Hypersomnolence in Psychiatric Disorders

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Learning Objectives

1) Definitions of hypersomnolence
2) Why do we care about hypersomnolence in psychiatric disorders
3) Differential diagnosis
4) Biological correlates of hypersomnolence in depression
5) Diagnostic challenges and related opportunities
Depression is Heterogeneous

Depressed mood or Anhedonia plus Additional Symptoms

S - leep
I - nterest
G - uilt
E - nergy
C - oncentration
A - ppetite
P - sychomotor
S - uidicality

Many Different Combinations of Symptoms Can and Do Occur
Sleep disturbance is the rule during a Major Depressive Episode

- Majority of patients will have a sleep complaint as part of MDE
- ≥80% of patients report insomnia\textsuperscript{1,2}
- ~20-30% report hypersomnolence\textsuperscript{3}
- Majority of research has been on insomnia in MDD, with little attention to hypersomnolence

\textsuperscript{1} Ohayon, Can J Psychiatry 2000; \textsuperscript{2} Weissman JAMA 1996; \textsuperscript{3} Kaplan and Harvey Sleep Med Rev 2009
Important Vocabulary

• Hypersomnolence
  – Excessive daytime sleepiness, often with excessive total sleep duration

• Hypersomnia
  – Excessive total sleep duration
  – [hyper- too much + L. somnus, sleep]

• Unfortunately, these terms are often used interchangeably
Hypersomnolence is important in Depression

• Significant cause of impairment
• Increases the risk of incident depression\textsuperscript{1,2}
• Treatment-resistant symptom\textsuperscript{3,4}
• Predicts risk of depressive relapse\textsuperscript{5,6}
• Associated with suicide attempts\textsuperscript{7,8}

\textsuperscript{1}Breslau Biol Psychiatry 1996; \textsuperscript{2}Roberts Am J Psychiatry; \textsuperscript{3}Worthington 1995; \textsuperscript{4}Zimmerman J Clin Psychiatry 2005; \textsuperscript{5}Kaplan Sleep Med Rev 2009; \textsuperscript{6}Kaplan J Affect Disord 2011; \textsuperscript{7}Goldstein J Consult Clin Psychol 2008; \textsuperscript{8}Fitzgerald JCSM 2011
Differential Diagnosis

• Sleep deprivation/restriction
• Primary Sleep Disorders
  – Obstructive Sleep Apnea
  – Restless Legs Syndrome
  – Circadian Rhythm Disorders
  – Narcolepsy
• Medical Disorders
• Medications
Evaluation: High Yield Areas

• 24-hour sleep/wake patterns
  – Sleep deprivation/restriction
  – Circadian rhythm abnormalities

• OSA/RLS Screening tools

• Narcolepsy
  – Cataplexy*
  – Sleep paralysis
  – Hypnagogic/hypnopompic imagery
Excessive Daytime Sleepiness

• Universal experience
• Can be described in different ways
  – Difficulty staying awake
  – Falling asleep easily
  – Feeling drowsy
  – Eyes burning or feeling heavy
  – Etc.
Measuring Excessive Sleepiness

• Can be measured subjectively or objectively

• Most commonly used subjective scale is the Epworth Sleepiness Scale (ESS)

• Most commonly used objective measurement is the Multiple Sleep Latency Test (MSLT)
Epworth Sleepiness Scale

- Individual rates (0-3) how likely they are to doze off in 8 situations
- Score $\geq 11$ suggests significant EDS

Johns 1991
Multiple Sleep Latency Test

- 4-5 nap opportunities ~2 hours apart
- Occurs after night of adequate sleep
- Sleep Onset Latency (SOL)
  - time from lights off to first to first epoch of sleep
- REM latency
  - time from sleep onset to first epoch of REM sleep If no sleep after 20 minutes, nap opportunity ends
- Pathological cut-points can vary
  - SOL: \(<8 \text{ min}\) (current); \(<5 \text{ min}\) or \(<10 \text{ min}\)
  - Sleep onset REM periods (SOREM): \(\geq 2\)
Normative MSLT Findings

5 Nap Protocol
- SOL 11.6±5.2 min
- 95% of values 1.2-20 min
- ~24% have MSL<8 min
- ~10% have MSL<5 min

4 Nap Protocol
- SOL 10.4±4.3 minutes
- 95% of values 1.8-19 min
- ~28% have MSL<8 min
- ~10% have MSL<5 min

A sizeable proportion of the population will be defined as pathologically sleepy depending on cutoffs used

Arand et al., SLEEP 2005
MSLT in Psychiatric Disorders

• MSLT is often used in Sleep Medicine to segregate Hypersomnolence in psychiatric disorders from other CNS disorders
  – Narcolepsy
  – Idiopathic Hypersomnia

• Significant problems with this strategy:
  – Limitations of normative values for MSLT
  – A sizeable number of patients will have excessive sleep propensity on MSLT using current thresholds
# MSLT in Psychiatric Disorders

<table>
<thead>
<tr>
<th>Studies</th>
<th>Estimate (95% C.I.)</th>
</tr>
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<tbody>
<tr>
<td>van den Hoed et al. 1981</td>
<td>10.60 (8.20, 13.00)</td>
</tr>
<tr>
<td>Reynolds et al. 1982</td>
<td>9.97 (5.75, 14.20)</td>
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<tr>
<td>Zorick et al. 1982</td>
<td>9.97 (5.26, 14.68)</td>
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<tr>
<td>Nofzinger et al. 1991</td>
<td>13.70 (12.20, 15.20)</td>
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<tr>
<td>Billiard et al. 1994</td>
<td>12.40 (10.60, 14.20)</td>
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<tr>
<td>Bassetti et al. 2003</td>
<td>7.83 (4.66, 11.01)</td>
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<tr>
<td>Shen et al. 2011</td>
<td>7.80 (5.35, 10.25)</td>
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<tr>
<td>Mariman et al. 2013</td>
<td>14.18 (11.68, 16.67)</td>
</tr>
<tr>
<td>Peter-Derex et al. 2013</td>
<td>13.20 (12.01, 14.39)</td>
</tr>
<tr>
<td>Kofmel et al. 2014</td>
<td>8.10 (6.30, 9.90)</td>
</tr>
<tr>
<td>Sobanski et al. 2014</td>
<td>10.27 (6.81, 13.73)</td>
</tr>
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**Overall (I^2=80%, P<0.01)** 10.92 (9.39, 12.45)

Plante DT, *Sleep Med Rev* 2017
~25% of Persons with psychiatric hypersomnolence will have pathologic sleep propensity using current cutoffs on MSLT
Few persons with psychiatric hypersomnolence have mean sleep latency below 5 minutes on MSLT
Cross-Sectional Associations Between Depression and Hypersomnolence

**SUBJECTIVE**

<table>
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<td>Epworth Score ≥ 11</td>
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<tr>
<td>Excessive Sleepiness &gt;50% of days</td>
<td>3.0</td>
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<td>4.0</td>
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<td>MSLT Mean SOL &lt; 8 minutes</td>
<td>Supported by &amp; others</td>
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Longitudinal Associations Between Depression and Hypersomnolence

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Supported by & others

Plante DT, et al. J Affect Disord 2017
Summary MSLT in Depression

• A mean sleep latency in the current pathologic range does not exclude hypersomnia related to a psychiatric condition.

• Paradoxical relationship between subjective and MSLT measures of sleepiness in course of depression:
  – Patients with psychiatric hypersomnia misperceive their sleepiness?
  – MSLT misses an important facet of sleepiness not quantified by MSLT?
  – MSLT simply inadequate to quantify hypersomnia in mood disorders?
Hypersomnolence is Multifaceted

• Other aspects besides MSLT sleep propensity
  – Excessive Sleep Duration
  – Psychomotor Vigilance
  – Drowsiness
  – Ability to Stay Awake

• Associated with subjective complaints of hypersomnolence

• Poorly or do not correlate with each other
Differences in Nosology

**DSM-5**
- Normal to increased sleep continuity
- Normal to prolonged sleep duration
- Short sleep latency

**ICSD-3**
- Low sleep efficiency
- Increased time in bed (with presumed low to normal sleep time)
- Prolonged sleep latency
- Increased wake after sleep onset
Inclusion/Exclusion Criteria

• Unipolar, unmedicated major depressive disorder
  – Hypersomnolence based on operationalized criteria used in DSM-5
  – No comorbid sleep disorders
  – No active drug use
  – Limited caffeine and nicotine use

• Healthy Controls
  – Age- and sex-matched to MDD
  – No sleep complaints and usual sleep duration 7-9 hours
### Sample Characteristics

<table>
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<tr>
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<th>MDD-HYP (N=22)</th>
<th>HC (N=22)</th>
<th>p*</th>
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<tbody>
<tr>
<td>Age</td>
<td>28.1 (5.8)</td>
<td>28.4 (5.6)</td>
<td>0.88</td>
</tr>
<tr>
<td>Sex (F/M)</td>
<td>18/4</td>
<td>18/4</td>
<td>-</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.5 (4.9)</td>
<td>25.2 (3.9)</td>
<td>0.65</td>
</tr>
<tr>
<td>BDI</td>
<td>22.3 (7.4)</td>
<td>1.1 (1.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ESS</td>
<td>12.4 (2.6)</td>
<td>4.6 (2.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HSI</td>
<td>21.0 (4.2)</td>
<td>3.4 (2.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PSQI</td>
<td>5.7 (2.0)</td>
<td>1.8 (1.4)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

MDD-HYP, major depressive disorder with comorbid hypersomnia; HC, healthy control; BDI, Beck Depression Inventory; ESS, Epworth Sleepiness Scale; HSI, Hypersomnia Severity Index; PSQI, Pittsburgh Sleep Quality Index.

Depression with hypersomnolence slept ~1.4 hours longer than matched healthy sleepers with otherwise similar sleep continuity and staging.

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<th>HC</th>
<th>p*</th>
</tr>
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<tbody>
<tr>
<td>TST (min)</td>
<td>526.9 (98.4)</td>
<td>447.6 (63.0)</td>
<td>0.003</td>
</tr>
<tr>
<td>TIB (min)</td>
<td>602.7 (100.2)</td>
<td>511.9 (62.6)</td>
<td>0.001</td>
</tr>
<tr>
<td>WASO (min)</td>
<td>61.6 (36.1)</td>
<td>51.8 (29.8)</td>
<td>0.33</td>
</tr>
<tr>
<td>SE (%)</td>
<td>87.3 (6.5)</td>
<td>87.3 (7.0)</td>
<td>0.99</td>
</tr>
<tr>
<td>SOL (min)</td>
<td>14.8 (13.3)</td>
<td>13.8 (9.6)</td>
<td>0.77</td>
</tr>
<tr>
<td>N1 (min)</td>
<td>36.9 (19.6)</td>
<td>24.1 (12.3)</td>
<td>0.01</td>
</tr>
<tr>
<td>N2 (min)</td>
<td>308.4 (65.4)</td>
<td>260.1 (56.9)</td>
<td>0.01</td>
</tr>
<tr>
<td>N3 (min)</td>
<td>78.5 (31.9)</td>
<td>71.1 (31.5)</td>
<td>0.45</td>
</tr>
<tr>
<td>N1 (%)</td>
<td>7.0 (3.5)</td>
<td>5.3 (2.5)</td>
<td>0.08</td>
</tr>
<tr>
<td>N2 (%)</td>
<td>58.6 (6.9)</td>
<td>57.4 (8.5)</td>
<td>0.62</td>
</tr>
<tr>
<td>N3 (%)</td>
<td>15.2 (6.4)</td>
<td>16.3 (7.7)</td>
<td>0.61</td>
</tr>
<tr>
<td>REM (min)</td>
<td>104.6 (41.3)</td>
<td>95.1 (33.5)</td>
<td>0.41</td>
</tr>
<tr>
<td>REM (%)</td>
<td>19.2 (5.8)</td>
<td>21.0 (5.9)</td>
<td>0.32</td>
</tr>
<tr>
<td>REML (min)</td>
<td>125.5 (79.1)</td>
<td>125.0 (49.6)</td>
<td>0.98</td>
</tr>
</tbody>
</table>
What about their sleep outside of the lab?

Were they just sleep deprived?
Hypersomnolent Depressed Participants had greater self-reported TST and TIB with lower self-reported sleep efficiency

*p < .05  **p < .01  ***p < .001
Hypersomnolent Depressed Participants had greater actigraphic TST and TIB with **similar** sleep efficiency.

*p<.05     **p<.01
Estimated vs. Actigraphic Sleep

Both groups similarly overestimated subjective sleep time and sleep efficiency relative to actigraphy.
How do these results compare to other studies?
Ad Libitum Total Sleep Time Compared to Controls

Patients with hypersomnia associated with mood disorders sleep ~50 minutes more than healthy controls

No significant differences in sleep continuity between patients with depression and comorbid hypersomnolence compared to controls.
Summary of Findings

• Depressed persons with hypersomnolence demonstrated increased sleep duration with normal sleep continuity compared to healthy persons

• These results are congruent with the prior literature

• Raise questions about ICSD-3 nosology

Conceptual Framework

EDS

Increased sleep duration with EDS

Insomnia with EDS as daytime consequence

Sleep Time

Quantifiable with EEG-based measurement of sleep

Clinophilia

??How to objectively measure

Candidate Measures of EDS

• Psychomotor Vigilance Task
  – Lapses and reaction time correlate with EDS\textsuperscript{1}
  – Depressive symptoms correlate with increased lapses and reduced reaction time\textsuperscript{2}

• Infrared Pupillometry
  – Pupillary Unrest Index (PUI) correlated with subjective EDS\textsuperscript{3,4}
  – PUI elevated in substantial proportion of persons with depression and EDS\textsuperscript{5}

\textsuperscript{1}Kim et al Sleep 2007; \textsuperscript{2}Yun et al Sleep Med 2015; \textsuperscript{3}Wilhelm et al Sleep 1998; \textsuperscript{4}Prasad et al Front Psychiatry 2011; \textsuperscript{5}Kofmel et al Neuropsychobiol 2014
PVT and PUI as candidate measures of sleepiness in depression

Patients with IDS-SR $\geq$ 26

- PUI $> 9.8$: 25.6%
- PVT Lapses $> 4.8$: 39.5%
- PUI or Lapses: 48.9%

N=43 (enrollment ongoing)

*Expected Proportion in Healthy Population
What about neurobiological correlates of sleepiness in depression?

Are there structures/circuits associated with clinical symptoms?
hdEEG Sleep Data: A transdiagnostic approach

Screening Visit 1
Sleep Diaries & Actigraphy

PSG Visit 2
Ad Libitum Sleep hdEEG

Waking EEG PM
Waking EEG AM T0
Waking EEG T1
Waking EEG T2
Waking EEG T3

Venn diagram showing:
- HYP+/MDD+
- HYP+MDD-
- HYP-/MDD+

vs. Healthy Controls
Similar topographic reductions of slow wave activity in hypersomnolence

Both hypersomnolent groups have very similar polysomnographic findings

Plante DT, et al. *In Preparation*
Reduced local slow wave activity correlates with daytime sleepiness

Plante DT, et al. *In Preparation*

$r = -0.41$
$p < 0.001$
Reductions in slow wave activity in persons with hypersomnolence occur predominantly in somatosensory cortex and suparmarginal gyrus.

Plante DT, et al. *In Preparation*
Reduced thalamocortical connectivity associated with EDS in similar regions

Is there a connection?

Adapted from Kilgore et al, Neuroreport 2015
ESS negatively correlates with rs-fc thalamostriatal connectivity

**DASH Dataset**
- N=67 (all female)
- Associations corrected for:
  - habitual sleep duration
  - depression severity
  - multiple comparisons

Plante DT, et al. *J Affective Disord* 2018
Striatum and Daytime Sleepiness

- Relationship between activity in caudate/putamen and reaction time on PVT\(^1\)
- Sleepiness in short sleepers associated with decreased sensory/motor connectivity to caudate/putamen\(^2\)
- Reduced D2/D3 receptor occupancy in the caudate/putamen and thalamus correlates with sleepiness after sleep deprivation\(^3\)
- Reduced dopamine transporter binding in caudate/putamen associated with EDS in Parkinson’s disease\(^4\)

\(^1\)Drummond et al Sleep 2005; \(^2\)Curtis et al Brain Behav 2016; \(^3\)Volkow et al J Neurosci 2008; \(^4\)Happe et al J Neurol 2007
Cortico-striatal-thalamic loops
Future Directions

• Other changes related to regional reductions in slow wave activity in persons with hypersomnia?
• Probe possible cortico-striatal-thalamic “sleepiness circuit”
• Using novel methods to quantify daytime sleepiness in depression
• Develop targeted, evidenced based strategies for treatment
Take Home Points

• Hypersomnolence is an important factor in psychiatric disorders
• Quantifying hypersomnolence in psychiatric disorders can be challenging
• Important to consider all relevant literature to minimize bias in nosological debates
• Area of unmet need in research at sleep-psychiatry interface
Acknowledgements

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Paul Peppard, PhD
Erika Hagen, PhD
Emmanuel Mignot, MD, PhD

PLANTELAB
Questions?