To Sleep, Perchance to Dream…
An Overview of Sleep
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And What Does A Digeridoo Have To Do With It?
But... What Is Sleep?

- A physiologic state of relative unconsciousness and inaction of the voluntary muscles, the need for which recurs periodically.
- --Stedman’s Medical Dictionary
How Do We Do It?

Why Do We Sleep?
- Six theories:
  - Construction—Build body and brain tissues
  - Maintenance—Maintain neural circuitry
  - Conservation—↑ energy requirements
  - Consolidation—Reinforce/unify memory
  - Evolution—Survival instinct and adaptation
  - Thermoregulation—Maintain homeostasis

Maintenance and Consolidation


Neurons In The Hippocampus Firing Backwards During Sleep: Reset The Cell For Improved Learning?
Sleep initiated fluid flux drives metabolite clearance from the adult brain. Xie et al. "Sleep revived fluid flux drives metabolite clearance from the adult brain." Science, October 18, 2013. DOI: 10.1126/science.1241224

Brain Cells Shrink And Toss Out The Trash During Sleep

Stages Of Sleep

Awake
Stage N1
Stage N2
Non-Restorative
Stage N3
REM (Neural Restore) Inhibits Sleep

Sometimes I sleepwalk. This morning I woke up downstairs on the couch next to this. I'm pretty sure I thought I was doing laundry.

Source: http://i.imgur.com/3nlanGD.jpg
How Much Sleep Is “Normal”?

<table>
<thead>
<tr>
<th>Humans</th>
<th>TST</th>
<th>Critters</th>
<th>TST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newborns</td>
<td>12-18 h</td>
<td>Brown Bat</td>
<td>19.9 h</td>
</tr>
<tr>
<td>Toddlers</td>
<td>12-14 h</td>
<td>Squirrel</td>
<td>14.9 h</td>
</tr>
<tr>
<td>School-Age</td>
<td>10-11 h</td>
<td>Mouse</td>
<td>12.1 h</td>
</tr>
<tr>
<td>Teens</td>
<td>8.5-9.25 h</td>
<td>Cat</td>
<td>12.1 h</td>
</tr>
<tr>
<td>Adults</td>
<td>7-9 h</td>
<td>Dog</td>
<td>10.6 h</td>
</tr>
<tr>
<td>Elderly</td>
<td>5.5 h</td>
<td>Giraffe</td>
<td>1.9 h</td>
</tr>
</tbody>
</table>

How Much Sleep Do Americans Actually Get?

Hmmm....
Costs of Sleep Insufficiency

- *Direct Costs:
  - Insomnia = $13.9 billion
  - Absenteeism / lost productivity = $41.1 billion
  - Insomnia-related accidents, alcoholism, depression-related costs = $77 - 92 billion
  - Famous accidents related to fatigue: Bhopal, Chernobyl, Exxon Valdez

  * 1995 estimates

Sleep Disorders--Diagnosis and Treatment
Common Sleep-Related Complaints--Adults

- Sleep Initiation—“I can’t get to sleep…”
- Sleep Maintenance—“…I can’t stay asleep”
- Unrefreshing Sleep—“…I wake up tired”
- Daytime Sleepiness—“I can’t stay awake…”
- Fatigue—“I have no energy…”

Common Sleep-Related Symptoms--Pediatric

- Snoring
- Enuresis
- Sleeping with Neck Hyperextended
- Insomnia
- Difficulty Waking in the Morning
- Falling Asleep in School


Common Sleep-Related Symptoms--Pediatric

- Irritability/Mood Instability
- Aggression/Hyperactivity/Oppositionality
- Anxiety/Withdrawal
- Somatic Symptoms and Complaints
- Attention and Memory Impairments

Sleep Evaluation

- OLDCARTS
- Medication Review
- Physical and Psychological Evaluation / Labs/Overnight Pulse Oximetry
- Two-Week Sleep Diary
- Epworth Sleepiness Scale
- STOP-BANG
- Mallampati Classification

Medications Affecting Sleep

<table>
<thead>
<tr>
<th>β-Blockers</th>
<th>€Wake €REM</th>
<th>€Fatigue, sedation, nightmares, insomnia</th>
</tr>
</thead>
<tbody>
<tr>
<td>β1-Antagonists</td>
<td>€TST €REM</td>
<td>€Transient sedation</td>
</tr>
<tr>
<td>β2-Agonists</td>
<td>€TST €REM</td>
<td>€Sedation</td>
</tr>
<tr>
<td>SSRI/SNRI</td>
<td>€TST, €REM, €RLS/PLMS</td>
<td>€Insomnia, sedation</td>
</tr>
</tbody>
</table>

TST = total sleep time; REM = rapid eye movement sleep stage; RLS/PLMS = restless leg syndrome/periodic limb movements of sleep; SWS = slow-wave sleep.
Medications Affecting Sleep

**Medications**

**TCAs**
- amitriptyline, doxepin, nortriptyline
- ↑ TST, ↓ REM,
- ↑ RLS/PLMS
- sedation

**Phenylpiperazine**
- trazodone
- ↑ TST, ↑ SWS,
- ↓ REM,
- ↑ RLS/PLMS
- sedation, hangover

**Buproprion XL**
- ↓ TST
- insomnia

**Antipsychotics**
- Zyprexa, Seroquel, Risperdal, Geodon
- ↑ TST, ↓ REM,
- ↑ RLS/PLMS,
- ↑ SWS
- sedation, hangover

**Benzodiazepines**
- ProSom, Restoril, Klonopin, Ativan, Xanax, Valium
- ↑ TST, ↓ SWS,
- ↓ RLS/PLMS
- sedation, hangover

**α-2-δ Ligands**
- Lyrica, Neurontin
- ↑ TST, ↓ SWS,
- ↓ REM,
- ↓ RLS/PLMS
- sedation, hangover; weight gain

**Alcohol**
- ↓ TST
- ↓ TST
- ↓ SWS
- ↓ REM
- ↓ RLS/PLMS
- sedation, hangover; weight gain; increased central apneas

**Opiates**
- ↓ RLS/PLMS
- Insomnia; increased central apneas

**TST** = total sleep time; **REM** = rapid eye movement sleep stage; **RLS/PLMS** = restless leg syndrome/periodic limb movements of sleep; **SWS** = slow-wave sleep
STOP-BANG QUESTIONNAIRE FOR OBSTRUCTIVE SLEEP APNEA

STOP
Do you SNORE loudly? (loud enough to be heard through closed doors)? YES NO
Are you TIRED, fatigued or sleepy during the day? YES NO
Has anyone OBSERVED that you stop breathing during sleep? YES NO
Do you have or have you been treated for high blood pressure? YES NO
PRESSURE?

BANG
BMI more than 35 kg/m²? YES NO
Age over 50 years old? YES NO
NECK circumference > 13.75 inches (40 cm)? YES NO
Male GENDER? YES NO

TOTAL
A score of ≥3 "Yes" answers = high risk for OSA


BEARS Sleep Screening Algorithm

• B = Bedtime Problems
• E = Excessive Daytime Sleepiness
• A = Awakenings During Sleep
• R = Regularity/Duration of Sleep
• S = Snoring

Mallampati Classification

[Images of Mallampati Classifications]

24-Hour Pulse Oximetry Study

[Graphs showing pulse oximetry data over 24 hours]
Obstructive Sleep Apnea

Why is it that the people who snore the loudest are the first ones to fall asleep?

Obstructive Sleep Apnea

Snoring / Hypopnea  Obstructive Apnea
Obstructive Sleep Apnea (OSA)

- Apneas = reduction of ≥ 90% normal breath intake for ≥ 10 seconds with ≥ 4% drop in \( \text{SpO}_2 \)
- Hypopneas = reduction of ≥ 30-89% normal breath for ≥ 10 seconds with ≥ 3% drop in \( \text{SpO}_2 \)
- Accompanied by continuing respiratory effort and arousals
- DX: Apnea-Hypopnea Index of ≥ 5 / hour with co-morbidities

Obstructive Sleep Apnea

Signs / Symptoms:
- Snoring
- Choking / gasping during sleep
- Insomnia / nocturnal awakenings
- Excessive Daytime Sleepiness
- Fatigue
- Nocturia
- Sweating
- Morning headaches
- Nocturnal GERD
- Kicking / twitching / thrashing
- Impaired cognition
- Mood changes
- Divorce
Obstructive Sleep Apnea

• Prevalence:
  • 4% men vs. 2% women over age 18
  • Risk of OSA after age 50, women = men
  • Increasing due to rising rates of obesity
  • 10% of people with OSA receive treatment

Obstructive Sleep Apnea

• Male
  • ≥ 40 years old
  • BMI ≥ 26
  • Central adiposity
  • Neck circumference ≥ 17 in.
  • Receding jawline

Obstructive Sleep Apnea

• Female
  • ≥ 50 years old
  • BMI ≥ 26
  • Central adiposity
  • Neck circumference ≥ 16 in.
  • Receding jawline
  • Petite women with thin necks / tiny airways
  • Or
Risk Factors for Pediatric OSA

- Enlarged Tonsils/T&A History
- Obesity
- Craniofacial Anatomy
- Genetic Disorders
- Allergies/Asthma/GERD
- Preterm Birth
- Family History


Pediatric OSA Diagnosis & Management

Diagnostic Criteria:
AHI = 1.0 event per hour; SpO2 < 92% by Polysomnography

Management:
- Tonsillectomy & Adenoidectomy
- Weight loss
- CPAP
- Allergy and Asthma Management


Obstructive Sleep Apnea

- Non-Invasive Ventilation

Treatment:
- Continuous Positive Airway Pressure (CPAP)
Obstructive Sleep Apnea

- **Dental Treatment:**
  - Mandibular Advancement Device

**Surgical Treatment:**
- Uvulopalatopharyngoplasty (UPPP)
- Nasal airway surgery
- Palate implants
- Tongue reduction
- Maxillomandibular procedures
- Tracheostomy
- Bariatric surgery
- Injection Snoreplasty

Inspire Upper Airway Stimulation System
- FDA approved 2014
- AHI 20 - 65 / hr.
- < 25% central apneas
- > 22 years of age
- CPAP intolerant
- Airway exam meets criteria
- BMI < 32
- 68% reduction in AHI

Source: [http://www.inspiresleep.com](http://www.inspiresleep.com)
Obstructive Sleep Apnea

- Nux Vomica 4x
- Belladona 6x
- Ephedra vulgaris 6x
- Hydrastis Canadensis 6x
- Kali Bichromicum 6x
- Teucrium marum 6x
- Histaminum hydrochloricum 12x
Obstructive Sleep Apnea

- Behavioral Approaches:
- Weight loss
- Positional therapy
- Stop smoking / 2nd-hand smoke exposure
- Avoid alcohol near bedtime
- Playing a double-reed instrument or digeridoo

Obstructive Sleep Apnea

- Excessive Daytime Sleepiness Due To OSA:
  - **ProHigil (modafinil)/ Nuvigil (armodafinil)**
    - DEA Schedule IV; Pregnancy category C
    - MOA: unknown, but may increase dopamine levels by inhibiting dopamine re-uptake
    - 60% protein bound; peak plasma time = 2-4 hours; half-life 15 hrs.
    - Hepatically metabolized; excreted 80% in urine
    - CYP1A2, CYP2B6, CYP3A4 inducer
Obstructive Sleep Apnea

- **Provigil / Nuvigil:**
  - A/E: >10% HA, rhinitis; 1-10% nervousness, syncope
  - Contraindications: History of LVH/MVP with CNS stimulants
  - Warnings: Risk of SJS; psych symptoms
  - Dosing:
    - Provigil—200 mg qAM; no more than 400 mg daily
    - Nuvigil—150 - 250 mg qAM

Obstructive Sleep Apnea

- **Non-Treatment:**
  - Impaired Cognition
  - Heart Disease
  - Stroke
  - Mood Disorders
  - Accidents / Errors
  - Insulin Resistance

I love you so much, if we got in a fight and went to bed angry, I wouldn’t unplug your sleep apnea machine.
Restless Leg Syndrome (RLS)  
Periodic Limb Movements (PLMs)

Are you playing footsie with me or is that just restless leg syndrome?

• **RLS**—
  • Neurological disorder with unpleasant or painful feelings in the legs along with the irresistible urge to move them.
  • Symptoms begin upon sitting / lying down and relieved temporarily with movement of legs.

Restless Leg Syndrome (RLS)  
Periodic Limb Movements (PLMs)

• **RLS**—
  • Symptoms start about middle-age and older; women > men.
  • May have genetic etiology, but generally unknown.
  • May also be related to brain iron-deficiency; check serum ferritin, transferrin.
  • Many RLS sufferers also have Periodic Limb Movements during sleep.
  • Affects approximately 5% of population.
Restless Leg Syndrome (RLS)
Periodic Limb Movements (PLMs)

- **RLS:**
  - Occurs most often in
    - Iron-deficiencies
    - Peripheral neuropathy
    - Chronic kidney disease
    - Parkinson’s Disease
    - Pregnancy
    - Certain medications (particularly stimulants—legal and illegal)

- **PLMs:**
  - Rhythmic, flexing movements of great toe, ankle, knee or hips every 20 - 40 seconds, usually bilaterally.
  - May cause arousals
  - About 80% of RLS patients have PLMs
  - Also common in OSA, narcolepsy, iron-deficiency and peripheral neuropathy and in elderly patients
  - Aggravated by stimulants, TCAs, SSRIs, levodopa
  - Recent studies suggest an association of PLMs with left ventricular hypertrophy

Restless Leg Syndrome (RLS)
Periodic Limb Movements (PLMs)

- **RLS / PLMs treatment:**
  - Requip
  - Mirapex
  - Neupro patch
  - Klonopin
  - Gabapentin enacarbil (Horizant)
Restless Leg Syndrome (RLS) Periodic Limb Movements (PLMs)

- **Requip/Requip XL (ropinirole):**
  - Pregnancy category C
  - Potent dopamine agonist
  - Metabolized by liver CYP1A2
  - Protein bound 40%
  - Peak: 1-2 hrs (IR); 6-10 hrs (ER)
  - Half-life: 6 hrs (ER)
  - Excreted: Urine
  - A/Es: Nausea, vomiting, somnolence, syncope, fatigue, dyspepsia

- **Cautions:** sleepiness, hypotension/ syncope, hallucinations, erratic and compulsive behavior, inappropriate sexual actions
- **Dosing:**
  - 0.25 mg/day PO, 1-3 hrs before HS; may titrate up to 4 mg/day.
  - If need to stop Requip and dose is < 4 mg/day, may discontinue without taper. If >4 mg/day, taper over 7-day period.
  - Safety and efficacy not established with CrCl < 30 mL/min or with hepatic impairment. Use with caution.

- **Mirapex/Mirapex ER (pramipexole):**
  - Pregnancy category C
  - MOA: dopamine receptor agonist
  - Peak: 2 hrs (IR); 6 hrs (ER)
  - Half-life 8.5 hrs (12 hrs in elderly)
  - Renal clearance: 400 mL/min; excreted in urine
  - Protein bound: 15%
  - A/Es: abnormal dreams; OCD behaviors, hypotension, syncope, increased eating, weight gain
  - Dosing: 0.125 mg/day PO 2-3 hrs before HS; may titrate to 0.5 mg if CrCl 20-60 mL/min
**Restless Leg Syndrome (RLS) Periodic Limb Movements (PLMs)**

- **Neupro patch (rotigotine):**
  - Pregnancy category C
  - MOA: Dopamine agonist; precise MOA for RLS/PLMS unknown.
  - Peak: 15-18 hrs; release rate 45% in 24 hr
  - Protein bound: 89.5%
  - Metabolized by N-deakylation and direct/secondary conjugation
  - Half life: biphasic—3 hr initially, then 5-7 hrs at steady state
  - Excretion: 71% urine; 23% feces

**Restless Leg Syndrome (RLS) Periodic Limb Movements (PLMs)**

- **Neupro patch (rotigotine):**
  - A/Es: itching/burning under patch; nausea, headaches, insomnia, dizziness, dry mouth, constipation, sweating, hypertension, abnormal dreams.
  - Dosing: 1 mg patch/24 hr; may increase by 1mg/24hr in weekly intervals up to 3 mg/24 hr. To discontinue, taper by 1 mg/24 hr every other day.

**Restless Leg Syndrome (RLS) Periodic Limb Movements (PLMs)**

- **Klonopin (clonazepam):**
  - DEA schedule IV
  - Pregnancy category D
  - MOA: long-acting benzodiazepine; increases GABA inhibition action; suppresses muscle contractions
  - Onset: 20-60 min
  - Peak 1-3 hr; 5-7 days steady state
Restless Leg Syndrome (RLS)

Periodic Limb Movements (PLMs)

Klonopin (clonazepam):
- Half-life 18-50 hr (adults); 22-33 hr (children)
- Protein bound 85%
- Metabolized hepatically CYP3A4
- A/Es: somnolence, abnormal coordination/ataxia, depression, dizziness, fatigue, memory impairment/confusion
- Contraindications: significant hepatic impairment, EtOH intoxication, myasthenia gravis, narrow-angle glaucoma, respiratory depression, psychotic reactions

Withdraw gradually by 0.125 mg every 3 days
Dosing: 0.125 mg initially, titrate up by 0.125 mg every 5-7 days, not to exceed 1 mg.

Horizant (gabapentin enacarbil):
- Pregnancy category C
- MOA: GABA analog
- Metabolism: extensive first-pass hydrolysis to form gabapentin, CO2, acetaldehyde and isobutyric acid. Absorbed primarily in the intestines. Must have food available for best absorption (75% with food; 42-65% fasting)
- Peak: 7.3 hrs with food; 5 hr fasting
- Contraindications: significant hepatic impairment, EtOH intoxication, myasthenia gravis, narrow-angle glaucoma, respiratory depression

Pregnancy category C
MOA: GABA analog
Metabolism: extensive first-pass hydrolysis to form gabapentin, CO2, acetaldehyde and isobutyric acid. Absorbed primarily in the intestines. Must have food available for best absorption (75% with food; 42-65% fasting)
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Withdraw gradually by 0.125 mg every 3 days
Dosing: 0.125 mg initially, titrate up by 0.125 mg every 5-7 days, not to exceed 1 mg.
Restless Leg Syndrome (RLS) Periodic Limb Movements (PLMs)

- **Horizant** (gabapentin enacarbil):
- Renal clearance 5-7 l/hr
- Excretion: 94% urine; 5% feces.
- A/E: somnolence, dizziness, headaches, fatigue, nausea, peripheral edema, weight gain, blurred vision, dry mouth, depression
- **Dosing:** 600 mg/day, with food, taken at 5 pm. Adjust to 300 mg/day for renal impairment CrCl 15 - 59 mL/min. Do not administer for CrCl < 15 mL/min.

Restless Leg Syndrome (RLS) Periodic Limb Movements (PLMs)

Contains:
- Water, Aloe Barbadensis Leaf Juice, Polyacrylamide, C13-14 Isoparaffin, Benzocaine HCl, Magnesium Ascorbyl Phosphate, Lavandula Angustifolia (Lavender) Oil, Salvia Officinalis (Sage) Leaf Extract, Cananga Odorata Flower Extract, Anthemis Nobilis Flower Extract, Tocopheryl Acetate (Vitamin E), Folic Acid, Retinyl Palmitate Vitamin A, Propylene Glycol, Laureth-7, Diazolidinyl Urea, Methylparaben, Propylparaben.

Insomnia

I have a condition that makes me eat when I can’t sleep. It’s called Insom-nom-nom-nom-nia.
Insomnia

Dx Primary Insomnia--
• Difficulty getting to sleep and/or staying asleep; duration > one month
• Causes clinically significant distress
• No other sleep/medical/psychological diagnosis
• No substance abuse present

Insomnia

• Psychophysiologic-- learned behavior; the harder the patient tries, the worse the insomnia
• Idiopathic--lifelong insomnia; may be due to neurological causes not currently understood
• Paradoxic--misperception of sleep

Insomnia

INSOMNIA = 1:51 A.M. + ETERNITY + 1:52 A.M. + ETERNITY + 1:53 A.M. + ETERNITY
Insomnia

Non-pharmacologic treatment--
• keep sleeping areas cool, dark, quiet
• use bedroom for sleep and sex only
• go to bed only when sleepy
• if not asleep in 20 - 30 minutes, get up and do something boring
• avoid naps
• avoid blue-light sources (TV, computers, etc.) before bedtime

Insomnia

Non-pharmacologic treatment--
• avoid heavy meals, exercise, caffeine, alcohol, hot baths just before bedtime
• progressive muscle relaxation, thought-stopping, biofeedback
• Cognitive Behavioral Therapy

Insomnia

Pharmacologic treatment--
Non-benzodiazepines
• Ambien
• Ambien CR
• Lunesta
• Sonata

Benzodiazepines
• Restoril
• ProSom
Insomnia

Pharmacologic treatment--

Low-Dose Sedating Anti-Depressants
- Remeron
- Silenor

Melatonin Agonist
- Rozerem

Orexin Antagonist
- Belsomra (suvorexant)

Insomnia

Belsomra (suvorexant)
- FDA approved August 13, 2014
- Antagonizes Orexin
- Available in 5, 10, 15 and 20mg tabs, starting late 2014 / early 2015
- Starting dose = 10 mg
- Impaired driving with 20 mg dose possible

Insomnia

Non-benzodiazepine hypnotics

Ambien (zolpidem):
- DEA schedule IV
- Pregnancy category C
- MOA: antagonist of omega 1 GABA receptors
- Peak: 1.6 hrs; delayed by food intake
- Half-life: 2.5 hr (IR); up to 8.4 hr for spray (Zolpimist)
- Metabolized hepatically CYP3A4, CYP2C9, CYP1A2, CYP2D6
Insomnia

Ambien (zolpidem):
• A/Es: dizziness, headaches, allergy, constipation, depression, memory loss, abnormal behaviors
• Dosing: 5 mg (IR, spray, sublingual) up to 10 mg per night.
• Women: metabolize zolpidem slower than men; adjust dose down.

Insomnia

Lunesta (eszopiclone):
• DEA schedule IV
• Pregnancy category C
• MOA: unknown; may interact with GABA
• Peak: 1 hr
• Half-life: 6 hrs (< 65 yrs); 9 hrs (> 65 yrs)
• Metabolized hepatically
• Excretion: urine
• A/Es: bad taste; headache, abnormal dreams
• Dosing: 1 - 3 mg / night

Insomnia

Sonata (zaleplon)
• DEA schedule IV
• Pregnancy category C
• MOA: GABA receptor agonist
• Peak: 1 hr
• Half-life: 1 hr
• Metabolized hepatically CYP3A4
• Excretion: urine (70%), feces (17%)
• A/Es: headache, dizziness, nausea
• Dosing: 5 - 10 mg at HS; may repeat if 4 hrs of sleep time available
Insomnia

Benzodiazepines

Restoril (temazepam); ProSom (estazolam)
- DEA schedule IV; Pregnancy X
- MOA: CNS depressant; increases inhibitory action of GABA on neurons
  - Peak: 2-3 hrs
  - Half-life: 9.5 - 12 hrs
  - Metabolism: hepatic CYP3A4
  - A/Es: confusion, dizziness, hangover, euphoria, amnesia, abnormal behaviors
  - Dosing:
    - Restoril: 15 - 30 mg / night
    - ProSom: 1 - 2 mg / night

Insomnia

Low-Dose Sedating Antidepressants

Remeron (mirtazapine):
- Pregnancy Category C
- MOA: Alpha 2-adrenergic antagonist; stimulates norepinephrine and serotonin
  - Peak: 2 hrs
  - Half-life: 20 - 40 hrs
  - Excretion: Urine (75%); feces (15%)
  - A/Es: somnolence; weight gain; dry mouth, hunger, constipation
  - Dosing: 15 - 30 mg / night

Insomnia

Low-Dose Sedating Antidepressants

Silenor (doxepin)
- MOA: Tricyclic antidepressant; exact mechanism for sleep unknown; may be Histamine H1 blocker.
  - Peak: 2 hrs
  - Half-life: 6 - 8 hrs
  - Metabolized: hepatically
  - A/Es: somnolence; dry mouth, constipation, blurred vision, nausea/vomiting
  - Dosing: 3 - 6 mg/night
Insomnia

Melatonin Agonist

Rozerem (ramelteon)
- Pregnancy category C
- MOA: melatonin receptor agonist
- Absorption: 84%
- Protein bound: 82%
- Metabolized: first-pass metabolism; then by CYP1A2
- Excreted urine 84%
- Dosing: "8 mg / night"

Insomnia

Diphenhydramine—Histamine
H1 antagonist

Doxylamine—H1 receptor competitor

L-tryptophan, Valerian, Melatonin, L-theanine—

"Well done, Jim. If only I could sleep at home like I do through your presentations!"

(the end.)