lives, consider washout of < 2 weeks

- Use clinical judgement regarding changes that could impact patient safety
- Patient should consult clinician PRIOR to starting any prescription/OTC prior to the study

Krahn et al., 2021

Medication Challenges

- Chronic use of certain medications suppress REM sleep
- Immediate discontinuation of REM-suppressing medication too close to the MSLT → REM rebound
- Study showed only 5.9% patients on REM-suppressing agents discontinued prior to testing and 1/3 took medication on evening of sleep study (Cairns, et al. 2019)
- Discontinuation may not be possible due to worsening depression, risk of suicide
- If MSLT negative and strong suspicion of narcolepsy
  - Consider re-test
  - Check CSF hypocretin if patient has cataplexy

Caffeine

- Difficult to address use prior to test
  - Approximately 80% world population consumes daily
  - (Heckman et al., 2010)
  - Variability in tolerance and withdrawal symptoms

- Study on regular caffeine intake by healthy men (Weibel et al., 2021)
  - Consumption 13.5 hours prior to bedtime→ delayed REM latencies
  - Caffeine-induced REM differences not detectable 44.5 hours after withdrawal

- Encourage abstention on days of PSG/MSLT, although patients may require longer taper

Medication Effects on Sleep Architecture Antidepressants

Drug Class	Sleep Latency	Sleep Continuity	Slow Wave Sleep	REM Sleep	Example Agents
SSRI	↑	↓	↓ ↔	↓	Escitalopram, fluoxetine*, paroxetine, sertraline
SNRI		↓	↓ ↔	↓	Duloxetine, venlafaxine
Tricyclic antidepressants	↓	↑	↔	↓	Amitriptyline, clomipramine, doxepin, imipramine
	↔	↔ ↓	↔ ↓	↓	Desipramine, nortriptyline
Monoamine oxidase inhibitors	↔ ↑	↓		↓ ↓	Phenelzine
Bupropion	↔	↔	↔	↔ ↑	Bupropion
Mirtazapine	↔ ↓	↑	↑	↔	Mirtazapine
Trazodone	↓	↔ ↑	↑	↔ ↓	Trazodone

Modified from Kryger, et al., 2022

Medication Effects on Sleep Architecture

Drug Class	Sleep Latency	Sleep Continuity	Slow Wave Sleep	REM Sleep	Example Agents
Acetylcholine modulators				↑	Donepezil
Adenosine modulators	↑	↓	↓		Caffeine
		↓	↓		Theophylline
Alpha-2 delta ligands	↔	↑	↑	↔ ↑	Gabapentin
	↓	↑	↑	↓	Pregabalin
Antihistamine, sedating	↔ ↓	↔ ↑	↔ ↑	↔ ↓	Diphenhydramine, doxylamine
Antipsychotic agents	↓	↑	↔ ↑↓	↓	Quetiapine
Lithium			↑	↓	Lithium
Antihypertensives		↑		↑	Prazosin
		↔ ↑	↑	↓	Clonidine

Modified from Kryger, et al., 2022

Medication Effects on Sleep Architecture

Drug Class	Sleep Latency	Sleep Continuity	Slow Wave Sleep	REM Sleep	Example Agents
Benzodiazepines/ NBRAs	↓	↑	↓	↓	Clonazepam, flurazepam*, lorazepam, temazepam
	↓	↑ ↔ zal	↔	↔ ↓ zol	Eszopiclone, zaleplon, zolpidem
Dopamine agonists			↑ ?	↓	Pramipexole
	↓	↑	↔	↔	Ropinirole
Melatonin agonists	↓	↔ ↑	↔	↔	Ramelteon
	↓	↑	↔	↔	Tasimelteon
Opioids	↔ ↓ acute	↔ ↑ acute ↓ chronic	↓	↓	Fentanyl, hydrocodone, methadone, morphine
Hypocretin Antagonists	↓	↑	↔	↑	Lemborexant, suvorexant
Sodium oxybate	↓	↑	↑	↔ ↓	Sodium oxybate
Steroids		↓	↔ ↓	↓	Prednisone

Modified from Kryger, et al., 2022

Medication Effects on Sleep Architecture

Drug Class	Sleep Latency	Sleep Continuity	Slow Wave Sleep	REM Sleep	Example Agents
Stimulants	↑	↓	↔ ↓	↓	Amphetamines, methylphenidate
Wake-promoting agents	↔ ↓	?	↔		Armodafinil, modafinil
Marijuana	↓		Long term ↓	Discontinuation ↑	Tetrahydrocannabinol
Alcohol	↓	↑ ↓	↑	↓	Acute
	↑	↓	↓	↓	Chronic
	↑	↓	↓	↑	Withdrawal

Modified from Kryger, et al., 2022

JCSM
Journal of Clinical Sleep Medicine

SCIENTIFIC INVESTIGATIONS

Urine Toxicology in Adults Evaluated for a Central Hypersomnia and How the Results Modify the Physician's Diagnosis

Christopher A. Kosky, MBBS, FRCP[1,2]; Anastasios Bonakis, MD[2,3]; Arthee Yogendran, MBBS[1,2]; Gihan Hettiarachchi, MBBS[2,4]; Paul I. Dargan, MD[5,6]; Adrian J. Williams, MBBS, FRCP[2]

[1]West Australian Sleep Disorders Research Institute, Sir Charles Gairdner Hospital, Perth, Western Australia; [2]Sleep Disorders Centre Guys' Hospital, London, UK; [3]National and Kapodistrian University of Athens, 2nd Neurological Unit, Attiko Hospital, Greece; [4]Medway Maritime Hospital, Gillingham, UK; [5]Clinical Toxicology, Guy's and St Thomas' Foundation Trust, London, UK; [6]Faculty of Life Sciences and Medicine, King's College London, United Kingdom

- 186 patients with suspected hypersomnia
- Positive drug screen in 33% patients undergoing MSLT
  - 81% did not report use of detected substance
- 97% of treating physicians had not suspected drugs/substances as possible etiology of hypersomnia

Drug Screen

- AASM task force concluded “drug screening may be indicated in adult patients depending on community and clinical circumstances.”
- Consider screening 1-2 days prior to MSLT when concern for non-compliance with washout period, unreported substances, or onsite collection not available

Krahn et al., 2021

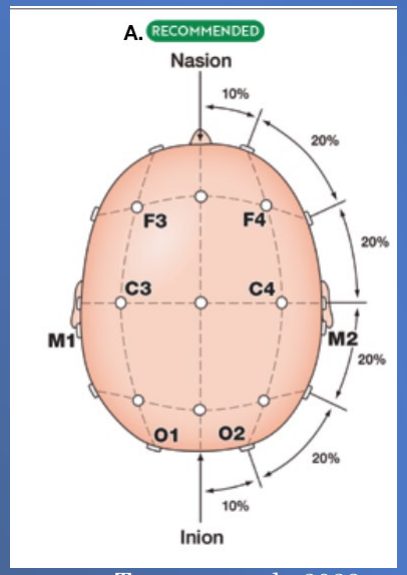
MSLT General Testing Procedures

- MSLT should follow attended PSG, allowing 7 hours minimum time in bed with 6+ hours TST
- Do NOT complete MSLT after split night study or titration study
- Abstain from caffeine, alcohol, marijuana, sedating or alerting agents on study day
- Avoid nicotine- if unavoidable, cessation 30+ minutes prior to nap trial

Krahn et al., 2021

MSLT General Testing Procedures

- Patients with OSA should use their current treatment during PSG and MSLT, with same pressure settings and mask interface used at home
- Minimum MSLT recording montage:
  - 3 EEG recording leads, 1 each for frontal (F3-M2 or F4-M1), central (C3-M2 or C4-M1), occipital (O1-M2 or O2-M1)
  - L & R eye EOGs
  - Mental/submental EMG
  - EKG
- Audiovisual recordings made during each nap trial accessible to interpreting clinician



Troester et al., 2023

Krahn et al., 2021

MSLT General Testing Procedures

- MSLT consists of 5 nap trials
  - 1st trial 1.5 to 3 hrs after termination of PSG
  - Subsequent trials 2 hours after start of prior trial
  - 4 nap trial acceptable only when results definitive for narcolepsy after 4 nap trials (mean latency ≤ 8 min and ≥ 2 SOREMPs)
- Patient should lie in bed for all nap trials
- Rooms should be dark, quiet, comfortable temperature
- Bio-calibrations prior to start of each nap trial

Krahn et al., 2021

MSLT General Testing Procedures

- Instructions at start of each nap trial: “Please lie quietly, assume a comfortable position, keep your eyes closed, and allow yourself to fall asleep.”
- Nap trial terminated:
  - If sleep onset not achieved in 20 minutes
  - If sleep onset is achieved, 15 minutes after sleep onset

  *Sleep onset: first epoch scored as any stage of sleep

Krahn et al., 2021

MSLT General Testing Procedures

- End stimulating activities/use of electronics 30+ minutes prior to each nap trial
- Avoid high intensity activity and prolonged light exposure throughout the day
- Obtain urine drug screen when indicated to avoid confounding study results
- Between nap trials: Out of bed, sleep not permitted

Krahn et al., 2021

MSLT Data Acquisition and Reporting

- Medications/Substances
  - Document usage within 24 hours of and during MSLT
  - Changes to medications within last 2 weeks
  - Drug screen type (if performed)
- Document pre-study data
- Deviations to Procedure Documented by sleep technologist
  - Adjustments to ideal testing times
  - Factors impacting study conditions

Krahn et al., 2021

MSLT Data Acquisition and Reporting

Recording parameters for each trial

- Start time, end time, TST, SOL, REML
  - Sleep latency: Time from lights out until 1st epoch ANY stage of sleep
  - REM latency: Time from 1st epoch sleep until first epoch REM sleep
- Mean sleep latency, Number of SOREMPs on MSLT and PSG
- If no sleep occurs on a trial, 20 minutes used as sleep latency value in calculation of MSL

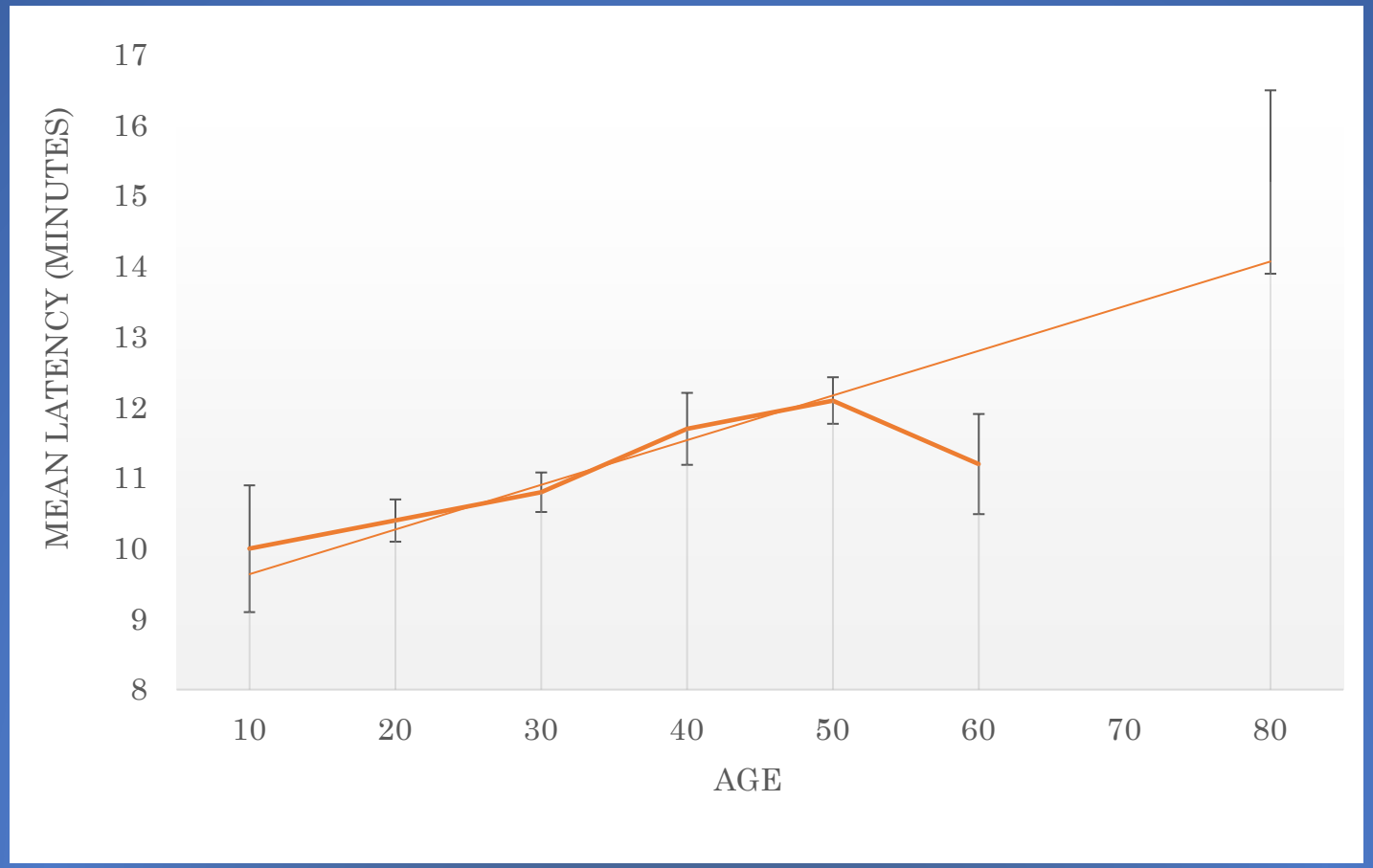
Krahn et al., 2021

MSLT Cases

Summary of Key Issues with Cases

- Case 1: Circadian rhythm disorders and timing of MSLT
- Case 2: Co-morbid sleep disorders and impact of MSLT
- Case 3: Medications and importance of urine drug screen

Effect of Age on Mean Sleep Latency in Normal Subjects



Arand D, et al., 2005

MSLT Repeatability (Retrospective study by Ruoff et al., 2018)

- Evaluated repeatability in NT1 (n=60) and NT2 (n=54) and controls (n=15)
- All subjects had documented HLA-DQB1*06:02 status and/or CSF hypocretin levels and completed 2 MSLTs
- Both MSLTs + for narcolepsy in 78% NT1, 18% NT2, 7% controls
- NT2 cases changed to IH 26% of time or to negative study 57% of time
- NT1 10-14 times more likely to have second + MSLT compared to NT2 and controls

Conclusions

- MSLT can provide useful, objective measurement of sleepiness
- Results can be confounded by several factors that should be recognized by providers
- Should not be only criterion for assessment of excessive daytime sleepiness or diagnosing disorder of hypersomnolence
- Importance of clinical history and other pertinent information

References

- Arand D, Bonnet M, Hurwitz T, Mitler M, Rosa R, Sangal RB. The clinical use of the MSLT and MWT. Sleep 2005;28(1):123-44.
- Bolla KI; Lesage SR; Gamaldo CR; Neubauer DN; Funderburk FR; Cadet JL; David PM; Verdejo-Garcia A; Benbrook AR. Sleep disturbance in heavy marijuana users. SLEEP 2008;31(6):901-908.
- Cairns A, Trotti LM, Bogan R. Demographic and nap-related variance of the MSLT: results from 2,498 suspected hypersomnia patients: Clinical MSLT variance. Sleep Med. 2019 Mar;55:115-123. doi: 10.1016/j.sleep.2018.12.013. Epub 2018 Dec 30. PMID: 30785052; PMCID: PMC6411434.
- Carskadon, M. A., & Dement, W. C. (1979). Effects of Total Sleep Loss on Sleep Tendency. Perceptual and Motor Skills, 48(2), 495–506. https://doi.org/10.2466/pms.1979.48.2.495
- Chervin RD, Aldrich MS. Sleep onset REM periods during multiple sleep latency tests in patients evaluated for sleep apnea. Am J Respir Crit Care Med. 2000 Feb;161(2 Pt 1):426-31. doi: 10.1164/ajrccm.161.2.9905071. PMID: 10673181.
- Dzodzomenyo S, Stolfi A, Splaingard D, Earley E, Onadeko O, Splaingard M. Urine toxicology screen in multiple sleep latency test: the correlation of positive tetrahydrocannabinol, drug negative patients, and narcolepsy. J Clin Sleep Med. 2015 Jan 15;11(2):93-9. doi: 10.5664/jcsm.4448. PMID: 25348245; PMCID: PMC4298782.
- Goldbart A, Peppard P, Finn L, Ruoff CM, Barnet J, Young T, Mignot E. Narcolepsy and predictors of positive MSLTs in the Wisconsin Sleep Cohort. Sleep. 2014 Jun 1;37(6):1043-51. doi: 10.5665/sleep.3758. PMID: 24882899; PMCID: PMC4015378.

References

- M.A. Heckman, J. Weil, E. Gonzalez de Mejia. Caffeine (1, 3, 7-trimethylxanthine) in foods: a comprehensive review on consumption, functionality, safety, and regulatory matters. J. Food Sci., 75 (3) (2010), pp. R77-R87
- Kosky CA, Bonakis A, Yogendran A, Hettiarachchi G, Dargan PI, Williams AJ. Urine Toxicology in Adults Evaluated for a Central Hypersomnia and How the Results Modify the Physician's Diagnosis. J Clin Sleep Med. 2016 Nov 15;12(11):1499-1505. doi: 10.5664/jcsm.6276. PMID: 27568897; PMCID: PMC5078705.
- Krahn LE, Arand DL, Avidan AY, Davila DG, DeBassio WA, Ruoff CM, Harrod CG. Recommended protocols for the Multiple Sleep Latency Test and Maintenance of Wakefulness Test in adults: guidance from the American Academy of Sleep Medicine. J Clin Sleep Med. 2021 Dec 1;17(12):2489-2498. doi: 10.5664/jcsm.9620. Erratum in: J Clin Sleep Med. 2022 Aug 1;18(8):2089. PMID: 34423768; PMCID: PMC8726366.
- Kryger, Meir, H. et al. Kryger's Principles and Practice of Sleep Medicine. Available from: Elsevier eBooks+, (7th Edition). Elsevier - OHCE, 2022.
- Troester MM, Quan SF, Berry RB, et al.; for the American Academy of Sleep Medicine. *The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology, and Technical Speciifications.* Version 3. Darien, IL: American Academy of Sleep Medicine; 2023.
- Weibel J, Lin YS, Landolt HP, Berthomier C, Brandewinder M, Kistler J, Rehm S, Rentsch KM, Meyer M, Borgwardt S, Cajochen C, Reichert CF. Regular Caffeine Intake Delays REM Sleep Promotion and Attenuates Sleep Quality in Healthy Men. J Biol Rhythms. 2021 Aug;36(4):384-394. doi: 10.1177/07487304211013995. Epub 2021 May 23. PMID: 34024173; PMCID: PMC8276335.
- Young TB. Epidemiology of daytime sleepiness: definitions, symptomatology, and prevalence. J Clin Psychiatry. 2004;65 Suppl 16:12-6. PMID: 15575799.