Orthomolecular Treatment for Insomnia

Aileen Burford-Mason, PhD

The Orthomolecular Treatment of Insomnia

Aileen Burford-Mason PhD

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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- Outdated concept: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

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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

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

- 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

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

- 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

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

- 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.

Sakami S et al. Neuroimmunomodulation. 2002-2003;10(6):337-43

- 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 autoimmunity

Coemergence of insomnia and a shift in the Th1/ Th2 balance toward Th2 dominance.

Sakami S et al. Neuroimmunomodulation. 2002-2003;10(6):337-43

- 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

Tuccori M et al. Drug Saf. 2008;31(12):1115-23

- 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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A single night of sleep deprivation increases ghrelin levels and feelings of hunger in normal-weight healthy men. *Schmid SM et al. J Sleep Res 2008;17(3):331-4*

- 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

A single night of sleep deprivation increases ghrelin levels and feelings of hunger in normal-weight healthy men. *Schmid SM et al. J Sleep Res 2008;17(3):331-4*

- Study: next day feelings of hunger, serum leptin and grehlin 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)

A single night of sleep deprivation increases ghrelin levels and feelings of hunger in normal-weight healthy men. *Schmid SM et al. J Sleep Res 2008;17(3):331-4*

- 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

Sleep and the epidemic of obesity in children and adults. *Van Cauter E, Knutson K. Eur J Endocrinol 2008 Aug 21.*

- 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 and the epidemic of obesity in children and adults. *Van Cauter E, Knutson K. Eur J Endocrinol 2008 Aug 21*

- 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

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

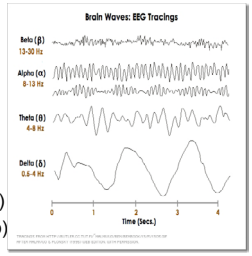
Note: picture in here of alpha waves

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

- Stimulates brain regions used in learning
  - Subjects taught a skill and then deprived of non-REM sleep can recall what they have learned after sleeping
  - Subjects deprived of REM sleep can not
- Important for infant brain development
  - Explains why infants spend more time in REM sleep than adults
- REM sleep helps boost next day mood

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

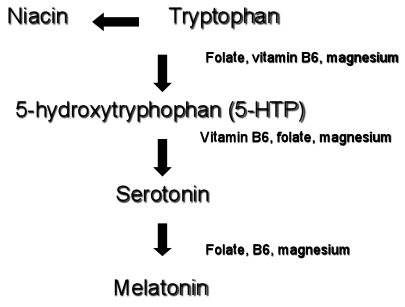
- Stimulating: facilitates sensory information accessing the brain
  - improves focus and concentration
- Antidepressant. Regulates mood, speech, focus and movement
- Made from tyrosine, a conditionally essential amino acid.
  - Synthesis requires B-vitamins (B3, B6, B12 and folic acid), vitamin C, magnesium, 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



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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

Dauchy RT et al. Lab Anim Sci. 1997 Oct;47(5):511-8

- 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)

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

Dauchy RT et al. Lab Anim Sci. 1997 Oct;47(5):511-8

- Study: All groups had tumours implanted at 12 weeks of age
- Results: Time to development of palpable tumours 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 modifyer: 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

Kimura K et al.Biol Psychol. 2007 Jan;74(1):39-45.

- L-Theanine blocks binding of glutamic acid (excitory 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

Kimura K et al.Biol Psychol. 2007 Jan;74(1):39-45.

- 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

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

Magnesium and sleep

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

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

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