Management of Narcolepsy and Disorders of Hypersomnia

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April 17, 2015

Learning Objectives

1. Review the differential diagnosis for Hypersomnia
2. Discuss how to approach adult and pediatric patients who are dealing with Hypersomnia
3. Review non-pharmacological and pharmacological treatments for Hypersomnia
Challenges Associated with Daytime Testing for Narcolepsy

Donna Arand, Ph.D.
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April 17, 2015

MSLT Protocol

• The MSLT consists of five nap opportunities performed at two hour intervals. The initial nap opportunity begins 1.5 to 3 hours after termination of the nocturnal recording. A shorter four-nap test may be performed but this test is not reliable for the diagnosis of narcolepsy unless at least two sleep onset REM periods have occurred.
• The MSLT must be performed immediately following polysomnography recorded during the individual's major sleep period. The use of MSLT to support a diagnosis of narcolepsy is suspect if TST on the prior night sleep is less than 6 hours. The test should not be performed after a split night sleep study.
• Sleep logs maybe obtained for 1 week prior to the MSLT.
• Standardization of test conditions is critical for obtaining valid results. Sleep rooms should be dark and quiet during testing. Room temperature should be set based on the patient’s comfort level.

MSLT Protocol
Use of Substances

Stimulants, stimulant-like medications, and REM suppressing medications should ideally be stopped 2 weeks before MSLT. Use of the patient’s other usual medications (e.g., antihypertensives, insulin, etc.) should be thoughtfully planned by the sleep clinician before MSLT testing so that undesired influences by the stimulating or sedating properties of the medications are minimized. Drug screening may be indicated to ensure that sleepiness on the MSLT is not pharmacologically induced. Drug screening is usually performed on the morning of the MSLT but its timing and the circumstances of the testing may be modified by the clinician. Smoking should be stopped at least 30 minutes prior to each nap opportunity.


Between Naps

- Out of bed
- No sleeping
- No caffeine
- No vigorous physical activity
- Avoid unusual exposure to bright sunlight
- Smoking discontinued 30 min prior to nap
- Stimulating activities end 15 min before nap
- Light breakfast 1 hr. before first nap
- Light lunch after noon nap
- This generally requires continuous observation by a laboratory staff member.

MSLT Protocol
Calibration & Termination

• Calibrations begin 5 min before start of nap
  - Lie quietly with your eyes open for 30 sec
  - Close both eyes for 30 sec
  - Without moving your head look to the right, then left, then right, then left, right and left again
  - Blink eyes slowly 5 times
  - Clench or grit teeth tightly together
  - “Please lie quietly, assume a comfortable position, keep your eyes closed and try to fall asleep”

• Termination of nap
  - Terminated after 20 min if no sleep occurs
  - If sleep occurs, the test is terminated 15 minutes after sleep onset (latency to first stage of sleep)


What does the MSLT measure?

• MSLT uses sleep latency to measure physiological sleepiness in the absence of alerting factors
• Alerting factors contribute to “manifest sleep tendency” and include:
  - External factors
  - Activity
  - Posture
  - Light
  - Caffeine, alcohol, drugs
  - Room Temperature
  - Noise
  - Internal Factors
  - Motivation
  - Sympathetic arousal
  - Noise
Common Problems

• Too much activity
• Caffeine use
• MSLT in shift workers
• Motivation to affect results
• PSG is a titration
• Less than 4 naps are done
• No PSG prior to MSLT

Activity Prior to MSLT

• Lying in bed watching TV 15 min (MSL 6.7min)
• Walking outside for 5 min (MSL 13 min) normal subjects

Effect of Caffeine on MSLT during Night

- Placebo
- Caff. 300mg

Impact of Directions and Motivation on MSLT & MWT

- 12 normal subjects 21-25 y.o.
- 3 days of testing using MSLT & MWT each day (60-90 min apart lasting max of 20 min & ended if spindles
  - Day 1 normal test instructions
  - Day 2 told to appear as sleepy as possible (i.e. fall asleep rapidly)
  - Day 3 motivated to be wakeful
- The subject with best performance was paid a bonus
- Results:
  - MSLT latency longer in wakeful condition than baseline
  - MWT latency shorter in sleepy condition than baseline

Effect of Motivation and Posture on MSLT & MWT

Test Retest Reliability of MSLT

- Test retest reliability = 0.97 in normals over 4-14 months
- Test retest reliability decreases for 3 naps =0.85 and 2 naps=0.65
- Test retest reliability of 2 SOREMPS = 0.93 in narcolepsy patients
Home vs Laboratory Prior Night Sleep Environment

- No difference in MSLT latency in normal subjects (18-35 y.o.) who slept at home prior to MSLT and those who slept in the laboratory


- Why are deviations from protocol problematic
- What should be done when deviations from protocol occur?
Why are Deviations Problematic?

- The MSLT diagnostic criteria are based on data from studies that followed the standard protocol
- When protocol deviations occur the results are not exactly comparable to standardized data so diagnostic criteria may not be valid

Handling Deviations from Protocol

- Stop any behaviors that deviate from protocol as soon as they are noticed
- Document time, duration and type of behavior in patient record and on recording
- Clinician should consider any deviations in protocol when interpreting results and repeat testing if determined it is needed
What conditions or deviations from protocol would make you feel that the MSLT is invalid or the results are not interpretable?

Pitfalls When Interpreting an MSLT

- 6 hrs. of nocturnal sleep is not adequate in a typically longer sleeper
- 2 SOREMPS and MSL < 8 alone does not confirm the DX of narcolepsy
- 2 SOREMPS with MSL >10 does not confirm a DX of narcolepsy or IH
- Results from an MSLT done at night in shift workers cannot be compared to standard norms
Pitfalls in the MWT

- Motivation can delay sleep latency “Faking the test”
- No cutoff for normal vs abnormal results
- No safety data showing the validity of MWT in real life situations

The MSLT is Robust

- Retest reliability of the MSLT is .97
- Sensitivity is high .78
- Specificity is high .93
- Mean sleep latency in narcolepsy is 3.1 sd=3
- Mean sleep latency in idiopathic hypersomnia is 6.2 sd=3
- Research Limitations
  - done in normal subjects not sleepy patients
  - Significant deviations in protocol
Diagnosis of Narcolepsy

• The diagnosis of narcolepsy is a clinical decision.
• The MSLT can help support that decision but it does not determine the diagnosis.
• The MSLT must be interpreted within the context of the patient history.
• The interpretation of the MSLT must take into consideration any deviations from protocol.

Cleveland Clinic

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Management of Narcolepsy and Hypersomnia breakout

Sally Ibrahim MD
Sleep Disorders Center
Cleveland Clinic
April 17, 2015

Case: Narc

- Narc is a 16 yo male, who has been failing classes
  - Teachers note falling asleep in classes daily; unable to complete tasks /assignments because he is too sleepy. Cannot stay awake.
  - Mom notes naps after school
  - BT-10pm up at 6am
  - He no longer likes going to school. Problems with peers; “loner”
  - Teacher recommended for him to see a neurologist for possible narcolepsy;
Neurology Consultation

• Pediatric Neurology
  - No major findings on neurological examination. He was able to stay awake in the room.
• History
  - Cannot wake up in the morning
  - + sleep related hallucinations (go with the paralysis)
  - + sleep paralysis – near nightly but can go a month without
  - ? cataplexy - gets upset with emotion, feels dizzy and anxious when excited; With laughter no weakness

PSG - MSLT

• PSG
  - TST was 7.5 hours; sleep efficiency was 75%, sleep latency 45 minutes (study start at 10pm); REM latency was 200 minutes; REM 12%
  - AHI 1; PLM index 0; normal REM atonia
• MSLT: (no sleep logs available)
  - Mean Sleep Latency: 7.9m
  - Number of Sleep Onset REM Periods: 2
Discussion

- Does the MSLT provide sufficient evidence of narcolepsy or raise other concerns?
  - No sleep on last nap?
- How would you treat this patient if you were receiving these results?

Course from Peds Neuro

- Started on Vyvanse
  - titrated from 40mg to 80mg → slight improvements (more focus, able to complete tasks)
- Still napped after school
  - Addition of Adderall 10-20mg in afternoon
    Helped with some naps but could still not get up in morning. Missing classes.
  - Failing school
- Thoughts?
- Pediatric neurology referred to sleep medicine
Sleep History

- Sleep timing:
  - BT is 10pm, sleep latency 3 hours
  - WT is 6am but never wakes up in time, often getting up at 8am, late for classes and sometimes missing school (30 days missed in past year).
  - After school: naps for 1-2 hours, refreshing (more refreshed since Adderall- can wake up better and finish home work).
  - Weekends: sleeps MN-3am- 2pm, still unrefreshed.
- No snoring, RLS, PLMs, parasomnias, bruxism, enuresis.

Sleep History

+ sleep paralysis and sleep related hallucinations
  - Waking from sleep at night- feels paralyzed, unable to move briefly, hears claps/doors/thumps, may feel he sees a shadow or dog in room. Brief (less than 1 minute). Occurs up to 4x/week. But can go up to one month without symptoms
  - No cataplexy- gets anxious and has anxiety symptoms when more excited about things.
  - Private questioning (mom out of room): HEEADSS
    - +depression, no SI, + THC use- very frequent- makes his mood better
Discussion

- Does this history help the diagnosis?
- Does this history change your management?
- Is motivation a problem?
- Could he have both narcolepsy and circadian rhythm disorder?

Follow up

- Referred to psychiatry and psychology to help with depression, motivation and drug use
- Adjusted rhythm- anchored wake time slowly over time.
- Over one year, was able to wake up by 9am on weekends consistently.
  - Getting up for school improved but still sleepy on school days
- Cut out afternoon Adderall, and reduced Vyvanse to 60mg (HR elevations were noted that guided this care)
Follow up

- Graduated
- Maintained schedule: MN-9am
- Came back to sleep clinic on Vyvanse 40mg
  - Was no longer using THC
  - Resolved sleep paralysis and sleep related hallucinations
    - Would get sleep paralysis once every 1-3 months
    - And he also re-connected with father over summer (who did not live with them) and his father has recurrent isolated sleep paralysis

Discussion

- Would you continue medications?
- What is working diagnosis?
- Would you re-test him?

Narcolepsy
Delayed Sleep Wake Rhythm Disorder
Isolated sleep paralysis
THC Drug use- resolved
Other?
**PSG – MSLT retest**

- **PSG:**
  - Testing using MN and 8-9am sleep time
  - Total sleep time 8 hours; sleep efficiency was 90%. Woke up at 8am. Sleep latency 15 minutes. REM latency 120 minutes, AHI 1; PLM index 1. O2 normal.

- **MSLT**
  - MSL: 19.5 minutes
  - No SOREMPs

**Discussion**

- Does this patient have narcolepsy?

- **Role of Urine toxicology at the time of MSLT?**
  - Boston Children's: 15 year period Katz et al JCSM 2014. No + drug screens on MSLT→ don’t need to do?
  - Dzodzomenyo S. et al JCSM 2015:
    - Age <13, all drug screens negative
    - Age ≥ 13; 10% + drug screen (THC mostly)
      - Those +for THC (not other drugs): 43% had MSLT findings consistent with narcolepsy
    - Recommended testing for Age ≥ 13
Follow up

• Stopped all stimulants
• Sleeping MN-9am, refreshed

• Difficulty with concentration, but not falling asleep anymore.
  - Focus is problematic at work. Forgetful with tasks.
  - Wonders about using stimulants for ADHD?

- Thoughts?

Thank you
Meanwhile: RP continues to be very sleepy

Silvia Neme-Mercante, M.D.
Sleep Disorders Center
Epilepsy Center
Cleveland Clinic
April 17, 2015
RP

• 46 year-old man, security officer
• Job
  - 1998-2011 worked as a guardsmen for the U.S. cost guard reserve. “I was on the boat, and it was a 24 hours job, 24x7”, always had to be alert”
    • Did not have a routine sleep schedule, able to sleep better after 3-4 AM
    • Napped when possible
  - 2011-present works as a security office in a hotel
• 5/29/2012 presented with:
  - Being unable to fall asleep
  - Excessive daytime
  - Works from 11PM to 6.30 AM 4 days a week, off 3 days
• Sleep history
  - Current sleep schedule
    • Goes to bed at 8 AM, takes him 2-3 hours to fall sleep. Unable to fall asleep (may work on his computer at times)
    • Takes a 2 hours nap when he is off work
    • TST is 7-9 hours fragmented
    • “I try to catch up on weekends but it does not help”
  - Did not have sleep problems prior to 1999
RP

- Past Medical History
  - Migraines
  - Palpitations (new onset)
  - Head trauma with LOC 1 week prior to office visit
- Social history
  - Denies alcohol or illicit drugs
- Physical exam
  - BMI 23
  - Neck circumference 18 inches
  - Friedman: 2
- Medication
  - OTC Ibuprofen

What additional relevant clinical information will be needed?
RP

- Denies CNS infections
- Denies cataplexy of hypnagogic hallucinations
- Reports 3 episodes of sleep paralysis between 2000-2013

What is the Differential Diagnosis?
Differential Diagnosis

- Insomnia
- Delayed Sleep Phase
- Shift Work Sleep Disorder
- Insufficient Sleep Syndrome
- Narcolepsy
- Idiopathic hypersomnia
- Other hypersomnias
- Sleep apnea
# RP sleep log

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**KEY:**
- Out of Bed
- In Bed
- Awake
- Asleep

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**MRI brain after head trauma: Normal**
27

RP

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ICSD DIAGNOSIS:
Primary Snoring [786.09]
What is the diagnosis?

Shift Work Sleep Disorder
 +/-
 Insomnia?
Shift Work Sleep Disorder
SWSD-ICSD 3

Diagnostic Criteria
Criteria A-D must be met
A. There is a report of insomnia and/or excessive sleepiness, accompanied by a reduction of total sleep time, which is associated with a recurring work schedule that overlaps the usual time for sleep.
B. The symptoms have been present and associated with the shift work schedule for at least three months.
C. Sleep log and actigraphy monitoring (whenever possible and preferably with concurrent light exposure measurement) for at least 14 days (work and free days) demonstrate a disturbed sleep and wake pattern.
D. The sleep and/or wake disturbance are not better explained by another current sleep disorder, medical or neurological disorder, mental disorder, medication use, poor sleep hygiene, or substance use disorder.

SWSD
NSF's 2005 Sleep in America poll

• 14% of Americans do shift work

• 61% Insomnia

• 30% Hypersomnia
SWSD: Who is at risk?

- Higher age
- Male
- Night shift workers
- Having shorter intervals (<11 h) between shifts
- Having insomnia

RP

- 6/2012 :
  - Increase TST during workdays
  - Melatonin in AM during workdays
  - Naps prior to work
  - Countermeasures at night
  - Remain standing
  - Bright lighting at work
  - Caffeine if needed
  - Sleep logs for 8 weeks and re evaluate patient
RP

- 10/2012
  - Able to fall asleep 1 hour earlier
  - TST 7-8 hours
  - Excessive daytime sleepiness still present at night when working
  - ESS=17 (19 at first visit)

How would you approach his sleepiness at work?
RP

• 10/2012
  - Started Modafinil 200mg ~ 1 hour prior to bedtime
  - 2 days later patient calls to report side effect

• 11/2012
  - Patient was switched to Armodafinil, target dose 150 mg prior to night shift

• 1/2013
  - ESS: 4
  - Having more difficulty falling asleep in am
  - Advised to take Armodafinil earlier
Armodafinil 150 mg versus Modafinil 200 mg

Tember et al., Neurology Research International, 2011
Armodafinil 100–250 mg in SWSD

98% of Pts rated as improved with regard to sleepiness during night shifts

Schwartz et al., Journal of Clinical Sleep Medicine, 2010

RP

- Re evaluated 6 months later
- Able to fall asleep in 45-60 minutes, still using melatonin
- Naps prior to shift work
- Armodafinil 200 mg 2 hours prior to night shift with no side effects
Summary

- Excessive sleepiness is a serious, debilitating, potentially life-threatening condition that often goes unrecognized despite its high prevalence, yet also treatable
NM: 37 yr female

- Excessive daytime sleepiness (EDS) since teens
  - Described as “lazy” in HS
  - Many near misses driving
  - Work hrs at waitress in coffee shop cut jeopardizing health benefits due to dozing on the job
- Sleep time: 7pm-5am workdays; 7pm-9am days off
- Naps 1-2 hrs after work & in car during breaks
- Epworth sleepiness score (ESS) - 21
- PMH: Hypertension on diltiazem & HCTZ
- PE: BMI 27.2 kg/m2, NC 32 cm, BP 142/86 mmHg, HR 88 bpm, Freidman 2
Questions: Diagnosis

- What is the differential diagnosis?
- What additional clinical information is required?
- How would you proceed?

Cataplexy triggered by laughter or intense anger
Sleep paralysis - feeling of suffocation; inability to scream
Hallucinations of person in her room or someone calling her
Vivid dreaming; rare dream enactment

Cataplexy
MSLT Results

Mean sleep latency of 1.2 minutes with 4/5 SOREMPs

Diagnostic Criteria for Narcolepsy with Cataplexy

- Daily periods of irrepressible need to sleep / daytime sleepiness lapses into sleep for at least 3 mo
- The presence of one or both of the following:
  - Cataplexy and MSL $\leq$ 8 min and $\geq$ 2 sleep onset REM periods (SOREMPs) on MSLT (NOTE: SOREMP on PSG may replace one on MSLT)
  - CSF hypocretin-1 $\leq$ 110pg/mL or $< 1/3$ of mean normal values

Questions: Treatment

- Describe your treatment recommendations including:
  - Nonpharmacologic therapies
  - Pharmacologic therapies
  - Patient-specific considerations (targeted symptoms, co-morbidities, gender-related concerns)
Non-Pharmacologic Recommendations

• Education of patient, loved ones, teachers, employers
• Good sleep hygiene
• Regular bedtimes & wake times
• Short scheduled naps
• Strategic caffeine
• Avoidance of heavy meals, alcohol, recreational drugs, CNS depressants
• Avoid driving and other potentially injurious activities when sleepy

Pharmacologic Recommendations

1. Methylphenidate ER 20 mg/day
2. Methylphenidate 10 mg tid prn
3. Modafinil, titrated to 600 mg/day
4. Sodium oxybate 4.5 g/night in 2 divided doses (bedtime/2.5-4 hr later – at least 2 hr after eating); increased by 1.5 g/night q 2-4 wks to 9 g/night
Combination therapy with modafinil 600 mg/day
Pharmacologic Therapies for Excessive Sleepiness & Cataplexy in Narcolepsy

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<th>EDS in Narcolepsy</th>
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**Xyrem® (sodium oxybate)**

- Indicated for treatment of EDS and/or cataplexy in narcolepsy patients >16 yr
- Standard of care by 2007 AASM practice parameter
- Sodium salt of $\gamma$-hydroxybutyrate
- Unknown MOA $\text{GABA}_B$ and GHB receptors
- Metabolized through Kreb cycle, 1 hr T1/2
- Functions as a neurotransmitter- effects NE, SER, DOP systems

Epworth Sleepiness Scale Scores with Sodium Oxybate

B = baseline, E = endpoint (week 8).

Permission to use this figure was granted by the AASM, May 2007.


Effect of Sodium Oxybate on Cataplexy in Narcolepsy

Adapted with permission from US XYREM Multicenter Study Group. SLEEP 2002;25:42
Sodium Oxybate Dosing Calculator

Dosing calculator

Recommended starting dose

1st Dose 2nd Dose = Total Nightly Dose

2.25 g 2.25 g 4.5 g
3 g 3 g 6 g
3.75 g 3.75 g 7.5 g
4.5 g 4.5 g 9 g

Effective dose range

- Due to short half-life, taken in 2 equal doses at night
- 1-2 weeks are recommended between dosage increases
- Follow-up every 3 months is recommended
- Should be taken at least 2 hr after eating


Sodium Oxybate Safety Information

- BLACK BOX: Should not be used with alcohol, CNS depressants
- High sodium load (1638 mg in 9 g dose) precludes use in certain clinical settings (HF, resistant HTN, impaired renal function)
- Use w/caution in setting of respiratory disorders
- No known drug interactions
- Pregnancy Category C
- Common side effects - nausea, dizziness, headache
- Xyrem Success Program - patient and provider support program developed in conjunction with FDA
  - Available only through central pharmacy
  - Pharmacists, nursing support available 24/7
Panel Discussion