Evaluating Hypersomnolence and Fatigue

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Photo from W Eugene Smith, Life Magazine
Learning Objectives
By the end of this program, the attendee should…

• Be familiar with the conceptual models of sleepiness (hypersomnolence) & fatigue
• Have improved understanding of neurobiology of underlying sleepiness & fatigue
• Be more aware of what we measure with tools designed to index sleepiness and/or fatigue
What is hypersomnolence?

Fatigue is perceived as a sense of drowsiness or tiredness with a desire to sleep at inappropriate times

What Causes Hypersomnolence?

1. Reduced Sleep Quantity
2. Reduced Sleep Quality
3. Mismatched Sleep Timing
4. Sleep Disorders
5. Medical Disorders
6. Neurological Disorders
7. Psychiatric Disorders
8. Drugs or Drug Withdrawal
What is fatigue?
Fatigue is perceived as a sense of tiredness, exhaustion, and/or lack of energy. Fatigue increases the chance of performance impairment or failure.

What Causes Fatigue?
1. Exceeding physical or mental capacity with increasing time-on-task, stress load, or both.
2. Increased External Stress Load from work demand &/or poor workplace design
3. Increased Internal Stress Load from medical, neurological, & psychiatric illness; psychological issues; drugs; & sleepiness).
Sleepiness is arguably the most important stressors provoking fatigue in humans.
Fatigue can be non-pathological (that is, part of the natural rest-activity cycle).
Fatigue can be pathological (evoked by a disease process).
Non-pathological fatigue improves with rest.
Sleepiness is...

- A serious, debilitating, and potentially life-threatening condition – *Dement*
- A state instability problem – *Dinges*
- A process that becomes manifest when the alertness system can no longer stave off or balance out physiological sleep drive – *Hirshkowitz*
Sleepiness, fatigue, exhaustion, and tiredness are terms that are used interchangably by the general population and government agencies.
## Sleepy Words

| all-in | gorked       | sleepy        |
| ---    | groggy       | slugged out   |
| beat   | heavy-headed | sluggish      |
| bedragged | knackered    | spaced        |
| burned out | knocked out | tired         |
| crashing | letargic     | toast         |
| dead   | narcotized   | tuckered      |
| drifting | played       | tuckered-out  |
| droggy | pooped       | wasted        |
| drowsy | punchy       | wiped         |
| exhausted | rundown     | whipped       |
| faded  | slap happy   | zoned         |
| fagged | gassed       | zonked        |
| fatigued | My favorites: Checking my eyelids for pinholes | yawned | SLOJ (sudden loss of judgment) |
The Faces of Sleepiness

Self-reported (introspective) Sleepiness

Physiological Sleepiness

Manifest Sleepiness
Scales Measuring Self-reported Sleepiness (Relying on Introspection)

- Profile of Mood States (McNair)
- Side Effects Checklist (assorted versions)
- Stanford Sleepiness Scale (Hoddes et al)
- Visual Analog Scales (assorted versions)
- Epworth Sleepiness Scale (Johns)
Profile of Mood States (POMS)

Subscales

T-A: Tension – Anxiety
D-D: Depression – Dejection
A-H: Anger – Hostility
V-A: Vigor – Activity
F-I: Fatigue – Inertia
C-B: Confusion – Bewilderment
S A: Sleepiness Alertness
Stanford Sleepiness Scale (SSS)

1. Feeling active and vital, alert, wide awake
2. Functioning at a high level, but not at peak, able to concentrate
3. Relaxed, awake, not at full alertness, responsive
4. A little foggy, not at peak, let down
5. Fogginess, beginning to lose interest in remaining awake, slowed down
6. Sleepiness, prefer to be lying down, fighting sleep, woozy
7. Almost in reverie, sleep onset soon, lost struggle to remain awake
Visual Analog Scale (VAS)

Wide Awake

Dead Tired
Measuring Self-reported Sleepiness with the Epworth Sleepiness Scale (ESS)

Rate the likelihood of dozing in the following situations

<table>
<thead>
<tr>
<th>Situation</th>
<th>Rating</th>
<th>Chance of dozing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitting and reading</td>
<td></td>
<td>0 = would never doze</td>
</tr>
<tr>
<td>Watching TV</td>
<td></td>
<td>1 = slight chance</td>
</tr>
<tr>
<td>Sitting, inactive in a public place (e.g. a theatre or a meeting)</td>
<td></td>
<td>2 = moderate chance</td>
</tr>
<tr>
<td>As a passenger in a car for an hour without a break</td>
<td></td>
<td>3 = high chance</td>
</tr>
<tr>
<td>Lying down to rest in the afternoon when circumstances permit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sitting and talking to someone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sitting quietly after a lunch without alcohol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In a car, while stopped for a few minutes in traffic</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Scales Measuring Self-Reported Fatigue

- BIFS – Brain Injury Fatigue Scale (Quinn) Differentiates ‘normal’ and pathological fatigue
- BNI- Barrow Neurological Institute Fatigue Scale (Borgaro et al, 2004 & 2005) Used for acute TBI
- FIS – Fatigue Impact Scale (Fisk et al, 1994) Used for MS fatigue
- FSS – Fatigue Severity Scale (Krupp et al, 1989) The most commonly used scale
- FAS – Fatigue Assessment Scale (Mead et al, 2007) Commonly used in CA research
- Subscales of EBIQ (Bateman et al, 2009)
- Subscale of Profile of Mood States (McNair et al, 1992)
Fatigue Severity Scale (FSS)

The FSS contains nine statements that rate the severity of your fatigue symptoms. Please read each statement and circle a number from 1 to 7, based on how accurately it reflects your condition during the past week and the extent to which you agree or disagree that the statement applies to you. A low value (e.g. 1) indicates strong disagreement with the statement, whereas a high value (e.g. 7) indicates strong agreement. It is important that you circle a number (1 to 7) for every question. During the past week, I have found that:

1. My motivation is lower when I am fatigued
2. Exercise brings on my fatigue
3. I am easily fatigued
4. Fatigue interferes with my physical functioning
5. Fatigue causes frequent problems for me
6. My fatigue prevents sustained physical functioning
7. Fatigue interferes with carrying out certain duties and responsibilities
8. Fatigue is among my three most disabling symptoms
9. Fatigue interferes with my work, family, or social life
Fatigue Assessment Scale

The following ten statements refer to how you usually feel. Per statement you can choose one out of five answer categories, varying from Never to Always. Please circle the answer to each question that is applicable to you. Please give an answer to each question, even if you do not have any complaints at the moment.

1 = Never, 2 = Sometimes; 3 = Regularly; 4 = Often and 5 = Always.

1. I am bothered by fatigue     1       2       3       4       5
2. I get tired very quickly      1       2       3       4       5
3. I don’t do much during the day     1       2       3       4       5
4. I have enough energy for everyday life  1       2       3       4       5
5. Physically, I feel exhausted     1       2       3       4       5
6. I have problems to start things     1       2       3       4       5
7. I have problems to think clearly    1       2       3       4       5
8. I feel no desire to do anything     1       2       3       4       5
9. Mentally, I feel exhausted     1       2       3       4       5
10. When I am doing something,     1       2       3       4       5
    I can concentrate quite well
Fatigue Assessment Interview

- When did it start?
- How long has it lasted?
- Has it got worse over time?
- Does anything make it feel better or worse? For example, exercise, eating or pain.
- Does it affect your daily living activities such as washing, cooking or walking?
- Do you have any problems sleeping?
- Do you have any other major problems in your life such as relationship or financial problems or work worries?
- Do you have any other symptoms with your fatigue, such as feeling or being sick, breathlessness or pain?
- Do you have any other medical conditions?
- Did you feel fatigued before your stroke/neurological condition was diagnosed?
- How long since you have had your bowels open?
- Are you having any problems with passing urine?
- What medication, herbs, or recreational drugs do you use?
Factors Influencing Self-report

- Sleepiness
- General self-awareness
- Sleep-related alteration of self awareness
- Expectations (demand characteristics)
- Motives
- Reference point
- Denial
- Alexethymia
- Memory
Self-reported sleepiness can be unreliable

- Patient with manifest sleepiness
- When asked, sleepiness was denied
- ESS total score was 5
The Faces of Sleepiness

- Self-reported (introspective) Sleepiness
- Manifest Sleepiness
- Physiological Sleepiness
Physiological Sleepiness Regulation

**Hypothalamic Drives**
- Thirst
- Hunger
- Sleepiness
- Libido

**Regulating Processes**
- Homeostasis
- Circadian Rhythms

*Fig. 3. The hypothalamic region seen from the base of a human brain. Posteriorly (below) are the rounded eminences of the mammillary bodies. In the center the pituitary stalk springs from the tuber cinereum. Note the prominent long hypophyseal portal vessels running along the dorsal aspect of the stalk. Anteriorly (above) lies the optic chiasma.*
Medication, Drugs, & Substances

Fatigue is commonly associated with soporific substances or withdrawal from stimulants
# Sleep Promoting Substances

<table>
<thead>
<tr>
<th>Soporifics</th>
<th>Chronohypnotics</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>GABA&lt;sub&gt;A&lt;/sub&gt; &amp; BZD</td>
<td>Melatonin &amp; Cicadin</td>
<td>DA agonists for RLS</td>
</tr>
<tr>
<td>Receptor Agonists</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antihistamines</td>
<td>Ramelteon (MT agonist)</td>
<td>GHB (Xyrem)</td>
</tr>
<tr>
<td>Orexin Antagonists</td>
<td>Agomelatine</td>
<td>Traditional Neuroleptics</td>
</tr>
<tr>
<td>(Suvorexant)</td>
<td></td>
<td>(Dopamine Antagonists)</td>
</tr>
<tr>
<td>Adenosine Agonists</td>
<td>Low dose doxepin (Silenor)</td>
<td>5HT 2a Inverse Agonist</td>
</tr>
<tr>
<td>(in development)</td>
<td></td>
<td>(Eplivanserin not approved)</td>
</tr>
</tbody>
</table>
Rx with Antihistaminergic Properties Associated with Sleepiness and Fatigue

- Diphenhydramine (Benedryl)
- Desyrel (Trazodone)
- Mirtazapine (Remeron)
- Amitriptyline (Elevil)
- Doxepin (Adapin, Sinequan)
- Quetiapine (Seroquel)
- Gabapentine (Neurontin)
Autonomic Nervous System Modulates Sleepiness via Sympathetic Activation
## Wake-Promoting Agents Mechanisms

<table>
<thead>
<tr>
<th>Substance</th>
<th>Underlying Action</th>
<th>Sleep Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caffeine</td>
<td>Adenosine receptor antagonist</td>
<td>Homeostatic and ANS</td>
</tr>
<tr>
<td>Traditional psychostimulants</td>
<td>enhance neurotransmission of DA, NE, &amp; 5-HT</td>
<td>ANS</td>
</tr>
<tr>
<td>- amphetamine {1927}</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- methylphenidate {1959}</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Modafinil’s</td>
<td>mechanisms unclear; likely H1 agonist &amp; DA transport effect</td>
<td>ANS and possible circadian</td>
</tr>
</tbody>
</table>
Two Wakefulness Pathways

- Striatum (motor)
- Nucleus accumbens (Reward/abuse)
- Peripheral autonomic effects
  - increased heart rate
  - increased blood pressure

- Ventrolateral preoptic area
- Anterior hypothalamus
- Tuberomamillary nucleus (histamine)
- Ventral tegmental Area (dopamine)

Wakefulness:
- minimal motor
- minimal reward

“Normal Wakefulness”

“Stimulant-induced Wakefulness”
Two Nights of Sleep Loss

From: “Project Sleep”
Multiple Sleep Latency Test (MSLT)

- 4-6, 20-min nap opportunities at 2 hr intervals, beginning 2 hrs after arising
- Comfortable bed, dark & quiet room
- Concurrent PSG recording
- Instructed to not resist sleep
- Measure sleep latency & note soREMs
MSLT- AASM SPC Indications

• Indicated as part of evaluation of patients suspected of narcolepsy (2 or more SoREMPs has a 0.78 sensitivity and 0.93 specificity for diagnosing narcolepsy)
• May be indicated to differentiate idiopathic hypersomnia
• Not indicated for routine evaluation of sleep-related breathing disorders, insomnia, or circadian dysrhythmias
• Repeat MSLT may be indicated
  – (a) when study conditions were inappropriate during initial test
  – (b) when results are ambiguous
  – (c) when earlier MSLT did not confirm narcolepsy
Evaluating Sleepiness: MSLT Timing

No Smoking  No Vigorous Activity  Prepare for bed  Biocalibration

-30 m  -15 m  -10 m  -5 m  0

SSS  Assume comfortable position

"Please lie quietly, keep your eyes closed and try to fall asleep"

-45 s  -30 s  -5 s  0
Evaluating Sleepiness: MSLT Timing

Test Session Termination Rules:
Experimental protocol: End at $T_2$
Clinical protocol: End at $T_1 + 15\ m$
Either version, if no sleep occurs: $T_0 + 20\ m$
Cumulative Effects of Constant Modest Sleep Restriction in Young Adults

From: “Project Sleep”

Carskadon & Dement, 1981
Multiple Sleep Latency Test Profiles
in Various Groups in Basal Conditions

Average Latency (minutes)

Clock Time

From: “Project Sleep”
Quantitative EEG for Assessing Sleepiness

- Inter-Individual differences are large
- Analytical techniques vary widely
- Bandwidth power differs according to:
  a. Age
  b. Comorbidities
  c. Medications.

Pupillometry can be used to assess physiological sleepiness.

<table>
<thead>
<tr>
<th></th>
<th>Relaxed Waking</th>
<th>Nrem Sleep</th>
<th>Tonic REM</th>
<th>Phasic REM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sympathetic</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>Parasympathetic</td>
<td>P</td>
<td>P</td>
<td>P</td>
<td>P</td>
</tr>
<tr>
<td>Heart Rate</td>
<td>70+</td>
<td>65+</td>
<td>60+</td>
<td>80+</td>
</tr>
<tr>
<td>Pupil Diameter</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
The Faces of Sleepiness

- Self-reported (introspective) Sleepiness
- Manifest Sleepiness
- Physiological Sleepiness
Manifest Sleepiness

Photo By: W Eugene Smith, From Life Magazine
Table 7.1. Cognitive Disorganization Scale. (See text for explanation) (From Morris, Williams and Lubin, 1960.) (Copyright ©1960, American Medical Association. Reproduced by permission.)

<table>
<thead>
<tr>
<th></th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Slowing of mental processes, some difficulty thinking of words (no undue interference with normal communication).</td>
</tr>
<tr>
<td>2.</td>
<td>Occasional mistakes or failures in thinking and speech which can be corrected easily.</td>
</tr>
<tr>
<td>3.</td>
<td>Loses train of thought, forgetting what he was thinking or talking about, leaving statements incomplete, etc. Sudden unexplained shifts in trend of thought or speech: can correct with effort if challenged.</td>
</tr>
<tr>
<td>4.</td>
<td>Some thoughts or statements become completely incoherent. Clarification is not altogether possible. Some confusion of fantasies, dreams, or intrusive thoughts, with reality.</td>
</tr>
<tr>
<td>5.</td>
<td>Rambling incoherent speech for brief periods, with failure to recognize errors. Unable to straighten out jumble of incoherent thoughts when challenged.</td>
</tr>
</tbody>
</table>
MWT AASM SPC Indications

- MWT 40 minute protocol may be used to assess an individual’s ability to remain awake when it constitutes a public or personal safety issue.
- 59% of normals remain awake entire 40 minutes across all 4 trials (using unequivocal sleep criteria).
- Latency <8 minutes is abnormal.
- Latency 8-40 is of unknown significance.
- Mean sleep latency (1st sleep epoch) is $30.4 \pm 11.2$ m
- Upper 95% confidence interval is 40 min
- Indicated for assessing response to treatment
Measuring Manifest Sleepiness with the Maintenance of Wakefulness Test (MWT)

- Clinical standard is now 4, 40-minute test sessions at 2 hour intervals
- 1st test session begins 2 hours after arising
- Street clothing
- Sit on bed with bolster pillow
- Darkened but not pitch black room
- Concurrent PSG recording
- Instruction “Resist falling asleep”
- Measure sleep latency & note microsleeps
MWT TEST SESSION TERMINATION

**Lights-out**

**Sleep-Onset**

**End**

Terminate test at:
1\(^{st}\) unequivocal sleep -or- \(T_0 + 40\) m if no sleep

Sleep-onset is:
Any epoch of sleep

Unequivocal sleep is:
1 epoch of stage 2,3,4 or REM -or-
3 consecutive epochs of stage 1 -or-
an epoch of stage 1 followed by an epoch of 2,3,4 or REM
NARCOLEPSY vs. NORMAL

MWT sleep latencies for the 530 patients along with those for the 64 normal subjects evaluated by Doghramji et al.
Robert (Bob) Wilkinson

Vigilance Testing

- Conducted pioneering work on the psychophysiology of performance
- Developed what became the standard auditory vigilance test
Vigilance & Performance Tests

- When workload is high, this is a performance task.
- When workload is low, this becomes a vigilance task.
- Vigilance tasks differ from performance tasks with respect to:
  1. little need for practice
  2. little need for ability
  3. little intrinsic stimulation
Fig. 1. A—Subject falling asleep. Upper line, vertex to ear; lower line, occiput to ear. B—A brief "'float,'" signalled at arrow.
Evaluating Sleepiness (From: Dawson & Reid, 1997)

Mean Relative Performance

Blood EtOH Equivalent (%)

Hours of Wakefulness
## Critical Evaluation Issues

<table>
<thead>
<tr>
<th>Possible Confounding Variables</th>
<th>Possible Intervening Variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Time on Task</td>
<td>1. Effort (Motivation)</td>
</tr>
<tr>
<td>2. Test Sensitivity</td>
<td>2. Sleepiness</td>
</tr>
<tr>
<td>3. Learning/Practice</td>
<td>3. Coping (Patience)</td>
</tr>
<tr>
<td>4. Loss of Novelty</td>
<td>4. Perseveration</td>
</tr>
<tr>
<td>5. Treatment Duration</td>
<td></td>
</tr>
<tr>
<td>6. Treatment Efficacy</td>
<td></td>
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</tbody>
</table>
Threshold Model:
Is it a test sensitivity effect
-or-
The phenomena being studied?

Sleepiness

Hours of Wakefulness

0 3 6 9 12 15 18 21 24 27 30 33 36 39 42 45
Test Limit Model

Is it a Ceiling Effect
-or-
The phenomena being studied?

Hours of Wakefulness
0 3 6 9 12 15 18 21 24 27 30 33 36 39 42 45

Sleepiness
Self-reported sleepiness generally follows the Adaptation Model.
MSLT results generally follow the Test Limit Model
Performance test results follow a combination of the Accumulation and the Threshold models.
Fig. 6.1 Core and optional sleep in mammals—general trends over the daily sleep period, and factors influencing them. See text for details.

From: Horne J: Why We Sleep; 1988
What do the following sleepiness countermeasures have in common?

- Drinking coffee
- Standing
- Pacing
- Chewing gum
- Loud music
- Exercising
- Cold water on face
- Engaging in conversation
- Thinking about sex
- Standing on one foot
Heroic Effort
Major Accidents Involving Sleepiness

- Exxon Valdez
- Space Shuttle Challenger
- Bhopal
- Three Mile Island
### Our Current Paradigm

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
<th>Label</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Inability to remain awake</td>
<td>Overwhelmingly Sleepy</td>
</tr>
<tr>
<td>II</td>
<td>Having difficulty remaining awake</td>
<td>Drowsy</td>
</tr>
<tr>
<td>III</td>
<td>Feels a desired to sleep</td>
<td>Tired (in the sleepy sense)</td>
</tr>
</tbody>
</table>

- How conscious are we of these ongoing processes?
- What are associated processes that correlate, influence, and/or masquerade? For example: denial, lack of awareness, depression, anxiety, physical fatigue, mental fatigue {from emotional stressors}, boredom, pain, 1’ or 2’ gain
Making Sense out of the Disconnects Between the Faces of Sleepiness

**Subjective (Self Report)**
- Bored? Depression? Malingering? Sleep Momentum?

**Manifest (Performance)**
- Motivation or Attention Problem? Insomnia?
- Attention or Motivation Problem?

**Physiological (Sleep Testing)**
- Unaware? Denial?
- High Attention? Good Strategies? Tolerant to Sleep Loss?
- High Motivation? Tolerant to Sleepiness? Unaware?
Learning Objectives
The attendee should now …

• Be familiar with the conceptual models of sleepiness (hypersomnolence) & fatigue
• Have improved understanding of neurobiology of underlying sleepiness & fatigue
• Be more aware of what we measure with tools designed to index sleepiness and/or fatigue
References:


4. Assessment of Fatigue- BMJ Best Practice updated 10/19/15 (Available Online)
Manifest sleepiness can be measured with ...

A. Pupillometry
B. Stanford Sleepiness Scale
C. Maintenance of Wakefulness Test
D. Quantitative EEG Analysis
A research MSLT is terminated ...

A. 15 minutes after sleep onset
B. When unequivocal sleep onset occurs
C. At sleep onset
D. 20 minutes from lights-out
The longest possible duration for a properly conducted MSLT is ...

A. 23 $\frac{1}{2}$ minutes
B. 30 minutes
C. 34 $\frac{1}{2}$ minutes
D. None of the above
Self-reported sleepiness can be assessed using ...

A. Visual analog scales
B. Side effect checklists
C. Profile of Mood States
D. All of the above
Self-reported sleepiness generally follows ...

A. An adaptation model
B. An accumulation model
C. A Threshold model
D. None of the above