DREAMING AN EPIPHENOMENA OF NARCOLEPSY
Lawrence Scrima, PhD, D,ABSM, FAASM

OBJECTIVES

Dreaming as Indicator of REM Sleep
Narcolepsy Symptoms, Etiological Considerations
Information Processing  Problem Solving

TREATMENTS FOR NARCOLEPSY

Dreaming - R Sleep As Diagnostic & Tx Efficacy Indicator

REM BEHAVIOR DISORDER

DREAMING: Indicator Integrator Solution Seeker
Terms

Dreaming: Emotional, Pleasant - Intense, Bizarre, Story-Like Mental Theater Typical of REM Sleep: REMentation: Fragmented, Logical Thoughts, Not Story-Like, Simple, Fleeting During Non-REM Sleep: Light Sleep: N1, N2 or Deep, Slow Wave Sleep: SWS: N3

Night Terrors: Typically Starting in N3: Single Terrifying Image

Hynagogic Hallucinations: Fleeting Perceptions or Hallucinations at Sleep Onset

REM Behavior Disorder: Loss of Atonia During REM Sleep, Enabling Movement & Ability to Act Out Dreams
Dreaming: Epiphenomena of REM Sleep – R or Paradoxical Sleep -PS

Sleep Research Helped Define Consciousness:
  Wake, Sleep, Slow Wave -NREM & Fast Wave - REM Sleep

Using Neural Trans-Section, Stimulation, Ablation, Polysomnographic Techniques & Behavioral Assessments

Normal % R: Infants 50% & Adults 20% of Total Sleep Time

Abnormal Dreaming-R: Absent, Decreased Increased, Early, Late, Fragmented, Intense
Narcolepsy

- Involuntary Excessive Daytime Sleepiness

  may include:

  - Cataplexy: Sudden loss of muscle tone in response to strong emotion
  - Hallucinations
  - Sleep Paralysis

- Affecting 125-200,000 or 1/2000 persons often emerges in teen’s and 20’s

- Chronic neurological & potentially disabling disorder. Impairs ability to engage in daily activities & can lead to injuries if not treated

- Effective treatment is now available
Narcolepsy: Neurological Condition

Presents With One or More of Following:

• Excessive Daytime Sleepiness & Sleep Attacks

• Abnormal REM Sleep Related Phenomena
  REMOS: REM Sleep Onset
  Cataplexy: REM Sleep Atonia while Awake

Sleep Paralysis, Hypnagogic Hallucinations

• Also: Fragmented Sleep, Automatic Behavior
  Periodic Limb Movements & REM Behavior Disorder

Amer Acad Sleep Med (2005), Intern Classif. Sleep Disorders, 2nd ed.
Narcolepsy: Importance of Dreaming - REM Sleep

Dreams Often Reported Transitioning to Sleep at Bedtime & Daytime Short Naps

In MSLT: REM in 2 of 4 to 5 Naps Dx Narcolepsy + Sleep Onset Mean ≤ 8'

Cataplexy is REM Atonia Breaking Into Wake State
Can be Accompanied by Hallucinations

Tx Suppress REM sleep: Amphetamine & Anti-Depressants
Stops Cataplexy Temporarily – Habituation - Side Effects

Withdrawal Results in Increased: Cataplexy & REM Sleep

Prolonged Use of REM Suppressing Medications:
  • Increase Risk for REM Behavior Disorder (BD)
  • Return of Cataplexy REM Sleep & Intense Dreams

Thorpy MJ et al 1990 Handbook of Sleep Disorders. Informa Health Care; 235–58
Thorpy M 2007, Sleep Medicine 8(4):427-440
PSG Results in Normal vs Untreated Narcoleptic Patient

Adapted from Rogers et al. Sleep. 1994;17:590.
Opposing Dreaming Theories

Meaningless: Characterization as Visual Hallucinations Propagated by Ponto-Geniculate-Occipital- PGO Waves Promoting Random Meaningless Hallucinations
Hobson JA  Consciousness 1999; 67: 188-215

Meaningful: Early Dreams: Recent Experiences Concerns Later Dreams: Older Experiences Concerns Last Dreams: Recent Experiences Concerns
Verdone P  Perceptual motor Skills 1965; 20: 1253-68
Meaningless Theory Weakness

Meaningless Dreams Prompted by PGO Waves
Does Not Adequately Address Story-Like Dreams
Pattern Characteristic of Recent then Remote
Then Recent Experiences & Concerns Content

PGO Waves Should Cause Random Stimulation
& No Pattern of Recent & Older Experiences
and Concerns
Purported Functions of Dreaming: REM Sleep

Promotes Emotional Stability:

Express Repressed, Unconscious Wishes: *Freud*

Express Suppressed Feeling Not Confronted: *Ferenczi*

Deprivation REM Sleep Causes:

- Anxiety, Irritability, Concentration Problems

  *Dement W 1960 Effects of Dream Deprivation Science 131;1705-7*

- Confusion, Paranoia, Irritability & Withdrawal

  *Agnew et al 1967; Perceptual Motor Skills 24; 851-8*
Dreaming for Information Processing:

Consolidation & Integration
Pearlman & Greenberg, *Perspectives Biology & Medicine* 1974, 513-21

Creativity & Divergent Thinking

Memory of Complex Associative Information
1984, *Integrative Psychiatry* 2: 201-40
Purported Physiological – Survival Functions of Dreaming or R Sleep

Endogenous Stimulation for Neural Structural Growth
Roffwarg et al Science 1966; 152: 604-619

Decrease GABA: Frontal Cortex, Thalamus & RAS
Increase Acetylcholine in Cortex

Survival: Periodic Surveillance of Environment

Fastest Arousal & Response from Sleep to Significant or Critical Signal
Williams et al 1966 Psychophysiology 2: 208-216
Information Processing & Memory Theories:

**Erase Memories**

Crick F, Mitchenson G. Nature 1983; 304: 111-4

**But - Neural stimulation Locating Seizure Foci**

Prompts Detailed Verified & Reproducible Mundane Vivid Memories


**Integrate Consolidate Refresh Experiences & Concerns**

Pearlman et al. 1974; Lewin et al 1975
Scrima L. Psychophysiology 1982; 19: 252-9
Integrative Psychiat 1984; 2: 201-40

**Prioritize Free Association & Solution Seeking**

Hartmann E. 1973; *Functions of Sleep*. Yale U. Press
Purported Functions of Dreaming

Endogenous Neural Stimulation:
Infants R Sleep: 50% TST To Expand Neural Networks

*Roffwarg et al. Science 1966; 152: 604-619*

Integrate Experiences, Optimize Adaptive Behavior, Survival

*Scrima L. Psychophysiology 1982; 19: 252-9; Integrative Psychiat 1984; 2: 201-40*

Dreaming Epiphenomena of Narcolepsy.
in Sleep Medicine Clinics 2010; 261-75
Dreaming: A Creative Problem Solving Process

Neils Bohr: Whirling Solar System - Solved Structure of Atom

August Kekule: Snake Eating its Tail - Solved Shape of Benzene Ring

Elias Howe: Cannibals Chasing with Spears With Holes in Tip - Solved - Sowing Machine

Writers & Artists Attest To: Obtaining Inspirations From Their Dreams
Sleep Improves Memory - Where's The Proof?

Early 1900's - Sleep Repeatedly Shown To Improve Memory

Sleep Passively or Actively Improves Memory?

Passive Theory: Sleep Prevents Retroactive Interference of Recent Experience

Active Theory: Dreaming Might Be Actively Involved in Enhancing Memory
Neuronal Activation Correlates - NAC Theory & Hypotheses:

Desynchronous EEG Occurs During Wakefulness When Learning & Initial Information Processing Takes Place & Also Occurs During R sleep

High Voltage, Slow Wave EEG Does not Occur During Learning, but May Prevent Retroactive Interference: RI

Since REM Sleep Normally Occurs 90’ After Sleep Onset, It is Difficult to Directly Study Effects of REM Sleep & Dreaming Without Including a Prior NREM Sleep
Narcolepsy Approach Paradigm - NAP
Enable Direct Study of REM Sleep Effect
Recall of Complex Associative Information & Rote Memory Tasks

NAC Theory Predicts:
That Memory of Complex Associative Information:
• Best After REM Sleep Naps – If Active Information Processing is Occurring
• Second Best After NREM sleep Naps – If Prevents Retroactive Interference (RI)
• Least After Awake - If RI Occurs & Rehearsal Is Prevented

Scrima L 1982 Psychophysiology 19:252-9
Narcolepsy Subjects Off all CNS Medications
To Directly Study REM vs NREM vs Awake Effects on Memory

3 Sessions: NREM Nap 20 Min VS REM Nap 20 Min -or Both VS Awake 20 Min

10 Ss Did 8 Lists Complex Associative Memory Task - 1 List / Day
10 Anagrams / List: 5 Letters Each w/ 2 Common Word Solutions
Anagram: torhn 2 Solutions: thorn north

Instruction: 1 Min / Anagram, Say the Solution Word, Spell It, Picture What it Represents & Make Some Association

Same Ss Did to 8 Lists of Rote Memory Trigram Task - 1 List / Day
8 Consonant Trigrams / List: 3 Capital Letters
Trigram: ZNH

Repeated Until Memorized In Order – Make No Associations

Scrima L 1982 Psychophysiology 19:252-9; 1984 Integrative Psychiatry 2:201-40
After Memory Task: 20 Min PSG Nap Or Awake 20 Min Card Game War
All Memory Tasks & Naps in Early PM or Early Evening

Post 20' Nap 3' Delay Get Up Sit in Chair
Then Told To Recite What They Remembered
Free Recall of Anagram Solutions or Trigrams 6'

Sometimes Ss would Recall a Dream involving Anagram Words & a few Solved a Word missed before the nap

Re-Solving Trial: Same as PreNap Acquisition

Awake Condition: Card Game “War” 20' w/ Experimenter

Free Recall Test, Then Re-Solving Trial

Scrima L 1982 Psychophysiology 19:252-9
Results: Complex Associative Free Recall Test

Overall Significant Results Repeated Measures ANOVA: $p < 0.05^*$
W/ Fixed Inter Sleep Interval: $p < 0.01^*$

*Geiser-Greenhouse Conservative F Test

Mean % Free Recalled Solutions After:

Awake: 26%  NREM: 46%  REM: 69%

Linear $p < .05$

Scrima L 1982 Psychophysiology 19:252-9
Planned Comparisons: Inter Sleep Interval Controlled Data:

- REM vs NREM  \( p < .05 \)
- REM vs Awake  \( p < .01 \)
- NREM vs Awake  \( p < .05 \)
- REM+ NREM vs Awake  \( p < .01 \)

First Direct Test & Proof: Effect of R Sleep - Perhaps Dreaming - On Memory of Complex Associative Information in Humans

Scrima L Psychophysiology 1982; 19: 252-9
2 Recent Studies

Using a Nap Method In Normal Subjects Reported:

• *REM Sleep Improves Creativity: Priming Associative Networks &

• ^Consolidating Emotional Human Memories

Growing support for NAC, Integrative & Creative Information Processing Theories, as Applied to:

Associative Information & Adaptive Behavior

Narcolepsy Epidemiology

Narcolepsy - Cataplexy: 0.02% of the U.S.

Europe, less in Israel, higher in Japan

About Equal Among Men & Women

Narcolepsy - Cataplexy at All Ages, but
Typically begins between Ages: 15 – 25

Cataplexy Typically Begins 1 or 5-10* yrs after EDS

Sleepiness: Clinical Presentation

- Pervasive drowsiness
- Sleep attacks
- Fatigue
- Microsleep episodes
- Visual disturbances
- Apathy
- Mood changes
- Automatic activity
- Impaired alertness
- Lethargy
- Impaired memory and concentration
- Poor performance in work/school
- Accident prone

Cataplexy: Clinical Presentations

- Ptosis – drooping eye lids
- Sagging jaw
- Hypophonic/slurred speech
- Nodding head
- Arm or leg weakness (knee buckling)
- Generalized weakness/paralysis
  - Ventilatory muscles spared
- Muscle twitching

Cataplexy: Emotional Triggers

- Laughter: 87%
- Joking: 73%
- Anger: 68%
- Excitation: 65.6%
- Surprise: 58.1%
- Stress: 54%
- Startlement: 50%
- Sex: 22%

Narcolepsy: *Etiology and Pathophysiology

- Genetic predisposition
- Hypocretin/orexin deficiency
- Autoimmune mediated (?)
- Neurochemical abnormalities
- Environmental triggers
Hypocretin

- Hypothalamic peptides
  - Localized in the dorsolateral hypothalamus
  - Wide projections throughout the brain
  - Projections found in the spinal column

- Peptide neurotransmitters
  - Arousal
  - Locomotion
  - Metabolism
  - Increase blood pressure/heart rate

Narcolepsy: Hypocretin Findings

- Decreased or absent levels of hypocretin in CSF
- Marked reduction in or absence of hypocretin-containing neurons
- CSF levels may have diagnostic role in future

CSF = cerebrospinal fluid.

Hypocretin Deficiency
in Human Narcolepsy

Cerebrospinal fluid

Lateral hypothalamic brain tissue

ICSD Dx Criteria:  I. Narcolepsy w Cataplexy

A. Complaint of EDS almost daily for ≥ 3 months
B. Cataplexy sudden muscle weakness triggered by emotions
C. Confirmed by Polysomnographic findings ≥ 6 hrs: sleep onset latency <8 min & REM Latency ≤15 min & MSLT findings: mean sleep latency <8 min, ≥2 SOREMPs or: from the previous night PSG: a REM sleep latency of < 15 min + 1 REM Nap on MSLT

Or: Hypocretin-1 levels, < 110 pg/mL a third of normal 90% CI

D. Not due to other sleep, medical, neurological or mental disorders, and not due to medications, or substance use disorder.

• II. W/out Cataplexy: A + C + D
• III. Due to Medical Condition: A + B or C + D w Med/Neuro

ICSD = International Classification of Sleep Disorders; EDS = excessive daytime sleepiness; MSLT = Multiple Sleep Latency Test; SOREMP = sleep-onset REM period.

First Double-Blind Study of GHB & 1 Year Open Label Label Continuation

1. Less Cataplexy: $p < 0.02$
2. Less Awakenings subj: $p < 0.04$ obj: $p < 0.006$
3. More Delta Sleep obj: $p < 0.05$

MSLT:
DB: a) Fewer REM naps: $p < 0.02$ Females, Males: NS

1 Yr: a) $p < 0.0$ b) SOL Increase: $p < 0.05$ c) Awake $p < 0.01$

GHB Effect on Cataplexy

Scrima, et. al Biological Psychiatry. 1989, 26: 331-343

Figure 1. Cataplexy events per day during baseline, placebo, and GHB treatment. For each patient, the mean number of cataplexy events per day was calculated for the baseline and for each week of both treatments. The figure shows the means and standard errors of patients’ baseline and weekly means for cataplexy.
GHB 24 Month Effect On Cataplexy & Sleep Attacks
Scrima et al Sleep Research 1989, 18: 77
Sodium Oxybate or GHB: Open-Label Extension Trial Efficacy in Cataplexy Over 12 Months

Stimulant Medications Maintained.

Prior 4-week trial 12-month extension

N=117 Start  N=80 End  P<0.001 vs baseline
### Long-Term GHB vs Baseline n=12 (6m & 6f)

<table>
<thead>
<tr>
<th>MSLT Measures</th>
<th>Baseline</th>
<th>4-14 Mths</th>
<th><strong>p</strong>&lt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep latency mean</td>
<td>1.4±0.7</td>
<td>3.0±1.9</td>
<td>0.05</td>
</tr>
<tr>
<td>Stage 0 after Sleep Onset (min)</td>
<td>1.8±2.6</td>
<td>2.8±3.8</td>
<td></td>
</tr>
<tr>
<td>Total Stage 0</td>
<td>9.0±5.6</td>
<td>17.8±11.2</td>
<td>0.01</td>
</tr>
<tr>
<td>No. REM naps</td>
<td>4.2±0.8</td>
<td>2.6±1.4</td>
<td>0.01</td>
</tr>
<tr>
<td>REM Latency mean*</td>
<td>2.9±1.5</td>
<td>4.4±3.6</td>
<td></td>
</tr>
<tr>
<td>Sleep Stages (min):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>11.9±10.8</td>
<td>21.3±10.7</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>22.6±10.8</td>
<td>33.4±17.2</td>
<td></td>
</tr>
<tr>
<td>Delta (3&amp;4)</td>
<td>2.5±7.4</td>
<td>0.3±1.0</td>
<td></td>
</tr>
<tr>
<td>REM</td>
<td>53.9±18.3</td>
<td>26.7±25.3</td>
<td>0.02</td>
</tr>
</tbody>
</table>

*If no REM occurred in a nap, REM latency was coded as missing.

**Paired-t results probability adjusted for 4 planned comparisons to control for type I error.

Survey of 35 Patients On GHB For ≤ 14 Yrs

<table>
<thead>
<tr>
<th>%</th>
<th># Patients</th>
<th>Positive Impact Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>83</td>
<td>29</td>
<td>Greatly Life-Altering</td>
</tr>
<tr>
<td>14</td>
<td>5</td>
<td>Moderately Positive</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>Slightly Positive</td>
</tr>
</tbody>
</table>

Cataplexy Severity Improved to Rare & Mild 97
Sleep Attacks & Sleepiness Improved to Mild 86
Sleep Paralysis (n: 23) Severity Improved - Mild 91
Hypnagogic Hallucinations (n: 27) Improved - Mild 91

Scrima et al Sleep 2000, 23: A293
Pre-onset Medical & Sleep History 100 Narcoleptics.

Scrima L., Miller, B. R., Sleep 1999, 22 Supplement: S155

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Sleep-Alertness Disorders Center, Inc.
1390 S. Potomac St., Suite 110, Aurora, CO 80012
Method

Retrospective review of 100 Narcoleptics: 44 males & 56 females


Diagnosed w/an MSLT test:

Sleep onset < 8 minutes and > 2 REM naps

61 had hypnogogic hallucinations & 68 had sleep paralysis

Patients filled out a Sleep, Medical, Psychological & Life Style Hx

Reviewed by a Board Certified Sleep Specialist for ≥1 hour.
## PREONSET MEDICAL HX 100 NARCOLEPTICS With Positive MSLT'S < 8’ SO & >2 REM NAPS

<table>
<thead>
<tr>
<th>Medical Factors:</th>
<th>&lt; 2 years</th>
<th>&gt; 2 years</th>
<th>?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head Injury-Mild with</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loss of Consciousness</td>
<td>35</td>
<td>16</td>
<td>2</td>
</tr>
<tr>
<td>Neck</td>
<td>5</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Whip Lash</td>
<td>5</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Allergies</td>
<td>26</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Tonsillectomy</td>
<td>0</td>
<td>32</td>
<td>4</td>
</tr>
<tr>
<td>Weight Gain &amp; Snoring or Apnea</td>
<td>4</td>
<td>5</td>
<td>35</td>
</tr>
<tr>
<td>Restless Legs</td>
<td>15</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Periodic Limb Movements</td>
<td>0</td>
<td>0</td>
<td>34</td>
</tr>
<tr>
<td>Chronic Pain</td>
<td>11</td>
<td>0</td>
<td>0</td>
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</table>
## Preonset Medical HX 100 Narcoleptics

With Positive MSLT’s < 8’ SO & >2 REM NAPS

<table>
<thead>
<tr>
<th>Medical Factors</th>
<th>&lt; 2 years</th>
<th>&gt; 2 years</th>
<th>_</th>
<th>?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious Disease &amp; / or High Fever</td>
<td>6</td>
<td>9</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>After Child Birth</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>1</td>
<td>4</td>
<td>0</td>
<td></td>
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<tr>
<td>Toxic Substance Exposure</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td></td>
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<tr>
<td>Silicone Breast Implant</td>
<td>1</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Physical Trauma (Shot, Burn, Seizure)</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td></td>
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<tr>
<td>Difficulties at Birth</td>
<td>0</td>
<td>2</td>
<td>0</td>
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<tr>
<td>Carbon Monoxide Poisoning</td>
<td>0</td>
<td>1</td>
<td>0</td>
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</table>
# Pre-Onset Medical HX 100 Narcoleptics

## MSLT’s < 8’ SO & ≥2 REM Naps

<table>
<thead>
<tr>
<th>Psychological–Environmental Stress Factors</th>
<th>&lt; 2 years</th>
<th>&gt; 2 years</th>
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<tbody>
<tr>
<td>Difficulty Maintaining Sleep</td>
<td>45</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Insufficient Sleep</td>
<td>17</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Psychological, Financial, Job, Death in Family</td>
<td>16</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Shift Work</td>
<td>11</td>
<td>3</td>
<td>1</td>
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<table>
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<tr>
<th>No Prior Event:</th>
<th>&lt; 2 years</th>
<th>&gt; 2 years</th>
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<tr>
<td></td>
<td>7</td>
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</table>
Pre-onset Medical & Sleep History 100 Narcoleptics

In Most Cases, > 1 Event within 2 years of Narcolepsy Onset:

Mild Head Injury: 35% &- or Neck Injury: 10% with Loss of Consciousness Lasting Secs - Hrs, w/out Immediate Obvious Sequelae,

Due to Abuse, Car, Sports or Other Accidents or Combination of Other Medical, Psychological, Environment Stress Factors:

Sleep maintenance 46% Allergies 26%,
Insufficient sleep 17% Psychological Stress 16%
Restless legs 15% Shift Work 11%

Scrima L, Miller BR Sleep 1999, 22 Supplement: S155

Similar to another survey’s report of 50% of 105 Narcoleptics who thought Symptoms began After a Medical or Stress Event.

Conclusion

Serious & Prolonged Medical, Psychological or Environmental Stress Factors Appear to be Possible Triggers Promoting Development of Narcolepsy Symptoms Particularly:

Multiple Head or Neck Injuries, w/ Loss of Consciousness, Or Whiplash

Chronic: Pain, Allergies, Sleep Apnea, Restless Legs, PLMD:

Difficulty Maintaining Sleep, Insufficient Sleep, Shift Work & Prolonged Stress
GENETIC PREPOSITION

HLA - DQB1*062 (57)

(Pathologically fragile membranes of SWS neurons)

(damaged / leaky SWS neurons)

Hypocretin cell die off < 90% (58, 38)

(narcolepsy)

(Pathologically fragile membranes of PS neurons)

(damaged / leaky PS neurons)

Hypocretin cell die off ≥ 90% (58, 38)

(cataplexy)

INTERRMITTENT CHRONIC LETHARGY / SLEEP ATTACKS

NARCOLEPSY
STRESS FACTORS

ENVIRONMENTAL, SOCIAL, PSYCHOLOGICAL

(4) + Comorbidities

REDUCED NOCTURNAL SWS + PS

PRIMARY PRESSURE TO SWS

(damaged / leaky SWS neurons)

PRESSURE TO PS

(damaged / leaky PS neurons)

(cataplexy)

INTERMITTENT CHRONIC LETHARGY / SLEEP ATTACKS

NARCOLEPSY
BP NARCOLEPTIC MALES <180 Lbs

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<tr>
<th>Age</th>
<th>18-24</th>
<th>25-34</th>
<th>35-44</th>
<th>45-54</th>
<th>55-64</th>
<th>65+</th>
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<tr>
<td>N</td>
<td>16</td>
<td>18</td>
<td>18</td>
<td>13</td>
<td>11</td>
<td>2</td>
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BLOOD PRESSURE

AGE

N: Number
BP NARCOLEPIC MALES >180 Lbs

<table>
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<tr>
<th>Age</th>
<th>N:</th>
<th>Norm Sys</th>
<th>Narco Sys</th>
<th>Norm Dis</th>
<th>Narco Dis</th>
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<td>18-24</td>
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<td>65+</td>
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BP NARCOLEPTIC FEMALES <160 Lbs

<table>
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<th>Norm Sys</th>
<th>Narco Sys</th>
<th>Norm Dis</th>
<th>Narco Dis</th>
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<td>18-24</td>
<td>19</td>
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<td>25-34</td>
<td>44</td>
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<td>35-44</td>
<td>17</td>
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<td>45-54</td>
<td>38</td>
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<td>55-64</td>
<td>18</td>
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<td>65+</td>
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BLOOD PRESSURE vs AGE

- Norm Sys
- Narco Sys
- Norm Dis
- Narco Dis
Treatment of Cataplexy w/ TCAs  SSRIs  SNRIs Can Cause or Aggravate REM Behavior Disorder

Clomipramine, Imipramine, Fluoxetine & Venlafaxine,

Commonly used to Treat:

Cataplexy  Sleep Paralysis  Hypnagogic Hallucinations

Also Cause or Exacerbate:

REM Behavior Disorder  &  Periodic Limb Movements
Weight Gain, Sexual Dysfunction, Anticholinergic Effects

Emphasize Need For Alternative Treatment for Cataplexy

Prevalence of RBD in Narcolepsy

Diagnosed 1992: 12%
2005: 36%
2006: 52%

Increased Awareness About RBD &/or More Use of Anti-Depressants?

Nightingale S et al. 2005 Sleep Med (3):253-258
Marelli S et al. 2006 Sleep 29 (Abstract suppl): A229-A230
Stimulants: Limitations  Side Effects

Nervousness
Irritability
Tremors Anorexia,
Weight Loss,
Sexual Dysfunction,
Psychosis,
Gastrointestinal Problems
Dyskinesias,
Palpitations
Insomnia
Rash
Habituation - Addiction
Rebound Hypersomnolence

Fry JM 1998, Neurology 50(2 suppl 1): 543-548
Stimulant Side Effects

Modafinil
- Headache, Nausea, Nervousness, Insomnia

Methylphenidate & Amphetamines
- Headache, Nervousness, Rash, Insomnia
- Cardiovascular Effects, Paranoia

Pemoline
- Hepatotoxicity (rare, can be fatal)

Billiard M et al. (1994), Sleep 17(8 suppl):S107-S112;
Fry JM (1998), Neurology 50(2 suppl 1):S43-S48;
Mitler MM et al. (1994), Sleep 17(4):352-371;
Littner M et al. (2001), Sleep 24(4):451-466
Modafinil in the Treatment of EDS

Modafinil is chemically Unrelated to CNS stimulants

Activation of Certain Hypothalamus Regions

Does Not Act Directly Through Dopaminergic Pathways

May Indirectly Inhibit GABA Release

Physician’s Desk Reference 2001 Montvale, Thomson PDR
Chemelli RM et al. (1999), Cell 98(4):437-451
Gamma- Hydroxybutyrate: GHB

GHB Binds to GABA-b Receptors & Promotes Sleep

Has Cerebral Protective Effects
Decreases Cerebral Glucose Utilization

In Narcolepsy Patients, Low Dose 25 mg/kg hs & 3-4 hrs Later:

Does Not Suppress REM Sleep, Fewer Stage Shifts p<.01*
Promotes SWS - N3 sleep p<0.5 & Sleep Continuity p<.05*

Effectively Treats Cataplexy: p<0.02**  Replicated: p<0.001^

*Scrima L et al 1990, Sleep 13(6) 479-90; Mamelak et al 2004, Sleep 27(7): 1327-34
R Sleep, Dreaming: Diagnostic & Efficacy Indicator

Diagnostic Indicator:

R Sleep or Dreams too soon after Sleep Onset: Sign of Depression

Intense Dreams or Dreams At Sleep Onset:
  R Sleep Deprivation or Prolonged R Sleep Suppression
  Loss of Hypocretin Cells &-Or Narcolepsy Developing

  R Sleep Deprivation - Severe Sleep Apnea
  Mania, Circadian Rhythm Disorder
  Drug Withdrawal: Stimulants, Anti-Depressants

Delayed Dreaming: CNS Drugs that Suppress R Sleep
  Sleep Apnea or PLMD that Suppresses N3 &-Or R Sleep

Efficacy Indicator: If Tx Normalizes Sleep, R Sleep & Dreams
Integrator, Solution Seeker, Survival Enhancer

R Sleep & Dreaming Have Qualities & Some Evidence For Enabling:

- Nightly Integration of Daily & Lifelong Experiences

  Orient to:

  Current Known, Sub-Conscious, Suppressed Concerns

- Source of Inspiration to Solve Problems

- A Process for Enhancing Adaptive Behavior & Survival
Sleep: Neurophysiology

Brainstem

Ascending Cortical Activation

REM/SWS Switch

Hypothalamus

Sleep/Wake Switch

Thalamus

Cortical Activation

Sleep Spindle

EEG Synchronization

Cortex

SCN

Circadian Clock

Brainstem

Ascending Cortical Activation

REM/SWS Switch

Courtesy of E. Mignot, MD. Stanford University.
Sleep: Neurochemistry

BF = basal forebrain cholinergic nuclei;
LDT/PPT = laterodorsal tegmental nuclei/pedunculopontine tegmental nuclei;
CR = caudal raphe; PRF = pontine reticular formation; Ach = acetylcholine

Courtesy of E. Mignot, MD. Stanford University.
Narcolepsy: Neurochemical and Neuroanatomic Abnormalities

REM ON
Cholinergic systems
Laterodorsal tegmentum and pedunculopontine nuclei

REM OFF
Serotonergic systems
Raphe nuclei

REM OFF
Adrenergic systems
Locus coeruleus

Dopaminergic systems
Ventral tegmental area
Substantia nigra

SLEEPINESS
Inhibition of dopamine uptake and increased release
Amphetamine stimulants

HYPOCRETIN DEFICIENCY

CHOLINERGIC HYPERACTIVITY

HYPOACTIVITY