The Orthomolecular Treatment of Insomnia
Aileen Burford-Mason PhD

Objectives
- Discuss the importance of sleep and the health and economic consequences of insomnia
- Show similarities between insomnia and short sleep (voluntary sleep curtailment)
- Demonstrate the link between reduced sleep time and multiple negative health outcomes, including obesity
- Provide an update on the orthomolecular treatment of insomnia and the research to support it

Insomnia
- Insomnia: Insufficient or poor-quality sleep marked by at least one of the following
  - Difficulty falling asleep
  - Difficulty maintaining sleep
  - Early waking
  - Feeling unrefreshed by sleep
- May be transient, intermittent, or chronic
- Chronic insomnia (Insomnia Syndrome): Difficulty sleeping most nights and lasting for a month or more

The importance of sleep
- Outdated concept:
  - Sleep is the brain's response to lower sensory stimulation from the environment
  - Necessary for rest and repair of the body
- Current concept: Not just "downtime" but an actively induced and highly organized brain state
  - Needed for learning, neuroendocrine regulation, and next day focus, concentration, and motor skills

How much sleep is enough?
- Needs vary from person to person and change throughout the lifecycle
  - Newborns sleep 16 – 18 hours
  - Preschool children sleep 10 – 12 hours
  - School-aged children and teenagers need a minimum of 9 hours
  - Most adults need 7 – 8 hours
- Older adults sleep less or spend less time in the deep, restful stages of sleep
  - However, there is no evidence to show that they need less sleep

Sleep deprivation
- Sleep curtailment is a hallmark of modern society
  - Compared with 20 years ago today's children and adults get significantly less sleep
- Voluntary or involuntary decrease in total sleep time
  - Reduces next day energy, alertness, and clear thinking, and slows reaction times
  - Interferes with consolidation of memory and learning
- Reduced sleep time increases the risk of many common diseases, including
  - Common viral illnesses
  - Diabetes, obesity, heart disease, and depression
The effects of a poor night sleep on mood, cognitive, autonomic and electrophysiological measures.

**Barrett KJ. J Integr Neurosci. 2008 Sep;7(3):405-20**

- **Study**: Subjects with six hours or more hours sleep (n=226) compared to those with < 6 h (n=112) the previous night
- **Next day they were assessed for**
  - Mood
  - Cognition
  - Autonomic and electrophysiological functioning

- **Results**: Subjects with < 6 hrs sleep had higher depression, anxiety, and stress scores; reported significantly poorer overall well being; made more errors on simple cognitive tasks; had increased heart rates; Performance on complex tasks was unaffected.
- **Conclusion**: the effects of one poor night’s sleep were similar but less severe than those reported in chronic insomnia.

The effect of sleep fragmentation on daytime function

**Am J Respir Crit Care Med. Martin SE et al. 1996;153(4 Pt 1):1328-32**

- **Background**: In patients with sleep apnoea impaired daytime function is common
- **Research question**: Is this due to sleep fragmentation or hypoxia?
- **Methods**: Normal subjects (n=16) were studied on 2 pairs of 2 nights
  - 1st night of each pair was for acclimatization
  - On the 2nd night subjects were either undisturbed or had sleep fragmented by sound pulses every 2 min
  - Next day subjects had a battery of standardized test for mood and sleepiness

- **Results**: Total sleep time did not differ between study nights
  - Fragmentation decreased next day energy and mood
- **Conclusion**: 1 night of sleep fragmentation makes normal subjects sleepier next day; impairs their subjective assessment of mood; decreases mental flexibility; reduces ability to sustain attention.

The economic burden of insomnia: direct and indirect costs for individuals with insomnia syndrome, insomnia symptoms, and good sleepers

**Daley M et al. Sleep. 2009 Jan 1;32(1):55-64**

- **Study**: estimated direct and indirect costs of insomnia in 948 Quebec adults (mean age = 43.7, 60%F)
- **Analyzed sleep, health, use of health-care services and products**
- **Also analyzed accidents, work absence, and reduced productivity**
- **Data also obtained from the Quebec government regarding medical consultations and hospitalizations**

- **Results**: Total annual cost of insomnia estimated at $6.6 billion (Cdn)
  - Direct costs: health-care consultations and transportation $257.8m; prescription medications $16.5m; OTC products $1.8m.
  - Alcohol used as a sleep aid $339.8m.
  - Indirect costs: insomnia-related absenteeism $970.6m; insomnia-related productivity losses estimated at $5.0 billion.
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Coemergence of insomnia and a shift in the Th1/Th2 balance toward Th2 dominance.

- **Background:** Immunity to foreign particles is controlled by two types of T-helper cells
  - Th1 cells promote cell mediated immunity – fight pathogens and eliminate cancer cells
  - Th2 cells drive humoral immunity – control the production of antibodies, etc.
- **Imbalances** of Th1 and Th2 cells contribute to immune dysfunction
  - Excess of Th1 a risk for chronic or acute infection; cancer
  - Excess of Th2 linked to the development of allergies and autoimmune diseases

Study: Insomnia, natural killer (NK) cells and Th1/Th2 balance examined in 324 men (20-64y)
Results:
- Insomnia found in 9.2% of participants
- Insomniacs had a significant shift in the Th1/Th2 balance towards Th2 cells
Conclusion: insomnia shifts the Th1/Th2 balance toward Th2 dominance
- Chronic insomnia may be a risk factor for the development of allergies and autoimmune diseases

Other factors which impact sleep
- Shift work
- Jet lag
- Alcohol abuse
- Genetics
  - Twin studies suggest insomnia under strong genetic influence (Sleep. 2006 May 1;29(5):645-9)
- Many prescription medications

Alcohol and sleep
- Virtually every type of sleep problem has been observed in alcohol-dependent patients
  - sleep patterns are fragmented and typical brain wave patterns altered
- Alcohol aggravates sleep disordered breathing (SDB) and increases effect on next day cognitive performance resulting from sleep deprivation
- Sleep changes may persist for months or even years of abstinence

Statin-associated psychiatric adverse events: a case/non-case evaluation of an Italian database of spontaneous adverse drug reaction reporting
- Investigated possible association of statins with memory loss, depression, suicide, aggression and antisocial behaviour.
- Compared all adverse reports (ADR) involving statins with ADR reports not involving statins (control)
- Most frequent ADR reported with statins were insomnia, somnolence, agitation, confusion and hallucination
- Only insomnia was higher for statins compared with all other drugs

Sleep and weight
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- **Observation**: Sleep loss disturbs endocrine regulation of energy homeostasis
- **Two hormones released during sleep regulate next day appetite**
  - Leptin which inhibits appetite
  - Grehlin which stimulates appetite
- **The dramatic increase in obesity parallels reduced sleep time over the same time period**


- **Study**: next day feelings of hunger, serum leptin and ghrelin compared in 9 healthy, normal-weight men
  - after one night of total sleep deprivation (SD)
  - after 4.5 hrs. sleep
  - after 7 hours sleep
- **Results**:
  - Ghrelin levels highest after total SD; intermediate after 4.5 h sleep
  - Stronger feelings of hunger after total SD compared to 7 h sleep (P = 0.02) or 4.5 h sleep (P = 0.041)


- **Serum leptin levels did not differ between sleep times**
- **Conclusions**: Just 1 nights sleep loss disrupted next day energy homeostasis, and increased appetite
- **Regular disruption or restriction of sleep may result in weight gain and contribute to the obesity epidemic**


- **Review article**: Epidemiologic studies show links between short sleep and increased BMI
- **Prospective studies show that children and young adults who are short sleepers are at increased risk of weight gain and obesity**
- **Conclusion**: decreased sleep duration appears to play a significant role in the current obesity epidemic


- **Review**: sleep curtailment in young adults results in a constellation of metabolic and endocrine alterations, including
  - decreased glucose tolerance and insulin sensitivity
  - increased evening concentrations of cortisol
  - increased ghrelin and decreased leptin levels
  - increased hunger and appetite

Sleep Stages
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Sleep Preparation

- **Stage 0**
  - Awake but sleepy – EEG shows mainly alpha waves (similar to meditation)
- Alpha waves are
  - blocked by eye movements or focused attention
  - indicate a person is resting and letting go of the day's concerns

  Note: picture in here of alpha waves

Sleep Stages

- Depth of sleep is not uniform throughout the night:
  - at certain times it is difficult to arouse a sleeper
  - at other times, the slightest sound will wake them
- Two different sleep states can be identified:
  - Rapid eye movement (REM) sleep
  - Nonrapid eye movement (NREM) sleep

Brain Waves and sleep

- **Fast Brain Waves**
  - awake
  - Beta waves (alert)
  - Alpha waves (relaxed)
- **Slow Brain Waves**
  - asleep
  - Theta waves (light sleep)
  - Delta waves (deep sleep)

Sleep Stages

- NREM sleep divided into 3 stages based on how easy it is to be aroused
  - stage 1 (drowsy sleep)
  - stage 2 (intermediate or light sleep)
  - stages 3 (deep sleep, delta sleep or slow wave sleep)
- During sleep we pass through all 3 stages of NREM sleep and then on to REM sleep
- The cycle then repeats from stage 1

NREM Sleep

- **Stage 1 (Drowsiness)**
  - Lasts 5-10 minute. Alpha waves disappear and are replaced by theta waves
  - Muscle activity slows and attention to the environment is cut off
  - Often accompanied by odd thoughts or images
  - Easily awakened
- **Stage 2 (Light or intermediate sleep)**
  - Eye movements stop, heart rate ↓, body temp. ↓
  - Two distinctive EEG patterns – sleep spindles and K-complexes

Deep Sleep: NREM Stage 3

- **Stage 3 (Deep Sleep or delta wave sleep)**
  - Delta waves are large, slow waves. Caused by the synchronized firing of many neurons
  - Blood flow ↓ to brain and ↑ to muscles
  - Restores physical energy and enhances immunity
  - Difficult to wake someone from deep sleep
  - Dreamless
- **Disrupted by**
  - Round-the-clock care giving (children, the sick, elders)
  - Excess noise or light pollution; alcohol and nicotine
  - May be the most vital stage
  - First stage a sleep-deprived brain tries to recover
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REM sleep

- Brain waves similar to awake state or Stage 1 sleep
- Rapid eye movements
- Atonia
  - Almost complete loss of muscle control
  - Penile erections (males) & vaginal moistening (females)
- Easy to awaken
- Usually a time of more intensive, vivid dreams

REM Sleep

- First period of REM sleep occurs about 70-90 minutes into the sleep cycle
  - Usually 3-5 REM episodes per night
- Time spent in REM sleep gets longer with each cycle
- Breathing rapid, irregular and shallow. Heart rate and BP increase
- Alpha and beta waves predominant (fast)
- Release of glycine blocks release of other neurotransmitters – dopamine, seratonin and histamine
- Most antidepressants inhibit REM sleep

Orthomolecular treatment of insomnia

The well-fed brain sleeps better

- The brain is a nutrient hog
  - Averages 2% of total body weight, but utilizes 20% of oxygen and nutrients
- There is therefore a high fixed cost of brain function
  - I.e., 10 times the requirements for oxygen and nutrients compared with other organs
- Good all-round nutrition is therefore fundamental to a good night’s sleep

The healthy diet

- Rich in “smart carbs” – fruits, vegetables, herbs, spices, legumes
  - Smart carbs are low in calories but high in nutrients (phytochemicals, fibre, vitamins and minerals, healthy fats)
- Low glycemic load – only modest amounts of unrefined starchy carbs (no white stuff!)
- Includes good fats at every meal
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Neurotransmitters involved in sleep

- Dopamine
- Serotonin
- Acetylcholine
- Melatonin
- γ- amino butyric acid (GABA)
- Histamine

The Behavioural Effects of Nutrients
Wurtman R. 1983 The Lancet I (May21), p1145-1147

- Neurotransmitters control moment-to-moment brain function
  - carry messages from presynaptic neurons to receptors on postsynaptic neurons
- The composition of our last meal profoundly affects brain levels of three key neurotransmitters
  - Dopamine
  - Serotonin
  - Acetylcholine

Dopamine

- Stimulating: facilitates sensory information accessing the brain
  - improves focus and concentration
- Antidepressant. Regulates mood, speech, focus and movement
- Made from tyrosine, a conditionally essential amino acid.
  - Synthesis requires B-vitamins (B3, B6, B12 and folic acid), vitamin C, magnesium, iron and copper
- Powerful aid to learning: dopamine neurons activated during REM sleep

Serotonin

- Calming: screens out sensory information.
- Made from tryptophan, an essential amino acid. Requires B-vitamins and magnesium
- High levels make us sleepy and clumsy
- Serotonin is metabolized to melatonin in the pineal gland
- Melatonin: master hormone
  - controls sleep/wake cycles, immunity and cancer resistance
  - pineal gland can only make it during sleep in complete darkness

Dopamine and serotonin are complementary

- Dopamine increases focus and concentration, while serotonin limits the amount of external information the brain receives
- Ideally, dopamine should dominate during the working day, while serotonin levels need to rise in the evening
- The passage of tryptophan from blood into brain is facilitated by eating something sweet near bedtime

Niacin ➔ Tryptophan

- Folate, Vitamin B6, magnesium

5-hydroxytryptophan (5-HTP)

- Vitamin B6, folate, magnesium

Serotonin

- Folate, B6, magnesium

Melatonin
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5-hydroxytryptophan (5-HTP)

- Intermediate between tryptophan and serotonin
- Obtained from seeds of an African shrub, Griffonia simplicifolia
- Unlike tryptophan, 5-HTP is not diverted to niacin or protein production
  - Well absorbed orally - 70% gets into bloodstream, compared with ~ 1% of tryptophan
- Supplements: 100-500mg. Start with 100mg before bed and gradually increase to find optimal dose

Melatonin and Sleep

- Role in sleep disorders well established
  - Maintains the internal clock governing the natural rhythms of body function
  - Required for effective Stage 3 (deep) sleep
  - Potent anticancer activity
- Enzymes needed for synthesis activated by darkness and depressed by light
- Supplements: Use 1-3mg before bed
  - For difficulty falling asleep, use immediate-release forms
  - For difficulty staying asleep, use sustained-release forms

Light contamination during the dark phase in "photoperiodically controlled" animal rooms: effect on tumor growth and metabolism in rats

- Background: melatonin suppresses tumour metabolism and neoplastic growth but synthesis is suppressed by light exposure during sleep
- Research question: Could minimal light exposure during sleep promote tumour growth?
- Study: Rats maintained under three conditions
  - Group 1: 12h bright light/12h complete darkness
  - Group 2: 12h bright light/12h light-contaminated dark
  - Group 3: 24h bright light (controls)

Results:
- Time to development of palpable tumors was 11, 9, and 5 days for groups 1, 2, and 3 respectively
- Tumour growth rates were similar in group 2 and 3 compared to group 1
  - Group 1: 0.72 g/d +/- 0.09
  - Group 2: 1.30 g/d +/- 0.15
  - Group 3: 1.48 g/d +/- 0.17

L-Theanine and sleep preparation
(gamma-ethylamino-L-glutamic acid)

- Unique amino acid from green tea
- Promotes relaxation through the generation of alpha-brain waves
- Immune modifier: Boosts innate immune resistance to infection (and perhaps tumors)
- Safety: extensively used in food in Japan since 1964 with no reports of adverse rx.
  - Safety in pregnancy not established
  - Interactions with medications not well studied
- Dose: 100-250mg before bed to calm and reduce sleep anxiety

L-Theanine reduces psychological and physiological stress responses

- L-Theanine blocks binding of glutamic acid (excitatory amino acid) to receptors in the brain
  - Could therefore influence psychological and physiological states under stress
- Study: 12 healthy individuals subjected to stress (mental arithmetic test) under 4 conditions:
  - L-Theanine taken at the start of experiment
  - L-Theanine taken midway
  - Two control trials using either placebo or nothing
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**L-Theanine reduces psychological and physiological stress responses**  

- L-Theanine resulted in ↓ heart rate (HR) and salivary immunoglobulin A (s-IgA) in response to stress
- These changes were attributable to decreased sympathetic nervous activation
- **Conclusion:** L-Theanine produces anti-stress effects and inhibits cortical neuron excitation

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**GABA (gamma-aminobutyric acid)**

- Most important and widespread inhibitory neurotransmitter in the brain  
  - Needed to inhibit over-stimulation  
  - Barbiturates and benzodiazepines stimulate GABA receptors
- Synthesis requires vitamin B6. Magnesium necessary for receptor binding
- **Supplements:** use for brain overload and sleep anxiety  
  - **Dose:** 500–2000 mg before bed on an empty stomach

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**Magnesium required for:**

- All energy-requiring metabolic processes  
  (ATP exists in cells primarily as MgATP)
- Protein synthesis
- Integrity of cell membranes
- Hormone and neurotransmitter synthesis and binding. Nervous tissue conduction
- Muscle relaxation following contraction

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**Magnesium and sleep**

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**Functional signs of chronic or acute magnesium deficits**

**Smooth muscle:**
- Shortness of breath
- Vascular headache
- Wheezing after exercise
- Frequency of urination
- Constipation

**Skeletal:**
- Leg cramps
- Muscle tension
- Fasciculations
- Myalgia
- Restless legs

**Cardiovascular:**
- Arrhythmias
- Palpitations
- ↑ Blood pressure

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**Magnesium – does anybody get enough?**

- **Daily adult requirement** 300–450mg
- **Average intake in North America** ~ 200mg
- **Foods richest in magnesium**
  - Nuts and legumes
  - Dark green vegetables
  - Whole grains
  - Seafood and meat
  - Chocolate (350mg per 8 oz bar!)
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The multifaceted and widespread pathology of magnesium deficiency
Johnson S. Med Hypotheses. 2001 Feb;56(2):163-70

**Magnesium is depleted by**
- Excess ethanol
- Excess dietary fat
- Excess salt and phosphoric acid (sodas)
- Profuse sweating (exercise, menopause)
- Intense, prolonged stress
- Excessive menstruation
- Most drugs deplete magnesium, esp. diuretics
- Physical, psychological and medical stress

**Identifying magnesium deficiency**
- Neither serum nor red cell magnesium are true indicators of tissue stores
  - only 1% total body Mg present in serum and this is tightly controlled
  - hypomagnesemia can occur when red cell magnesium is normal.
- Individual needs for magnesium hard to predict
  - Vary depending on stress levels, diet and medication use, and individual genetics
- Therefore a standard dosing regime may not provide optimal intakes for all individuals

**Correcting magnesium deficiency**
- Alternative approach is to gradually increase magnesium to bowel tolerance
  - A deficit will inhibit normal GI peristalsis, resulting in sluggish bowel function. This observation can be exploited to achieve optimal tissue stores
  - Excess will cause diarrhea
  - Aim for 2-3 soft, formed bowel movements daily
- Use amino acid or protein chelated forms
  - Better absorption and tissue retention

**Summary: Orthomolecular treatment of insomnia**
- **Optimal diet:**
  - High in vegetables and fruit
  - Low glycemic load
- Small sweet snack near to bedtime
- Sleep in complete darkness or wear an eye mask

**Summary: Orthomolecular treatment of insomnia**
- **Supplements:**
  - L-theanine for sleep induction
  - GABA for brain overload or sleep anxiety
- 5-HTP or Melatonin
  - Start with a low dose and increase gradually
- Optimize magnesium intake
  - Consider Epsom salt baths before bed