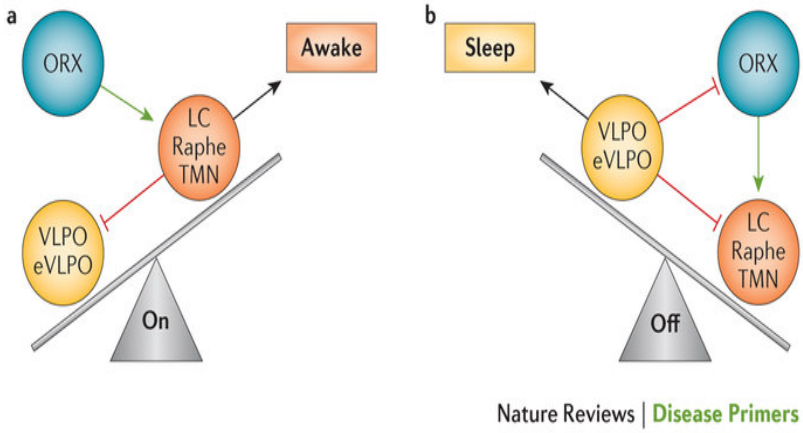
Sleep Physiology Highlights
How to Support Normal Sleep Patterns with ETI Formulas*

The goal of this article is to outline the major stages of normal sleep patterns, including the neuronal mechanisms that provide such, as well as to present current ETI formulas targeted to help with sleep problems.

Sleep plays a crucial role in human brain functioning and general physiology, including metabolism, appetite regulation and the functioning of immune, hormonal and cardiovascular systems (National Sleep Foundation, 2006). However, even after nearly 70 years of scientific research, it is still difficult to answer basic questions about sleep: "What is the state of the brain during sleep?" and "How does the brain and body control sleep?"



From https://www.researchgate.net/publication/282421003_Insomnia_disorder

ORX - the hypocretin/orexins system; VLPO - the ventrolateral preoptic nucleus; TMN - the tuberomammillary nucleus; Raphe - the raphe nucleus; LC - the locus coeruleus

Physiology of Sleep

Stages of Sleep

Stages of sleep have been generally divided into: one stage of rapid eye movement (REM) sleep and four stages (Stages 1–4) of non-rapid eye movement (NREM) sleep, which are categorized by increasing sleep depth (Rechtschaffen & Kales, 1968). Deeper sleep stages (Stages 3 and 4) are described as slow-wave sleep (SWS), which is believed to be the most restorative type of sleep (Rechtschaffen & Kales, 1968; Tasali, Leproult, Ehrmann &Van, 2008). REM and NREM sleep are associated with many physiological changes, involving "brain activity, heart rate, blood pressure, sympathetic nervous system activity, muscle tone, blood flow to the brain, respiration, airway resistance, renal function, endocrine function, body temperature, and sexual arousal" (National Sleep Foundation, 2006).

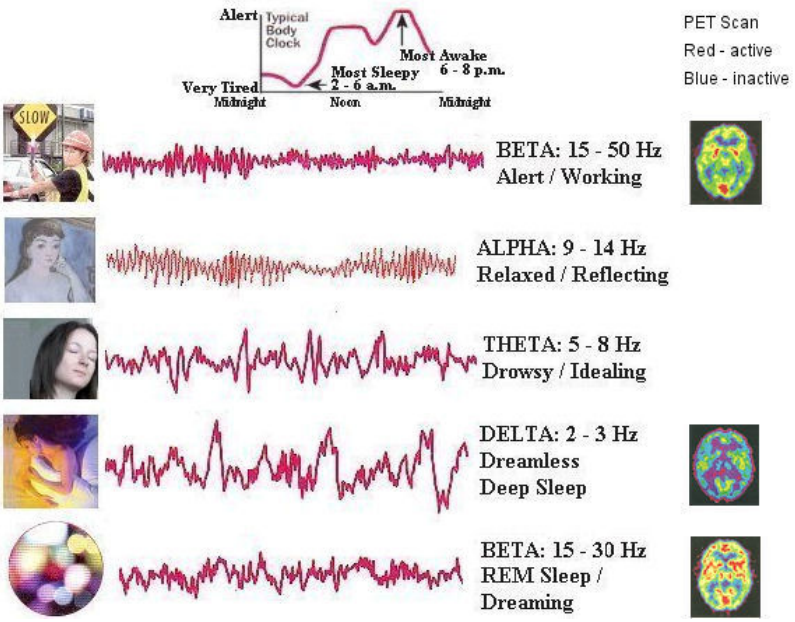
REM sleep is "an active period of sleep marked by the intense brain activity. Brain waves are fast and desynchronized, similar to those in the waking state. Breathing becomes more rapid, irregular, and shallow; eyes move rapidly in various directions and limb muscles become temporarily paralyzed. Heart rate increases and blood pressure rises. This also is the sleep stage in which most dreams occur" (National Sleep Foundation, 2006). REM sleep is assumed to "play a role in memory consolidation, the synthesis and organization of cognition, and mood regulation" (Bonnet, 2011).

NREM sleep is described as a decrease in physiological activity. As sleep deepens, a person's brain waves slow down and gain amplitude, both breathing and the heart rate slow down, and the individual's blood pressure drops. NREM sleep contains three stages (National Sleep Foundation, 2006):

"Stage 1 is a time of drowsiness or transition from being awake to falling asleep. Brain waves and muscle activity begin slowing down in this stage.

Stage 2 is a period of light sleep during which eye movements stop. Brain waves become slower, with occasional bursts of rapid waves and spontaneous periods of muscle tone mixed with periods of muscle relaxation. The heart rate slows and body temperature decreases.

Stages 3 and 4 is called 'slow wave sleep' (SWS) and is characterized by the presence of slow brain waves (called delta waves) combined with smaller, faster waves. Blood pressure falls, breathing slows, and temperatures drops even lower, with the body becoming immobile. It is most difficult to be awakened during SWS, and people may feel groggy or disoriented for several minutes after they wake up from this stage." For more details, see Picture 1.

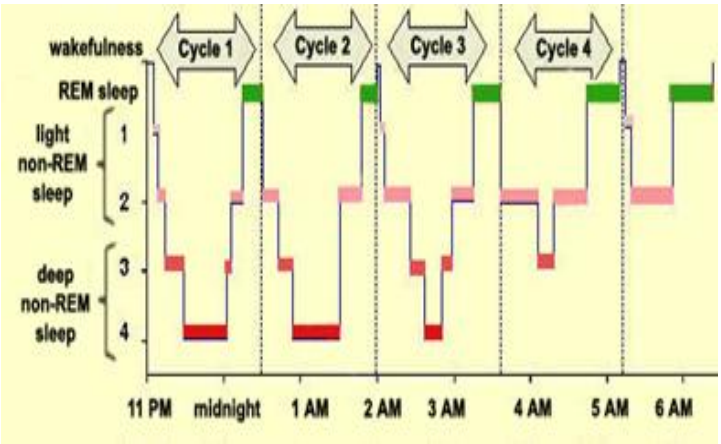


Picture 1. From https://universe-review.ca/R10-11-gradient02.htm

Beta waves occur during daily wakefulness. They have the highest frequency and the lowest amplitude, compared to other waves. These patterns also show a lot of variability.
Alpha waves occur during wakefulness and periods of relaxation (i.e., during meditation). These waves are slower, and have less amplitude and variability than beta waves.
Theta waves occur during stages 1 and 2 and are slower in frequency and greater in amplitude than alpha waves.
Delta waves occur during stage 3 sleep and are the slowest waves with the highest amplitude. Delta sleep is the deepest sleep.

Sleep Cycles

Sleep is divided into 90-minute cycles of rapid eye movement (REM) and non-rapid eye movement (NREM) sleep. These 90-minute cycles recur three to six times during the night. For more details, see Picture 2.



Picture 2. From http://healyourselfathome.com/HOW/NEWSTARTS/7_REST/stages_of_sleep.aspx

Sleep Effects

Sleep influences the body's major systems, involving thermoregulatory, musculoskeletal, endocrine, respiratory, cardiovascular, gastrointestinal, immune systems, mental health and general quality of life (Van Cauter &Tasali, 2011; Colten & Altevogt, 2006; Krueger & Obal, 2001).

The human body temperature is higher during the day and drops at night until around 4:00 AM, when it starts to rise again (Van Cauter &Tasali, 2011). "Most muscles relax during non-rapid eye movement (NREM) sleep and become atonic during rapid eye movement (REM) sleep, except for the ocular muscles and the diaphragm" (Colten & Altevogt, 2006). There are short increases in a person's blood pressure and heart rate during K-complexes, sleep arousals, and large body movements (Colten & Altevogt, 2006).

"Sleep and mood have a bidirectional relationship and mental health is both impacted by and impacts how well a person sleeps. Lack of sleep can be caused by other mental health (i.e., psychiatric) conditions that a person is experiencing, and can, in turn, impact those conditions of sleep" (Colten & Altevogt, 2006).

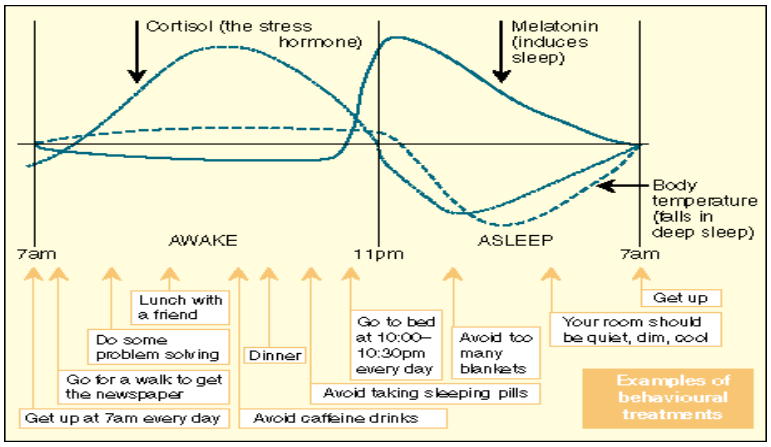
Many factors that regulate the immune response have also been shown to modulate sleep, especially non-rapid eye movement (NREM) sleep. For example, research data has shown "a bidirectional interaction between NREM sleep and both interleukin-1β (IL-1) and tumor necrosis factor-α (TNF)" (Krueger & Obal, 2001).

Age-dependent sleep changes have been shown to decline in total sleep time, sleep efficiency and SWS (Ohayon, et al., 2004).

The secretion of some hormones increases during sleep, such as growth hormone, prolactin and luteinizing hormone, while the secretion of other hormones, including thyroid stimulating hormone (TSH) and cortisol is suppressed (Van Cauter &Tasali, 2011). Growth hormone (GH) is normally secreted in the first several hours after the beginning of sleep and generally is released during slow-wave sleep (SWS). Cortisol is at its greatest heights in late afternoon; melatonin is released in the dark and is inhibited by light (Buxon, Spiegel &Van Cauter, 2002); thyroid hormone secretion happens in the late evening (Colten & Altevogt, 2006).

It has been proposed that overactivity of the hypothalamic-pituitary-adrenal (HPA) axis can affect sleep function and subsequently increase secretion of cortisol and norepinephrine, thereby encouraging wakefulness (Buckley & Schatzberg, 2005). For more details, see Picture 3.

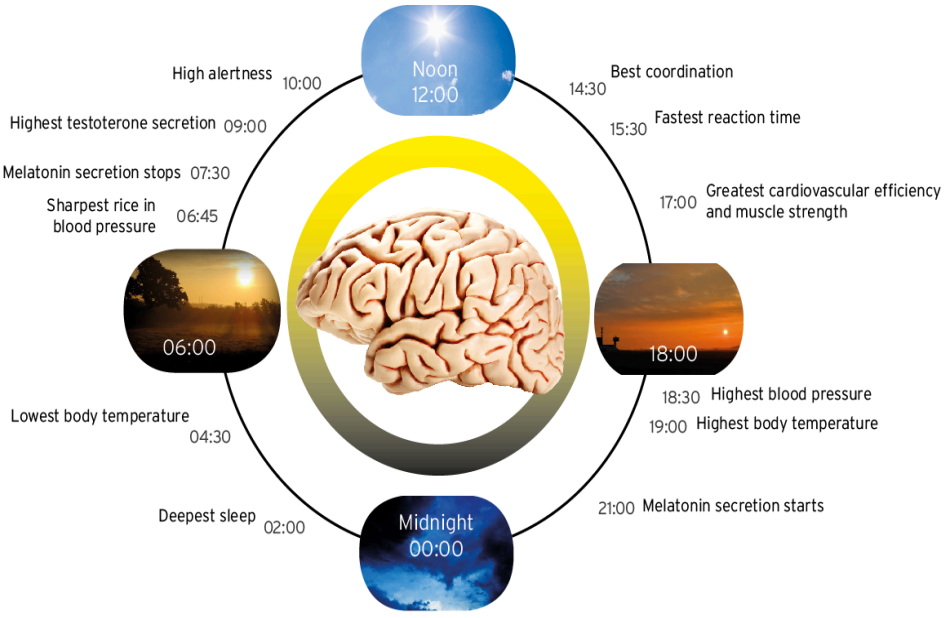
"Research indicates the amount of sleep a person regularly gets can also affect their health. "Adults who report getting 5 or fewer hours of sleep a night were 2.5 times more likely to have diabetes, compared to people who sleep 7 - 8 hours per night. Interestingly, people who sleep for 9 or more hours also have higher rates of diabetes, so perhaps both insufficient sleep and too much sleep are both unhealthy when it comes to insulin and the development of diabetes" (Colten & Altevogt, 2006).



Picture 3. From http://www.alphapw.com/category/sleeping/

Circadian Rhythms and Sleep

Circadian rhythms work to synchronize one's sleep pattern with a day and night cycle through the suprachiasmatic nucleus (SCN) of the hypothalamus, which gets direct input from nerve cells in the retina acting as intensity detectors.

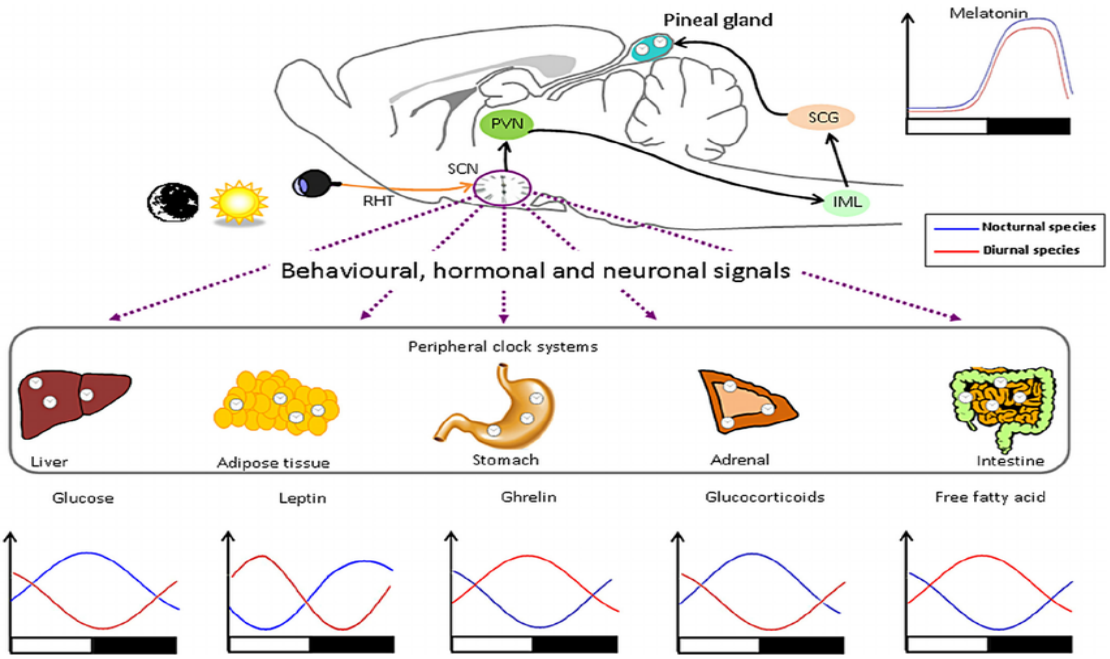


Picture 4. From http://gaininghealthnaturally.com/sleep-super-important-to-regulate-blood-sugar-levels/

"Light travels from the retina to the SCN, that signals the pineal gland to control the secretion of melatonin. This hormone acts to synchronize the circadian rhythms with the environment and the body through melatonin receptors in nearly all tissues. The SCN also works with a series of clock genes to synchronize the peripheral tissues, giving rise to daily patterns of activity.

Without time signals, individuals maintain a free-running biological rhythm that is usually just slightly longer than 24 hours" (Reppert & Weaver, 2002).

Communication and synchronization among SCN neurons is essential for generating a strong rhythm at the SCN's tissue level, which is communicated to other brain structures, thus influencing many of the body's functions (Albrecht, 2012). For more details, see Picture 5.



Picture 5. From https://www.researchgate.net/figure/272098829_fig3_Fig-3

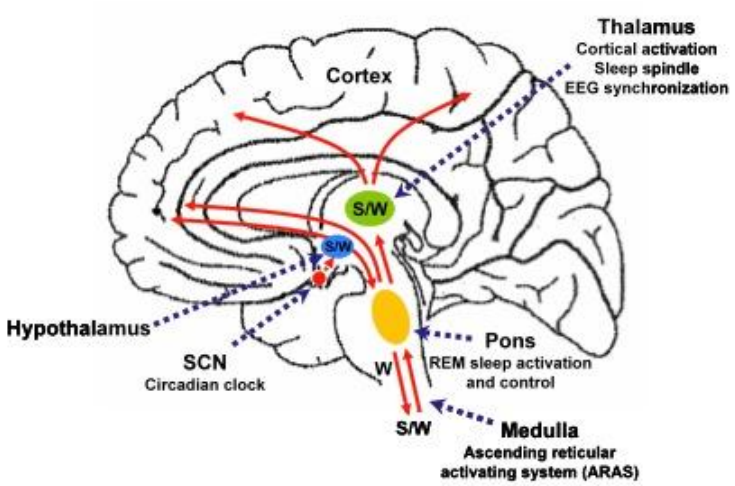
A reduced SCN rhythm has been shown to be related to a decreased amplitude of the behavioral activity rhythm and can lead to metabolic disorders. Also, an interrupted behavioral rhythm can negatively affect the amplitude of the SCN's rhythm (Knutsson, 2003; Kecklund & Axelsson, 2016).

Light is known to affect human chronobiology more than any drug on the market. Studies show a negative association between using electronic devices at night and sleep (Czeisler, 2013). According to a recently published study, using "a tablet at night just before sleeping while in bed induces circadian phase delay and melatonin suppression, alters sleep quality, and reduces cognitive performance in the subsequent morning" (Chang, et al., 2015).

The American Medical Association (AMA) recognizes that "disruption of circadian rhythmicity and sleep from the indiscriminate use of electric light at night may well increase risk of many of the diseases of modern life, including not only certain cancers, but also obesity, diabetes, and psychiatric disorders" (Stevens R., et al., 2013).

Neuronal Subgroups and Sleep Homeostasis

The hypothalamus is a multifunctional center that regulates circadian, sleep and feeding behaviors, as well as incorporates central and peripheral neuroendocrine, endocrine and peptide signals (Saper, 2006; Chou, et al., 2003). "The bodily homeostatic mechanisms and sleep homeostasis rely on the complex integrative activity of various neuronal subgroups within the hypothalamus: 1) the sleep regulation center's ventrolateral preoptic nucleus (VLPO); 2) the paraventricular nucleus (PVN) containing the neurons that synthesize corticotropin-releasing hormone (CRH) and neurons that mediate preganglionic output to the autonomous nervous system; and 3) the lateral hypothalamus, an area that contains the hunger-stimulating and wakefulness-promoting peptide orexin (hypocretin) and melanin-concentrating hormone (Saper, 2006).



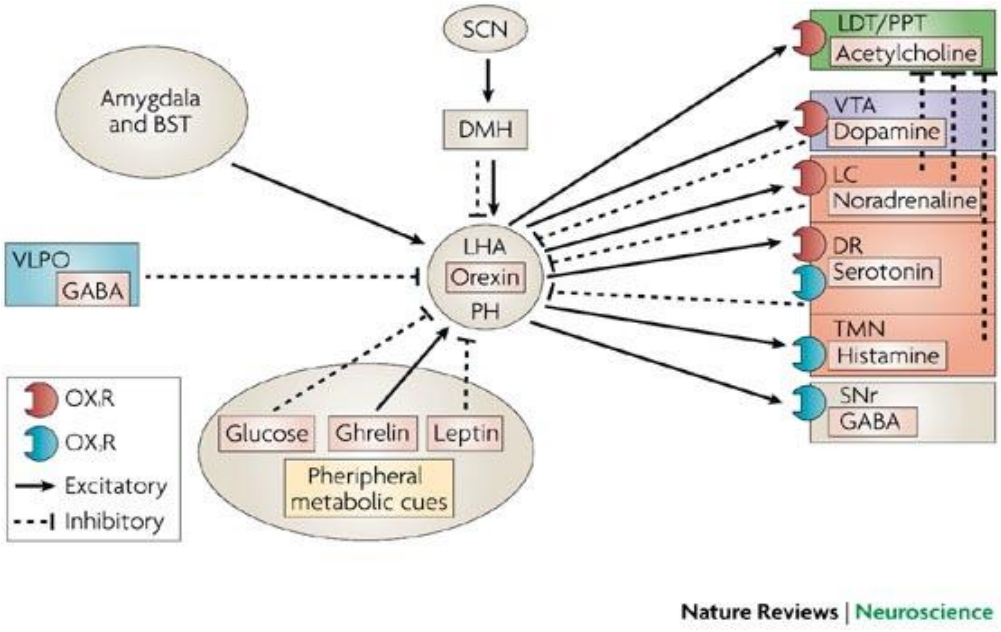
Picture 6. From http://sleepdisorders.sleepfoundation.org/chapter-1-normal-sleep/neurobiology-of-sleep/

At the end of the day, the circadian awakening signal declines, permitting the homeostatic sleep drive to begin prevailing. As the homeostatic drive increases, neurons in the median and ventrolateral preoptic (VLPO) areas of the anterior hypothalamus become more active. "These neurons use the inhibitory neurotransmitters γ-aminobutyric acid (GABA) and galanin. GABA and galanin inhibit all wake-promoting areas in the lateral hypothalamus, posterior hypothalamus, and brain stem arousal centers, leading to the onset of sleep" (Saper, Chou & Scammell, 2001).

The Orexin System

Orexin A and B are excitatory hypothalamic neuropeptides that participate in many physiologic functions, such as "sleep/wake rhythms and thermoregulation, control of energy metabolism, cardiovascular responses, feeding behavior, and spontaneous physical activity (SPA)" (Thannickal, et al., 2000). Mostly located in the perifornical region of the lateral hypothalamus, orexin is found in two forms: the neuropeptide orexin A and orexin B (Sakurai, et al., 1998; de Lecea, 1998). The orexin system has a wide distribution of cognate receptors on central, as well

as peripheral targets, thus controlling many physiological mechanisms, such as feeding, energy metabolism, arousal, onset of REM, reward and autonomic function (Burdakov, 2013; de Lecea, 2014; Karnani & Burdakov, 2011; Mahler, et al., 2012; Nixon, et al., 2015). This system is believed "to stabilize the flip-flop switch off, and thus consolidates states of wakefulness and sleep" (de Lecea, 2014). Clinical studies have confirmed the importance of orexin signaling in human pathophysiology, as malfunctions in this system can lead to conditions such as narcolepsy (Peyron, et al., 2000), obstructive sleep apnea (OSA) (Ahmed, et al., 2012; Baumann, 2012), post-traumatic stress disorder (Strawn, et al., 2010), insomnia and age-related fluctuations in sleep and energy spending (Hara, et al., 2001). For more details, see Picture 6.



Picture 7. The orexins activity is modulated by their specific receptors (OX1R, OX2R) and transmits signals throughout the G-protein class activating a cascade that leads to an increase in intracellular calcium concentration.

In particular, GABA (Xie, et al., 2006), noradrenaline and serotonin appear to inhibit the activity of orexin neurons (Yamanaka, et al., 2003). Furthermore, agonists of ionotropic glutamate receptors have been shown to excite orexin neurons, while glutamate antagonists, according to research, reduce their activity (Li, Gao, Sakurai & van den Pol, 2002), demonstrating that glutamatergic neurons can activate orexin neurons. The orexin system appears to be critical for maintenance of the wakefulness state, as demonstrated by studies indicating narcolepsy is caused by an orexin deficiency in human and animals (Chemelli, et al., 1999; Lin, et al., 1999). "Narcolepsy is the result of orexin-containing neurons loss, which tends to increase their activity during wakefulness activating aminergic nuclei such as locus coeruleus, raphe nuclei, and tuberomamillary nucleus with maintaining a wake state and preventing of the inappropriate transitions into sleep" (Saper, Chou & Scammell, 2001).

Sleep-Associated Disorders

Insomnia

Insomnia is defined as a persistent difficulty falling or staying asleep, and is associated with a significant weakening in function or reduced quality of life (American Psychiatric Association, 2013; Ohayon & Reynolds, 2009). Multiple data suggest that insomnia is generally associated with a state of hyperarousal, which contains changes involving activation of the sympathetic nervous system and reduced homeostatic drive for sleep. It should be noted some authors consider that insomnia is an adaptive aspect under circumstances of noticed threat (Edinger, et al., 2008; Edinger, Means & Krystal, 2013).

Narcolepsy

A person with the condition of narcolepsy experiences excessive daytime sleepiness. Evidence suggests this condition possibly involves an autoimmune route, specifically autoimmune damage of the hypocretin (orexin) neurons in the hypothalamus (Faraco, et al., 2013). Several studies have recognized genetic alternatives linked with narcolepsy, including variants in the human leukocyte antigen loci that are involved in immune responses (Partinen, et al., 2014). Infectious mediators are also thought to act as an environmental trigger for narcolepsy (Faraco, et al., 2013). "Potential links to H1N1 influenza have received the most attention, including potential triggers by influenza vaccines. Following the vaccination campaign against the H1N1 epidemic in 2009–10, increased cases of narcolepsy were reported in Europe" (Partinen, et al., 2014). Also, high levels of antibodies to *streptococcus pyrogenes* have been related to narcolepsy (Mignot, 1998).

Circadian rhythm disorders

Circadian rhythms are created by a set of core clock genes and the molecular machinery that exists in the suprachiasmatic nucleus (SCN), and in cells throughout the body (Partch, Green & Takahashi, 2014). Recent data demonstrate strong evidence that the timing of sleep and sleep deprivation can have an intense influence on the circadian rhythms (Archer & Oster, 2015). It is now known that circadian rhythm disorders have a genetic basis that is modified by age-related and environmental factors. "Perspectives from evolutionary medicine include the concept of evolutionary mismatch, where changes in environments and lifestyles today differ from those in our ancestral past in ways that create new health problems. Potential sources of mismatch include: more widespread use of electrical lighting and new social connectivity enabled by technology; populations that live at exceptionally high densities, resulting in sleep disruptions due to noise and perceived risks at night; changes in other dimensions of health that may impact sleep, such as rising rates of obesity; and changes in diverse sleep practices" (Jones, et al., 2013).

Effects of disrupted sleep on hormones and metabolism

Sleep shortening is associated with "dysregulated neuroendocrine control of appetite that includes a reduction of the satiety factor leptin, an increase in the hunger-promoting hormone ghrelin, and an increase in daytime levels of endocannabinoids" (Reutrakul & Van Cauter,

2014). Sleep loss may modify the capability of leptin and ghrelin to work correctly, producing an internal result of inadequate energy availability.

Disrupted sleep and reward networks in the brain

Research has shown specific benefits result from sufficient amounts of sleep. "Neuroimaging, neurophysiological, and clinical studies suggest that emotional and reward networks are activated during sleep. Such activation may promote the reprocessing of emotional or rewarded information during sleep and dreaming and optimize affective regulation and behavioral responses during wakefulness" (Perogamvros & Schwartz, 2012).

Disrupted sleep and neurodegenerative diseases

A recent study found that patients with Alzheimer's disease (AD) still have clock gene expression in multiple brain regions, the cingulate cortex and the pineal gland, but for them there is "a loss of typical phase coherence within regions, and of phase relationships between regions" (Cermakian, et al., 2013).

Parkinson's disease (PD) includes damage of multiple wake-active neuronal populations (Stern & Naidoo, 2015), as well as the decrease of hypothalamic hypocretin neurons in the numbers. (Fronczek R, et al., 2007).

Huntington's disease (HD) is a progressive sleep disorder with reduced sleep efficiency and total sleep duration (Goodman & Barker, 2010; Aziz, et al., 2010). Human patients with HD have demonstrated a substantial loss of vasopressin, oxytocin and hypocretin neurons (Goodman, et al., 2011; Morton J, et al. 2005).

Sleep Support Based on ETI Formulas

The following specific combinations of ETI formulas are suggested for different sleep-related conditions, with the understanding that practitioners should take the liberty to fine-tune dosages and periodicity of the client's intake, as well as to combine different formulas to create a personalized approach to the individual client to support his/her normal sleep pattern.

Also, it is viewed as essential to energetically harmonize and clean the environment where the client is sleeping. ETI Formula Clean Sweep has proven to be an excellent choice for this purpose.

1. *Difficulty in falling asleep, when it is accompanied with stress and a pattern of overactive thoughts*

Description: Helps to decrease symptoms of transient and short-term sleeplessness, due to any stressful life experience, disturbance of one's sleep schedule, or an unconducive sleep environment, accompanied with a pattern of overactive thoughts.

Formulation and Dosage:
During the day. Combined dosage of Stress Relief (10 drops) and Adaptogen (5 drops) in 2-4 oz. of water. Drink in the morning and in the middle of the day; continue up to two weeks.
At night. Combined dosage of Jujube Sleep Aid (10 drops) and Clear Mind + Iron (5 drops) in 2-4 oz. of water. Drink about one hour before bed; continue up to two weeks.

Precautions. Increase the amount of water, up to 4-6 oz., for individuals with GI sensitivity to minerals in the solution.

2. Difficulty in falling asleep, when it is accompanied with excessive worry and/or emotional distress

Description: Helps to decrease symptoms of generalized sleeplessness, due to a high level of stress, accompanied with panic disorder and/or social anxiety disorder.

Formulation and Dosage:
During the day. Combined dosage of Adrenal Support (10 drops) with Stress Relief (5-10 drops) in 2-4 oz. of water. Drink in the morning and in the middle of the day; continue up to two weeks.
At night. Combined dosage of Goodnight (5 drops), Stress Relief (5 drops) and Adrenal Support (5 drops) in 2-4 oz. of water. Drink about one hour before bed; continue up to two weeks.

Precautions: Increase the amount of water, up to 4-6 oz., for individuals with GI sensitivity to minerals in the solution.

3. Difficulty in falling asleep, when it is accompanied with pain

Description: Helps to effectively, energetically support a person's normal sleep pattern through decreasing some nonspecific pain symptoms.

Formulation and Dosage:
During the day. Combined dosage of Vital360 (10-20 drops) with Stress Relief (5-10 drops) in 2-4 oz. of water. Drink in the morning and in the middle of the day or when it is necessary to decrease the pain level.
At night. Combined dosage of Goodnight (5 drops), and Stress Relief (5 drops), and Vital360 (5 drops) in 2-4 oz. of water. Drink before bed; continue up to two weeks.

Precautions: Increase the amount of water, up to 4-6 oz., for individuals with GI sensitivity to minerals in the solution.

4. Nighttime sleep disruption, when it is accompanied with nocturnal hypoglycemia

Description: Helps to effectively, energetically support exhausted adrenal glands that are stressed out by anxiety or fatigue, pain, fear, relationship stress, money stress, work stress or old abuse stress, and thereby energetically support the blood sugar level at night.

Formulation and Dosage:
During the day. Combined dosage of Adrenal Support (10 drops) with Stress Relief (5 drops), and GI Aid (5 drops) in 2-4 oz. of water. Drink in the morning and in the middle of the day; continue up to two weeks.
At night. Goodnight – 15 drops in 2-4 oz. of water. Drink before bed; continue up to two weeks.

Precautions: Increase the amount of water, up to 4-6 oz., for individuals with GI sensitivity to minerals in the solution.

5. *Difficulty in falling asleep, when it is accompanied with restless leg syndrome*

Formulation and Dosage:
At night. Combined dosage of Goodnight (10 drops), Magnesium (3-5 drops), and Vital360 (10 drops) in 2-4 oz. of water. Drink before bed time; continue up to two weeks.

Precautions: Increase the amount of water, up to 4-6 oz., for individuals with GI sensitivity to minerals in the solution.

6. *Fragmentation of sleep, waking unusually early*

Description: Hypothalamus-pituitary-adrenal (HPA) axis hyperactivity can lead to the fragmentation of sleep, decreased slow-wave sleep, and shortened sleep time (Herman & Cullinan, 1997). To complicate matters, sleep disturbances can worsen HPA axis dysfunction, thereby worsening the whole sleep cycle. This pattern requires the energetic balance of the HPA axis during the day, as well as an energetic support of the shift to the sleep homeostasis pattern in the evening.

Formulation and Dosage:
During the day. Combined dosage of Hypothalamus Support (5 drops) with Adrenal Support (5 drops), and Stress Relief (5 drops) in 2-4 oz. of water. Drink in the morning and in the middle of the day; continue up to two weeks.
At night. Jujube Sleep Aid – 5-10 drops at 6 pm and 5-10 drops at 8 pm; continue up to two weeks.

Precautions: Increase the amount of water, up to 4-6 oz., for individuals with GI sensitivity to minerals in the solution.

∗ **Disclaimer:**

(i) The preceding information is provided for educational purposes only.

(ii) These statements have not been evaluated by the Food and Drug Administration (FDA). The information provided is not intended to diagnose, treat, cure or prevent any diseases or medical problem

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