

# Nutritional Modulators of Sleep Disorders

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**Abstract:** *Background:* Clinical evidence indicates that insufficient sleep and poor sleep quality appear to be common consequences of shift work. These rhythms appear to have independent influence on the function of the endocrine system, circadian brain function and gastrointestinal tract. Insufficient sleep and its poor quality due to shift work interfere with beta cells, leptin and ghrelin functioning, resulting in factors for the development and exacerbation of insulin resistance. Human studies found that insufficient sleep alters the levels of leptin and ghrelin, two hormones involved in the regulation of appetite and body fat. Leptin, released by fat cells, signals the brain to feel satiety. Ghrelin, produced in the stomach, signals hunger. Investigations reported that temporarily sleep-deprived individuals experienced hormonal changes along with greater cravings for sweet and fatty foods. A further reason for their cravings is related to the stress hormone cortisol, which can rise with sleep deprivation and contribute to hunger. In addition to altered hormone levels, people who stay awake longer have more opportunity to eat, and late-night eating often includes high-caloric foods. Weight gain is only one of the many side effects of insufficient sleep, but it can lead to long-term health problems, including diabetes. Although more sleep will not automatically result in weight loss, sufficient sleep and a regular sleep schedule are critical in controlling appetite and promoting a healthy eating pattern. Research on sleep and appetite reveals a consistent link between a lower amount of sleep and a higher body mass index (BMI), a ratio of weight-to-height that indicates overweight. Studies showed those who slept less than eight hours a night were more likely to be overweight.

*Methods:* Internet search and discussion with colleagues.

*Results:* Recent research indicates that disruption of sleep can influence food intake and food and nutrients can influence sleep. There is evidence that high protein and carbohydrates meals can influence moods, attention and concentration among normal adult subjects with respect to age, gender and meal time. Women reported greater sleepiness after two hours of carbohydrate meal as opposed to a protein meal. On the other hand men reported greater calmness after a carbohydrate as opposed to a protein meal. Age of subjects may also influence the response to meals. After a carbohydrate or protein rich breakfast, persons older than 40 years felt more tense and less calm with a protein-rich than carbohydrate-rich meal. In general older subjects preferred carbohydrate than protein meals. Carbohydrate meals are also reported to impair objective performance; carbohydrate rich foods either in breakfast or lunch have exhibited negative influence on neural response such as impaired objective performance and poor sustained attention. A meal consumed close to bedtime is associated with sleep disturbances. Further, solid foods as well as large meals may cause more sleepiness than liquid foods. Studies have also shown that the larger the meal, the sleepier the person thereafter. In the evening the sleep-facilitating effects of carbohydrates may be beneficial. However, manipulation in the energy content of meals for a single day may cause increase in markedly different levels of insulin without changes in plasma glucose.

*Conclusions:* The findings indicate that food intake can influence sleep and disruption of sleep can cause increased consumption of fast ready-prepared foods which have adverse effects resulting in obesity, diabetes and CVDs.

**Keywords:** Late night sleep, nutrition, food, circadian, herbs, CNS-ENS interaction.

## INTRODUCTION

In developed countries, mortality due to non-communicable diseases (NCDs) is about 80% of total deaths

and in developing countries, 60% deaths occur due to these problems [1]. Exposure to traditional occupational hazards; toxic chemicals, temperature extremes, and noise have been minimized to the extent that they now represent a modest risk to Western world populations but in developing countries these environmental factors continue to be an important cause of morbidity and mortality [1, 2]. In middle income countries, these problems are enormous. Apart from

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these factors, diet and lifestyle factors of the populations and other characteristics of the workplace where they work and live, such as work design, organization, management, and their societal contexts appear to be important in the pathogenesis of NCDs [1-5]. In this connection, shift work altering the circadian rhythm of sleep, appears to be an important occupational factor that has potential health implications [2-16]. Shift work indicating disturbance in sleep rhythm, can be classified in one of two ways. In rotating shift work, the employee's hours of work change in to morning, afternoon, and night shift. In permanent, the work pattern may be constant but occupy unusual hours of the day. In developed countries, around one-fifth of workers may have irregular working schedules which may have adverse effects on sleep, resulting in to NCDs [2-15].

There are biologically plausible reasons to anticipate a link between shift work and NCDs; obesity, type 2 diabetes mellitus, hypertension and coronary artery disease (CAD) (Fig. 1). Circadian clocks, located both in the suprachiasmatic nucleus of the hypothalamus and peripheral tissues, regulate this circadian with the normal synchrony between the light-dark cycle [2-4]. Alteration in sleeping and eating may cause a mismatch of circadian rhythms, triggering a cascade of biological changes that have potential effects on brain body connections that influence the human homeostatic systems. The body systems adapt to daily changes in light and dark such that the body anticipates periods of physical exertion and sleep [2-4]. Circadian disruption may accelerate development of NCDs in predisposed subjects and populations [3-6, 8, 9, 11-15]. Clinical evidence indicates that insufficient sleep and poor sleep quality appear to be common consequences of shift work [3-6, 8-9, 11-15]. These rhythms appear to have independent influence on the function of the endocrine system, circadian brain function and gastrointestinal tract [2-6, 8, 9, 11-15]. Insufficient sleep and its poor quality due to shift work interfere with beta cells functioning resulting in to risk factors for the development and exacerbation of insulin resistance [9-13, 16]. Sleep disorders may cause increases in appetite, polyphasia leading to adiposity [8, 15]. A recent meta analysis of eight longitudinal studies showed a strong association between shift work and weight gain, a major risk factor for CVDs and diabetes [8, 15]. There may be behavioral changes potentially associated with shift work, such as increased consumption of ready prepared fast foods rich in trans fat, saturated fat, w-6 rich oils and refined carbohydrates. Reduction in physical activity could independently contribute to biological processes predisposing to NCDs. It is possible that nutritional factors may have important role in the pathogenesis of sleep disorders by their influence on gut brain connections [2, 4, 5, 9].

### **SLEEP DISORDERS AND RISK OF NONCOMMUNICABLE DISEASES**

Sleep disorders are associated with increased intake of refined and preserved foods in conjunction with decreased physical activity which results in to obesity [8]. Meta analysis of eight articles on shift work and obesity that met the inclusion criteria [15]; five of them were considered to be high- and three of them low-quality studies. Five studies presented weight-related outcomes adjusted for potentially relevant confounders (age, gender, bodyweight at baseline,

and physical activity). Strong evidence for a crude association between shift work exposure and body weight increase was found. In order to further clarify the underlying mechanisms, more and better high quality studies about this subject are necessary [15]. Obesity is a potential risk factor for diabetes mellitus therefore sleep disturbance due to shift work can also predispose type 2 diabetes [9-13]. (A longitudinal study was carried out on a day-shift work group (n = 3203) and alternating-shift work group (n = 2426) of a steel company in Japan who received their annual health checkups over a 10-year period between 1991 and 2001(9). The association between job schedule type and onset of diabetes mellitus (glycated hemoglobin A1c > or =6.0% or medication) was investigated by multivariate pooled logistic regression analyses. The odds ratio (95% confidence interval) for the development of diabetes mellitus in the alternating shift work group compared with the day shift work group was 1.35 (1.05-1.75). The study revealed that the alternating shift work is an independent risk factor for the onset of diabetes mellitus [12]. Morikawa *et al.*, from Japan also reported that male factory workers on shift work, showed increased risk of type 2 diabetes mellitus [10]. The Nurses' Health Study [11] examined association between rotating shift work (>3 nights/month plus days and evenings) and type 2 diabetes mellitus among 177,000 female nurses, aged 25-67 at baseline followed up for up to two decades. This large-scale study revealed a graded association between the duration of working life of the nurses engaged in shift work and risk of developing diabetes. Compared with women who reported no shift work, participants with 1-2 years of shift work had a 5% excess risk of type 2 diabetes mellitus, rising to 20% after 3-9 years, 40% after 10-19 years, and almost 60% for >20 years [11]. The mechanism underlying early-onset diabetes was due to accelerated loss of beta-cell function and loss of beta-cell mass attributed to increases in beta-cell apoptosis. Disruption of circadian rhythms may increase the risk of diabetes by accelerating the loss of beta-cell function leading to insulin resistance which is characteristic in type 2 diabetes and CVDs [9, 13].

Sleep disorders due to shift work or because of other reasons have been associated with elevated blood pressures, coronary artery disease (CAD) and decreased heart rate variability (HRV), factors that may increase the long-term risk of cardiovascular-related mortality and morbidity [2-4, 6]. Meta-analysis of prospective cohort studies indicating quantitative estimates of the association between work stress and incident CAD or CVD mortality was carried out by Kivimaki *et al.*, [15]. These workers assessed 14 cohort studies including, 83 014 employees, the age- and gender-adjusted RR of CAD for high versus low job strain was 1.43 (95% CI) 1.15-1.84, but the ratio decreased to 1.16 (95% CI) 0.94-1.43) after adjustment for risk factors and potential mediators. The age- and gender-adjusted RR for a combination of high efforts and low rewards was 1.58 (95% CI) 0.84-2.97) for 11 528 employees, and no further reduction in RR was observed when other factors were considered. For organizational injustice, among 7246 subjects, the age- and gender-adjusted, and multiple-adjusted RR were 1.62 (95% CI) 1.24-2.13) and 1.47 (95% CI) 1.12-1.95), respectively. The data suggest an average 50% excess risk for CAD among employees with work stress. Lo *et al.*, from Taiwan reported that shift-work may be associated with elevated

blood pressure (BP) and decreased heart rate variability (HRV) [16]. This study explored the effect of shift-work on dynamic changes in autonomic control of HRV (cardiac stress), systolic blood pressure and diastolic blood pressure, (vascular stress), and recovery in the same subjects working different shifts. The authors recruited 16 young female nurses working rotating shifts--day (08:00-16:00 h), evening (16:00-00:00 h), and night (00:00-08:00 h)--and 6 others working the regular day shift. Each nurse received simultaneous and repeated 48-h ambulatory ECG and BP monitoring during their work day and the next off-duty day. While working the night shift, the nurses showed significant increases in vascular stress, with increased SBP of 9.7 mm Hg. The changes of SBP and DBP peaked during waking time at the same time on the day off as they did on the working day. Whereas HRV profiles returned to baseline level the SBP and DBP of night shift workers remained significantly higher. ( $p < .001$ ). It is possible that sleep disorders can influence eating patterns as well as diet and nutrients can have their influences on sleeping pattern. Several metabolic pathways were identified to be influenced by short sleep; the chronic sleep loss or restriction seems to adversely affect carbohydrate metabolism and appetite regulation [17, 18].

### EFFECT OF MEALS ON SLEEP

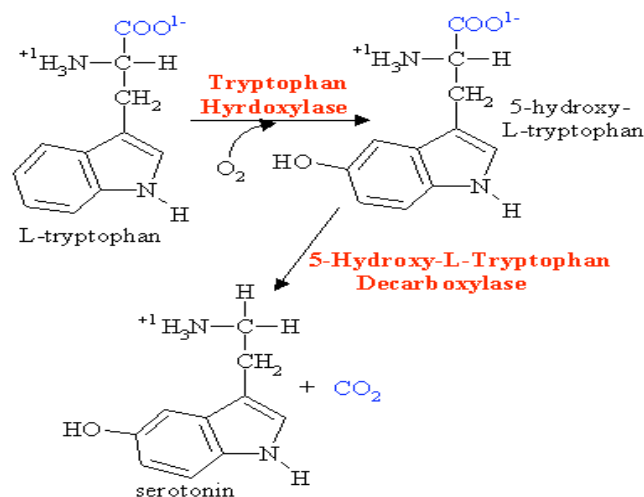
Clinicians treating narcoleptics have reported that rapidly absorbing carbohydrates induce sleepiness in the afternoon among their patients. While studies with normal individuals using different foods demonstrated that, carbohydrates at lunch induce afternoon sleepiness more than proteins [19]. Spring *et al.*, conducted a detailed study about the effects of high protein and carbohydrates meals on moods, attention and concentration among normal adult subjects [20]. Their results were interesting with respect to age, gender and meal time. Women reported greater sleepiness after two hours of carbohydrate meal as opposed to a protein meal. On the other hand men reported greater calmness after a carbohydrate as opposed to a protein meal. Age of subjects was also found to influence the response to meals; after a carbohydrate- or protein-rich breakfast, persons older than 40 years felt more tense and less calm with protein-rich than carbohydrate-rich meal. In general older subjects preferred a carbohydrate meal than a protein meal. Carbohydrate meals are also reported to impair objective performance; carbohydrate-rich foods either in breakfast or lunch have exhibited negative influence on neural response such as impaired objective performance and poor sustained attention [21].

### Glycemic Index

The mechanism by which a high GI carbohydrate meal shortens Sleep Onset Latency (SOL) is currently unknown. However Afaghi *et al.*, hypothesized a possible mechanism. According to them, high-GI carbohydrate meal alters plasma concentration of insulin and tryptophan to large neutral amino acid (LNAAs) and the ability of tryptophan to entry into the brain. The entry of tryptophan is competitive against LNAAs and forms the major precursor for brain serotonin [22]. It is now known that the plasma tryptophan:LANN ratio is affected by both dietary carbohydrates and dietary protein. The metabolic effects of glucose feeding on sleep are well documented. During late 1970 and early 1980, studies demonstrated that after consuming rapidly absorbing

carbohydrates or after a glucose tolerance test, insulin is rapidly increased. This rapid increase of insulin is associated with an increase in the ratio of tryptophan to large neutral amino acids (LNAAs) causing abnormal neuroglycopenic symptoms, this was referred as "sugar drunkenness." Afaghi *et al.*, also demonstrated recently the effect of glucose release from rice meal on SOL. According to the study, a high-GI (HGI) meal given 4h before bedtime significantly shortened SOL by 48% compared to a low-GI meal given 4 h before bedtime. Further HGI meal given 4 and 1 h before bed time brought about a significant difference in SOL with a mean difference of 38.3%. It is demonstrated 2 to 4 hours after ingestion of a high carbohydrate meal, a peak occurs in the ratio of free tryptophan to branched-chain amino acids, which induces the changes [22]. These findings have been supported by several studies from different regions, suggesting an effective non pharmacologic approach to the management of insomnia to be valuable; against the notorious side effects of medications for inducing sleep [23]. Warm milk is known to help individuals to sleep, contains tryptophan; tryptophan hydroxylase converting it to 5-hydroxytryptophan (5-HTP) i.e., an intermediate metabolite of L-tryptophan in the serotonin pathway an outline for which is shown in Fig. (1). Therapeutic doses of 5- HTP is found to be an effective supplement in individuals with a deficiency of this enzyme converting L-tryptophan to 5-HTP, the rate-limiting step in serotonin synthesis. Factors such as stress, insulin resistance, vitamin B6 deficiency, and hypomagnesemia inhibit tryptophan hydroxylase [24].

The reduction in free fatty acid (FFA) is modulated through the increased load of insulin that follows glucose ingestion. A similar metabolite effect has been demonstrated after a HGI meal. The effect of alternating plasma glucose concentration has been suggested to influence sleep. Scheen and colleagues reported glucose infusion during the early nocturnal sleep [25]. Therefore the amount of food eaten and manipulation of dietary intake may affect sleepiness as well as sleep onset latency. There has been fragmented evidence about different nutrients influencing sleep and the effect of essential fatty acids and essential amino acid especially the tryptophan [26].



**Fig. (1).** Synthesis and metabolism of serotonin from tryptophan (5-HT).

The timing of meals is also known to influence sleep. A meal consumed close to bedtime is associated with sleep disturbances [19]. Further solid foods are reported to cause more sleepiness than liquid foods. Studies have also shown that the larger the meal, the sleepier the person thereafter [27]. It is postulated that filling the stomach with plenty of food might have a stronger effect than the constituents of the meal. In the evening the sleep-facilitating effects of carbohydrates may be beneficial. However, Driver and co-workers manipulated the energy content of meals for a single day and reported markedly different levels of insulin without changes in plasma glucose [28]. In this study, there was no influence of dietary intake and the associated metabolic changes on markers of sleep. The authors suggested a degree of plasticity in the sleep response to changes in total energy intake. In this study, the amount of protein did not differ in the diets, possibly suggesting a role for the composition of the diet rather than total energy content. More extreme dietary conditions may result in more significant alterations in sleep. There is some evidence showing that essential fatty acids may modulate sleep. Fagioli from Italy studied eight children who were fed on total parenteral nutrition without essential lipids and seven other children who received a daily supplement of essential lipids in their parenteral nutrition [29]. Slow-wave sleep was significantly decreased in the group of children who did not receive fatty acids as compared to those who did [30].  $\omega$ -3 Fatty acids are also necessary for early brain development and infant sleep. Cheruku *et al.*, measured plasma docosahexaenoic acid (DHA) from 17 women at parturition [31]. They found a significant positive correlation with concentration of DHA and quality of the newborn infants' sleeping patterns as measured by a sleep mattress method. This is thought to relate to more mature brains of the newborn infants.

A vegetarian diet with high fiber and slowly absorbing carbohydrates induce alertness during waking time. Some of the positive effects are explained by antioxidant effects of different phytochemicals, but also the effects certain neurotoxic molecules at low levels (subtoxic) cause alertness [32]. This is of interest to sleep specialists because antidepressants are also used in treating insomnia, especially if it is thought to be associated with underlying depression. More research is recommended to find out if natural substances affect sleep-wake behavior. Spices may also affect sleep, perhaps by a neurohormonal action. In one study on six young men, chilies and mustard in the evening meals reduced slow-wave and stage 2 sleep, reduced total time awake, and prolonged sleep onset. The spicy food in the evening has been demonstrated to elevate body temperature during the first sleep cycle; it could be possible that capsaicin affects sleep by increasing body temperature [33].

### **Nutrition and Fatigue**

Nutrients are known to influence fatigue. Studies on observational behaviors report changes in fatigue-relating symptoms correlating with changes in plasma component of insulin, glucose and amino acids. Carbohydrate meals especially significantly increase fatigue [34]. There is some evidence that rapidly absorbing carbohydrates in particular cause more sleepiness and fatigue after lunch than slowly absorbing carbohydrates and proteins. Fatiguing effects

of the post carbohydrate-rich lunch initiate with a corresponding increase in plasma tryptophan and terminate much before the tryptophan levels decrease. Hence fatigue after a high-carbohydrate lunch could not be explained by reactive hypoglycemia or sweet taste. Davis *et al.*, hypothesized the role of tryptophan in inducing fatigue as a post lunch effect [35]. This association has been confirmed by several other studies [36]. It is believed that the CNS and subjective fatigue after carbohydrate intake may be related to an increase in tryptophan relative to other competitive amino acids. Pure fat intake may also have a negative influence on CNS arousal [37]. A general feeling of mental or central fatigue was noticed after a pure isocaloric fat meal. The ratio of tryptophan to LNAAs was decreased after a pure fat or mixed meal and rose after a pure carbohydrate meal. There is increasing evidence that a reduced amount of ingested  $\omega$ -3 fatty acids is associated with fatigue, depression, and problems of attention [38].  $\omega$ -3 Fatty acids have been tested in the treatment of subjects with attention deficit disorder and in subjects with depression, female subjects with borderline personality disorder, fatigue in multiple sclerosis, memory disturbances, dementia, and some other neuropsychiatric diseases. Randomized controlled studies have demonstrated the beneficial effect of  $\omega$ -3 acids, however there are conflicting evidence suggesting the need for more well-conducted randomized studies for confirmation. Decreased DHA and decreased brain-derived neurotrophic factor (BDNF) have been implicated in bipolar disorder. According to Bell, 71% of narcoleptics and 9% of healthy adults suffer often or always from postprandial sleepiness [39]. The vigilance level has a bimodal pattern i.e., alertness is at its lowest level after midnight, and there is another dip in alertness occurring during the afternoon independent of whether one has been eating or not. The effects of different types of meals have been studied in clinical settings. People also tended to feel more sleepy and fatigued 2–3 hours after a high-fat, low-carbohydrate meal than after low-fat, high-carbohydrate breakfast in general.

### **Nutritional Disorders and Sleep**

An increased realization of sleep-related health problems have led to evidence related to specific behaviors associated with disturbed sleep. Key evidence of the role of poor nutrition in sleep is drawn from subjects with primary anorexia nervosa [40]. This is a suitable illustration to explain the effect of food restriction on sleep behavior although the condition does exhibit extreme effects. Anorexic patients suffer from interrupted sleep and early morning waking, weight management problems and usually encounter severe weight loss associated with carbohydrate starvation. Anorexia nervosa is the major problem among adolescents, it could be probable that, the disturbed sleep and semi starvation state is partially be due to the neurotic psychosomatic response to their emotional difficulties. In a systematic study of sixty patients with anorexia nervosa, Crisp *et al.*, reported that sleep disturbance together with other manifestations of increased arousal such as diffuse restlessness, tended to be a feature of more severe cases. They did not find sleep disturbance relationships to factors such as age, duration of illness, feeding pattern or type of diet. Only ten patients of the whole experimental population series showed evidence of clinical depression. It was

concluded that the sleep disturbance was directly related to malnutrition, and it was suggested that nutritional factors may play a significant role in the genesis of insomnia even common psychiatric conditions, especially depressive illness [41].

### Effect of Fasting on Sleep

Sleep was thought to be important mainly for the brain and had little restorative value. It is now known that sleep not only is important for the brain, but also has a restorative function [42]. The relationship is complex. Fasting was associated with shorter sleep in some human studies and with increased sleep in others.

Decreased energy intake due to fasting, seems to be associated with an increase of slow-wave sleep and a decrease of rapid eye movement (REM) sleep and sleep stages 1 and 2. In the earlier studies this was explained by the restorative function of slow wave sleep [43]. In experimental studies, markers of oxidative stress were lower in cultured neuronal cells treated with caloric restriction serum compared with those treated with ad-lib serum [44]. Calorie restriction protects the brain against aging and disease; the effects of an intermittent type of fasting during Ramadan differ from those of continuous fasting. In one study, the main finding was that during Ramadan sleep latency was increased and sleep pattern was modified. Slow-wave sleep and REM sleep decreased during Ramadan. The effects of Ramadan fasting on nocturnal sleep have been explained by changes in drinking and meal schedule, rather than an altered energy intake, which may be preserved [45].

### Sleep Disruption and Eating Habits

Sleep can be affected by an individual's food habit and behavior and food timing. There are evidences that eating at night alters the metabolic profile of the individual, and some evidences that even a small redistribution of food intake to the nighttime alters the level of blood lipids, which acts as a factor predisposing to cardiovascular morbidity [46-48]. Before bed time food behavior such as consumption of coffee, tea and other food carrying stimulants appear to reduce sleep quality [49]. Likewise intake of milk, food with a high glycemic index, cereal preparations, vitamin supplements are reported to improve sleep quality [22]. Nevertheless, there is still a lacuna in understanding about eating pattern and nutrient intake of subjects suffering from poor sleep. Another nutritional factor involved with sleep quantity and quality is hydration. In a recent survey of sleep habits of athletes at the Australian Institute of Sports, a major reason for sleep disturbances was waking during the night several times to urinate. One reason for this is the need for rehydration following afternoon or evening training sessions or competition, possibly resulting in hyperhydration in some individuals. It may also be related to the intake of high volumes of low-sodium fluids (i.e. water) in the period between cessation of exercise and bedtime [50].

Eating pattern such as regulation of eating time, especially skipping breakfast; nocturnal eating and eating or drinking before bed have been found to directly influence the quality of sleep. Patients suffering from the night-eating syndrome report morning anorexia (frequently skipping breakfast), evening hyperphagia (consumption of more than

50% of total daily calories after 7 p.m.) and difficulties in initiating and maintaining sleep. Half of the nocturnal awakenings have been reported to be associated with food intake and the relative calorie intake of 300 kcal [51, 52]. The nocturnal eating syndrome is characterized by recurrent awakenings from sleep that is characterized as non-rapid eye movement (NREM), associated with immediate compulsive eating (small amounts of food, such as yogurts or fruits) due to an urgent craving for food that lacks any real feeling of hunger; recapture of sleep is easy after having snacked, but is 'impossible' without eating. Nearly all patients complain about difficulties to fall asleep, to maintain sleep, or both. In such subjects, daytime eating disorder and other psychiatric, medical or hormonal disorders were usually absent [53]. Finally, sleep-related eating is characterized by eating episodes that usually starts with an awakening out of slow wave sleep; these episodes are phenomenologically well comparable to binge eating episodes, but the patients usually do not remember them the next morning. In contrast to bulimics, these patients never purge, although they may restrict food intake or exercise during daytime. Sleep-related eating is very often described in association with sleep walking, but also with periodic movements in sleep, eating disorder diagnosis, and, occasionally, with sleep-related breathing disorders [54, 55]. Systematic and controlled electroencephalographic (EEG) sleep studies are limited to explain binge eating disorder and the night-eating syndrome [56].

Studies have expressed concern about the altered eating habits of night workers, since they tend to "nibble" their way through crisps and chocolate bars during the night shifts rather than eat a healthy and substantial meal in the middle of it. The timing and type of food eaten by shift workers are determined more by the opportunity afforded by the work schedule than by hunger [7, 57]. The common problem among the night workers especially those who have worked at night for longer times, was indigestion and an increased frequency of gastrointestinal disorders and ulcers [58].

### Alcohol

Alcohol can be viewed as having both positive and negative influence on sleep, although the consumption of alcohol before sleep is considered to be detrimental to sleep quality and quantity. Due to the relatively fast metabolism of alcohol, the effects of alcohol on sleep can differ between the first and second half of the night. It is reported to decrease sleep latency, reduction in REM sleep, and an increase in non-REM sleep, which typically occurs in the first half of sleep [59]. Sleep during the second half of the night is interrupted with frequent waking, increased dreaming, and increased REM sleep [60]. Feige *et al.*, [7] examined the effects of alcohol consumption and reported low blood alcohol level of 0.03% or 0.1% on polysomnographically recorded sleep. Results suggested a minimal effect on a 0.03% blood alcohol level (considered normal consumption) on sleep parameters, while sleep latency decreased significantly when the blood alcohol level was 0.1% (considered abuse of alcohol). When examining the night's sleep in two halves, the higher alcohol dose resulted in a significant suppression of sleep stage 1 (light sleep), a reduced number of waking, increased slow wave sleep, and decreased REM density. However, during the second half of sleep, this dose resulted

in an increase in light sleep that is likely to cause an overall impairment in sleep quality and quantity [7]. This has been considered as a hypnotic-like effect of alcohol intake at high doses especially before sleep and subsequent sleep disturbance during the second half of the night. Therefore alcohol is recommended as a suitable hypnotic aid. Other alcohol-related factors, including tachycardia, perspiration, stomach complaints, headaches or a full bladder, may also disturb sleep [7]. Previous research has also shown that alcohol can impair daytime performance and increase fatigue as a consequence of disturbed sleep [61].

### **Caffeine**

Caffeine chemically is methylxanthine considered a mild stimulant to central nervous system and is most commonly used substance [62]. Caffeine can be found in range of products, with coffee and tea being the most common sources. There is a widely held belief that caffeine may impair sleep, although individual differences in tolerance are commonly reported. Dark chocolate is stimulating; 100 g of 70% chocolate corresponds to 1–2 cups of coffee depending on strength of the coffee and size of the cup. Caffeine is absorbed rapidly, and peak activity is achieved in 30–60 minutes. The duration of action is usually 4–6 hours, but in elderly subjects with slower metabolism the duration may be up to 16–20 hours. Insomniacs are usually advised to avoid coffee after 6:00 p.m., but in some sensitive persons with insomnia, coffee intake at noon may disturb falling asleep in the evening.

Porkka-Heiskanen and her collaborators [63] have recorded human sleep electroencephalograms (EEGs). The longer the previous wakefulness period is the longer and deeper is the following sleep. The inhibitory neuromodulator adenosine is one promising sleep-inducing factor. Its concentration is higher during wakefulness than during sleep, it accumulates in the brain during prolonged wakefulness, and local perfusions as well as systemic administration of adenosine. Its agonists induce sleep and decrease wakefulness. The hypothesis is that adenosine accumulates in the extracellular space of the basal forebrain during wakefulness, increasing the sleep propensity. The increase in extracellular adenosine concentration decreases the activity of the wakefulness-promoting cell groups, especially the cholinergic cells in the basal forebrain. When the activity of the wakefulness-active cells decreases sufficiently, sleep is initiated. During sleep, the extracellular adenosine concentrations decrease, thus inhibiting wakefulness-active cells. Caffeine acts as an antagonist to adenosine. Thereby it is a neuronal stimulant; its property depends on its ability to reduce adenosine transmission in the brain.

A large amount of caffeine, usually over 300–500 mg (depending on individual sensitivity), causes restlessness, anxiety, trembling, tinnitus, and feelings of euphoria/delirium. Everyday use of more than 500 mg of caffeine leads to 'caffeinism' with insomnia, fatigue, and different psychosomatic symptoms. It has been estimated that 10–20% of coffee drinkers may experience caffeinism. However chronic coffee drinkers develop tolerance to caffeine, hence people tolerate more than 10 cups of coffee daily. Chronic coffee drinkers also exhibit withdrawal symptoms on discontinuing coffee drinking [48]. Two or three cups of

coffee (or in sensitive persons just one cup) before bedtime is followed by difficulty falling asleep and restless sleep. In a review of the effects of caffeine on sleep, Bonnet and Arand [64] suggest that caffeine administered within 2 h of bedtime increase sleep latency, decrease slow wave sleep, and decrease total sleep time. These effects can occur with doses of 100 mg or greater. Landolt *et al.*, administered 200 mg of caffeine in the morning and analyzed the sleep stages and EEG power spectra during the subsequent night in nine healthy men. They also measured caffeine levels in saliva, which decreased from a maximum of 17 mmol/L one hour after intake to 3 mmol/L at 23:00 in the evening. Compared to placebo, sleep efficiency and total sleep time were significantly reduced after the morning intake of caffeine. Decrease Slow-wave sleep and increase of stage 1 sleep are repeated after drinking coffee [65, 66].

### **DIETARY FACTORS AND SLEEP**

Several nutritional substances have traditionally been associated with promoting sleep. Researchers have recently begun to investigate their effectiveness as a substitute for pharmacological interventions.

#### **Tryptophan**

Tryptophan, a pharmaceutical supplement is widely used in Canada, England, and Germany to treat sleep disorders. It is an essential amino acid occurs in significant quantities in dairy products, eggs, fish, and nuts. Physiologically tryptophan is converted to serotonin (5-hydroxytryptamine: 5-HT) which in turn forms a precursor for melatonin in the brain. An imbalance in serotonin is known to affect regulation of sleep processes [67]. It has also been shown that tryptophan supplement reduces sleep onset latency by 45% without changing other variables associated with sleep [68]. Arnulf and colleagues [69] reported increased sleep fragmentation, increased sleep REM (rapid eye movement) latency, and increased REM density following daytime tryptophan depletion. Markus *et al.*, [70] investigated the effects of evening ingestion of tryptophan on subsequent morning alertness and attention. The source of tryptophan was  $\alpha$ -lactalbumin, which is reported to contain the highest tryptophan content of all food protein sources [71]. This resulted in a 130% increase rate of tryptophan: LNNAC rate cause reduced sleepiness and higher task-related brain activity the following morning, and improve sleep onset latency and alter REM sleep onset latency.

#### **Vitamins and Minerals Affecting on Sleep**

Claims for sleep improvement have been advanced for a variety of products and nutrient supplements for which there is evidence of mild efficacy [72]. Some literature also exists to support soporific claims for other nutritional supplements. Evidence from these studies points to the possibility that sleep may be affected by vitamin and mineral intake or lack of these substances [73].

#### **B-complex and Sleep**

B-complex vitamins are reported to have sleep improving effect and prevent insomnia. Research evidences suggest deficiency in vitamin B6 promote psychological distress and



ensue sleep disturbance [74]. Serotonin (5-HT), found in raphe neurons of the brainstem is believed to be involved in sleep onset. Insomnia is reported to occur when serotonergic cells of the dorsal raphe are lesioned. Since vitamin B6 is essential for the synthesis of serotonin, deficiency of B6 disturbs sleep and supplements may facilitate sleep [75, 76].

Vitamin B12 has an effect on biological rhythm. Clinically, B12 has been reported to improve the symptoms of sleep-wake rhythm disorders. Orally administered B12 has been reported to stop free-running of the sleep-wake rhythm in patients suffering from non-24-h sleep-wake syndrome [73]. B12 has also been suggested to have favorable effects on delayed sleep phase syndrome and irregular sleep-wake pattern [77]. Experimental human studies, together with clinical ones, have suggested that the clinical efficacy of B12 may be related to its effect on the entraining mechanism of the biological clock. B12 has been reported to modulate human melatonin secretion; midnight bright light with B12 deficiency suppressed melatonin secretion to a greater degree than that without B12 deficiency [78]. Studies that have demonstrated that B12 can shorten the length of the sleep-wake rhythm and affects the circadian aspect of sleep propensity [79].

Supplementation of vitamin B complex vitamins have shown to be helpful in treatment of nocturnal leg cramps [80].

### Iron and Sleep

Iron has an important role in many enzymatic processes. Sufficient iron in the CNS is necessary for normal functioning of dopamine receptors. Iron and tetrahydrobiopterin are co-factors of tyrosine hydroxylase i.e. an essential regulatory enzyme for dopamine synthesis. Iron is also linked to functions of GABA, serotonin, and opioid peptides. In experimental cell cultures, dopaminergic cells of the substantia nigra can be destroyed by chelation of iron by desferoxamine. Iron also has a catalytic effect in oxidative mechanisms of the CNS. In Restless legs Syndrome (RLS), S-ferritin and soluble transferrin receptor is often reported low (45 mg/L), in which case giving iron per se, or intravenously in more severe cases, forms part of the treatment. Oral supplementation of bivalent iron is effective together with vitamin C to increase absorption of iron from the gut. Several studies have shown the benefits of intravenous iron, beginning with the early experiences from Sweden in the 1950s. Observations made on young children sleep disturbances, fatigue, and possible learning disturbances were related to iron deficiency [81]. These workers studied the effects of 5 days of sleep deprivation on the circadian rhythm and serum iron in a group of six healthy male volunteers and compared with a control group with sleep cycles. Sleep deprivation was found markedly reduced the mean level of iron, disturbed the shape of the daily course of serum iron, and gradually decreased the period of circadian rhythm. Forty-eight hours of recovery resulted in only a partial normalization of all the observed changes.

Iron deficiency is considered a putative cause for restless legs syndrome (RLS), a human sensorimotor disorder characterized by a circadian presentation of symptoms during the evening hours that disrupts one's ability to sleep

[82]. Restless legs syndrome (RLS) is a well defined sleep-related disorder characterized by abnormal sensations in legs at rest, associated with an urge to move the affected legs [83]. The symptoms become worse at night, and the patients often develop difficulty with sleep initiation and halfway awakening. Several clinical studies have reported a higher incidence of RLS in iron deficiency anemia, suggesting a relationship between low serum iron levels and RLS [84]. Although the mechanism of development is unknown, there is circumstantial evidence for a role of the dopaminergic system and iron status in the pathophysiology of RLS [85]. Dopamine synthesis require tyrosine hydroxylase. This enzyme needs iron as a cofactor for hydroxylation of tyrosine [83]. Therefore, iron deficiency affects dopamine production indirectly, and dopaminergic agents are effective in therapy for idiopathic RLS [86]. Although serum iron levels, in contrast to tissue iron levels, are highly variable and may be affected by diet, stress, sleep behavior, and individual circadian rhythms, serum ferritin is regarded as a more reliable indicator of iron deficiency. A higher proportion of iron in the brain is found in ferritin, which serves as a storage protein for intracellular iron [87]. O'Keeffe *et al.*, [88] investigated the relationship between ferritin status and RLS in 18 elderly patients and age-matched control subjects. They reported that serum ferritin levels were low in RLS patients compared with control subjects. They also reported that regardless of presence of low serum ferritin, iron status *per se* is important in development of RLS [82].

### Calcium

Literature related to the effect of calcium is very limited; the reason could be non availability of methodology to assess calcium status. Maximum understanding about role of calcium is from studies reported on nephritic patients as they suffer from insomnia [89-91].

Relative hypercalcemia has been shown to be associated with insomnia in hemodialysis patients [92]. In this study, a reduction of dialysate calcium concentration (1.75-2.00 mmol/L to 1.25 mmol/L) and subsequent serum calcium level from 9.9mg/dL to 9.4 mg/dL ( $P < .0001$ ) led to significant reduction in insomnia. Those patients with persistent insomnia dropped from 20.5% ( $n = 15$ ) to 5.9% ( $n = 4$ ). Occasional insomnia dropped from 37.0% ( $n = 27$ ) to 22.1% ( $n=15$ ) while those without insomnia increased from 42.5% ( $n = 31$ ) to 72.0% ( $n = 49$ ).

### Magnesium

Magnesium is considered to promote sleep in humans. The natural N-methyl-D-aspartate (NMDA) antagonist and GABA agonist, magnesium ion, plays a key role in the regulation of sleep and endocrine systems such as the hypothalamic-pituitary-adrenal (HPA) system and renin-angiotensin-aldosterone system. Magnesium ion partially reverses sleep EEG and nocturnal neuroendocrine changes occurring during aging [93]. Some evidence suggests a self regulatory mechanism by which Mg participates in sleep regulation. Magnesium enhances melatonin secretion from the pineal gland by stimulating serotonin N-acetyl transferase activity, the key enzyme in melatonin synthesis. In contrast, melatonin may decrease serum magnesium by

melatonin's effects on magnesium distribution. However, magnesium may decrease melatonin production [93]. The similarities of the effect of magnesium ion and lithium ion furthermore support the efficacy of magnesium ion as a mood stabilizer that lithium ions are shown to play a role essentially similar to the magnesium ions in the brain. According to Durlach and co-workers [93], the mental health pattern induced through simple magnesium deficiency is a neurotic problem and never psychotic. The general symptom related to deficiency is insomnia and consequences are anxiety, panic attack disorders, depression hyper-emotionality, asthenia and headache, dizziness, nervous fits, lipothymias (repeated fainting), and sensations of a "lump in the throat" and of "blocked breathing", all of which can be effectively treated with magnesium [94, 95].

The process of normal aging is accompanied by changes in sleep-related endocrine activity. During aging an increase in cortisol and a decrease in renin and aldosterone concentration occur. In aged subjects more time is spent awake and slow-wave sleep is reduced. In conclusion magnesium (200–400 mg) is extremely effective in promptly inducing sleep when taken at bedtime, and sleep is vital to recovery from depression.

## HERBS

Use of herbs for their medicinal properties is known from time immemorial. Ayurveda and unani medicine are the ancient sciences for treatment. They are basically dependent on herbs. A variety of common elements are managed by simple herbs that are available at home and are referred as "Home remedies". Management of sleep problems was one such process wherein certain herbs are known to be effective in inducing sleep without any side effects. Literature provides sufficient information regarding a few herbs: Passionflower, Valerian, Hop, etc. They are used in Unani and Ayurvedic lines of treatments [96].

### Passionflower (*Passiflora incarnata*)

Passionflower was used in traditional remedies as a "calming" herb for anxiety and insomnia. During the early twentieth century, this herb was included in many over-the-counter medicines in form of powder, decoction or tablet as sedatives and sleep aids in combination with other calming herbs such as valerian and lemon balm. It is also used in homeopathic medicine to treat pain, insomnia, and nervous restlessness. In 1978, the FDA (USA) exercised a ban on these preparations due to lack of supportive evidence. Later animal studies reported its dose-dependent sedative effect of an aqueous extract [97].

Today, professional herbalists use passionflower often in combination with other calming herbs in treatment of insomnia, tension, and other health problems related to anxiety and nervousness [98]. Although Valerian is claimed as a remedy for poor sleep, scientifically designed studies are not available. The possible components in passionflower considered to exert remedial effect are flavonoids, indole, alkaloids, maltol, ethyl-maltol, and cyanogenic glycosides.

### Valerian (*V. officinalis L*)

Valerian is a traditional herbal sleep remedy that has been studied with a variety of methodological designs using

multiple dosages and preparations in human studies. Valerian improves subjective experiences of sleep when taken before bed time for a one- to two-week period. It also claimed to be a safe sedative/hypnotic for patients with mild to moderate insomnia [99]. Valerian is one of the herbs that is mostly studied, the aqueous, alcohol, or dilute alcoholic extract are made available for use as a pharmacological preparation. The components which are purported to have the potentiality to exert remedial effects are in general divided into the following categories: sesquiterpenes (volatile oil components that account for valerian's unpleasant odour), valepotriates, and amino acids such as GABA and glutamine. The valepotriates, for example, do not extract in aqueous media but are extracted in dilute alcohol and tend to have a more prominent anxiolytic than sleep-inducing effect [100]. Because they degrade quickly, dry formulations are also available. It is considered that the effects are due to either the individual constituents or a synergetic effect can occur in combination of the components present. Several studies have examined the effects of valerian on sleep, including randomized placebo-controlled designs. The dose administered ranged from 400 to 900 mg, 30 to 60 minutes before bedtime was effective. Also aqueous extract of valerian, comprising predominantly of sesquiterpenes and without valepotriates, was given to 18 normal subjects with normal sleep in a randomized, cross-over, double-blind, placebo-controlled trial. The results obtained were significant among young patient than the older subjects. 63% older adults with poor sleep reported improvement in sleep and had subjective improvement with placebo; however differences were not statistically significant. In young poor sleepers, there was a statistically significant improvement with valerian treatment (45% of young subjects with valerian had improved sleep vs. 16% with placebo ( $P < 0.01$ )). There was no significant difference in subjective daytime sleepiness between placebo and valerian [101].

### Hop (*Humulus lupulus*)

Hop is cultivated throughout the world and used mainly as an ingredient in beer making. In addition to exerting a diuretic effect, hop is best known as a remedy for restlessness, irritability, anxiety, tension, and disordered sleep. Historically, hop harvesters were noted to be very sleepy after picking the flowers, and is used in pillows as aromatherapy for sleep problems and nervous conditions. Common hops are also used orally for insomnia. The German Commission E, Germany's equivalent to the Food and Drug Administration (USA), approved its uses. The FDA includes hop on its generally recognized as safe (GRAS) list. Based on animal and human studies 100 different compounds have been suggested to be present in hop, the volatile chemical dimethylvinyl carbinol (2-methyl-3-butene-2-ol), is considered to cause sedative and hypnotic effects.

In human adults, combination of hop and valerian is a viable alternative to benzodiazepine medication for the treatment of non-chronic and non-psychiatric sleep disorders [102]. In an open trial involving 10 children 2 to 14 years old, daily administration of a herbal mixture containing hops, chamomile, and valerian produced sedative effects without side effects. However in certain sensitive subjects this may cause reaction, such as dermatitis. Herbalists recommend



that hops be used with caution by patients on treatment for depression or psychosis [103].

### **Kava Kava (*Piper methysticum*)**

Kava kava is the root of *Piper methysticum*, a Polynesian plant. It is used as an extract which has a potent anxiolytic, sedative, sleep inducing, and aphrodisiac. The German Commission E recommends it for the treatment of nervous anxiety, stress, and restlessness [104]. Kava kava, or simply kava, contains lactones and pyrones such as methysticin, kawain, dihydromethysticin, and yangonin, all of which affect the CNS. Animal and human studies indicate that kava has muscle relaxant, anticonvulsant, analgesic and anxiolytic effects [105]. Kava enhances sleep, reduces sleep latency (the time it takes to fall asleep), and increases slow-wave sleep without altering (REM) sleep [106]. Research has documented its medicinal properties although several adverse effects have also been reported, therefore it is not recommended in many countries [107].

### **Chamomile (*Matricaria recutita*)**

Chamomile is one of the most widely used medicinal plants in the world for relieving anxiety and intestinal colic and to promote sleep. Chamomile's main active constituents are chamazulene, apigenin, and bisabolol. Animal trials suggest that it is efficacious as a mild sedative and anxiolytic, but no randomized controlled trials have evaluated these effects in humans. Chamomile tea is generally safe, but causes hypersensitivity in certain individuals especially those who exhibit sensitivity to ragweed and related plants should use caution [108].

There are 2 types of chamomile plants used in herbal preparations, German chamomile (*Matricaria recutita*) used for restlessness and insomnia and Roman chamomile (*Chamaemelum nobile*) used orally for a variety of digestive, menstrual, and naso-oral mucosal symptoms and topically for eczema, wounds, and inflammation. Sedative effects of German chamomile may be due to the benzodiazepine-like compound in the flower head [109].

### **Lemon Balm (*Melissa officinalis*)**

Lemon Balm, a perennial herb native to southern Europe, is used traditionally to treat sleep disorders, anxiety, depression, tension headaches, and nervous stomach and has been approved by the German Commission E and FDA GRAS list [104]. Lemon balm is frequently combined with other sedative herbs, such as valerian, hop, and passionflower. No known clinical studies have evaluated lemon balm for sleep disorders in children.

### **Lavender (*Lavandula angustifolia*)**

A common ingredient in perfumes, soaps, bath and talc powders, candles, and scented sachets, lavender is recommended by the German Commission E to treat restlessness, difficulty sleeping, and functional disorders of nervous origin [110]. It is often administered topically during a massage or as aromatherapy. Lavender's most potent sedative compounds include linalyl acetate and linalool. Lavender aromatherapy leads to electroencephalographic changes that reflect a more relaxed mental state [110, 111]. Many studies support its use as a mild anxiolytic

and sedative, especially when used as aromatherapy as when drops of the essential oil are placed on the pillow at bedtime. This simple measure may allow patients to reduce or eliminate their dependence on sedative sleep medications and improve daytime alertness [112, 113].

## **ENTERIC NERVOUS SYSTEM (ENS) AND SLEEP**

Cholecystokinin and many other humoral factors have a role in the CNS-ENS network. The regulation of the sleep-wake cycle is complex, and there are different theories about same. The important brain transmitters in sleep-wake regulation include norepinephrine, acetylcholine, 5-hydroxytryptamine (5-HT), dopamine, glutamate, histamine, adenosine, aminobutyric acid (GABA), and hypocretin. Also, prostaglandins and different peptides have an effect on regulation of alertness/sleepiness. In the past, the focus was on norepinephrine, acetylcholine, and 5-HT. They all play important roles, but do not explain "why we sleep." The role of adenosine and regulation of brain energetics is probably central. During wakefulness, extracellular adenosine increases; this increase of adenosine decreases wakefulness and causes sleepiness. Caffeine, the most common stimulant, is an adenosine receptor antagonist [114].

## **ROLE OF NEUROSTEROIDS**

Cholesterol is transported to glial mitochondria, where it is converted to pregnenolone a precursor for a variety of different neurosteroids such as allopregnanolone and dehydroepiandrosterone (DHEA). Allopregnanolone activates neuronal GABA receptors having anxiolytic, sedative, sleep-inducing, and anticonvulsant effects. Benzodiazepines, alcohol, and gamma hydroxybutyrate increase brain levels of allopregnanolone. Thus these drugs may potentiate GABAergic transmission directly and also by increasing allopregnanolone. Neurosteroids have been implicated in many neurologic and psychiatric disorders such as depression. Depression is associated with reduced levels of allopregnanolone in cerebrospinal fluid. Antidepressant treatment with fluoxetine increases allopregnanolone levels. There is also some evidence that DHEA helps in the treatment of depression. The beneficial effect of DHEA correlates with a decrease of glucocorticoids, which are increased in depression. There is increasing evidence about many important roles of neurosteroids in regulation of vigilance as well. Hormesis refers to a process in which low doses of a given toxic substance induce beneficial effects while larger doses of the same substance are toxic to cells and organisms [115].

## **Estrogen and Progesterone**

The effects of estrogen on sleep are numerous and complicated. Estrogen tends to decrease sleep latency, decrease the number of awakenings after sleep occurs, and increase total sleep time. The number of arousals doubles during the luteal (low estrogen) phase of the menstrual cycle. Temperature regulation in the body is also influenced by estrogen; low levels are associated with increase in both peripheral and central temperature resulting in the hot flushes characteristic of menopause [116].

Progesterone directly affects sleep, it acts as an anxiolytic agent through its actions as GABA (7-aminobutyric acid)

agonist. Progesterone peaks sharply during the mid-luteal phase of a normal menstrual cycle and then drops before menses; these changes are associated with increased arousals and other sleep difficulties. Progesterone also affects breathing by acting as a respiratory stimulant, a mechanism that may explain the remarkably low incidence of obstructive sleep apnea during pregnancy despite the prominent weight gain and changes in body habitus [116].

### Melatonin

Melatonin (N-acetyl-5-methoxytryptamine) is a pineal hormone, though not exclusively so, that is suggested to be associated with the control of circadian rhythms. A hormone produced by the pineal gland, melatonin (N-acetyl-5-methoxytryptamine) is sold over the counter as a supplement to support normal sleep. Melatonin has been used to treat disorders of the sleep cycle in shift workers, insomniacs, and travelers with jet leg [117, 118]. It is also a powerful antioxidant with immunologic and neuroprotective effects. Although data for adults conflict, melatonin has proved helpful as a treatment for sleep cycle disturbances in children with a variety of neuro-developmental, psychiatric, and developmental disorders [119]. For example, in an open study, 15 children (most of whom were neurologically disabled) with severe, chronic sleep disorder were treated with 2 to 10 mg of oral melatonin at bedtime. The health, behavioral, and social benefits of treatment were significant, with no adverse side effects [120]. In a randomized, controlled study, 25 children with attention deficit hyperactivity disorder and chronic sleep onset insomnia were given 5 mg of melatonin or placebo for four weeks; melatonin decreased sleep latency and increased total sleep time [121]. A high dosage of melatonin has been associated with daytime side effects such as reduced alertness, increased fatigue, sleepiness, headache, dizziness, and irritability. No drug interactions have been reported, but four of six children with multiple neurologic deficits who began taking 5 mg melatonin to treat sleep-wake disturbance had an increase in seizure activity [122]. The optimal dosage of melatonin is unknown, but the typical dosage ranges from 1 to 5 mg, given before bedtime.

Melatonin is biosynthesized from serotonin an outline for which is shown in Fig. (2), while tryptophan is a precursor in the entire biosynthetic process. Melatonin of pineal origin is synthesized at night or in darkness. Sunlight is a powerful inhibitor of melatonin, almost all daily excretion of pineal melatonin occurs at night. In addition, some foods are naturally high in melatonin, most notably cherries; hence it can be taken as a supplement for promoting sleep. Melatonin also induces a hypothermic effect, with reductions in core temperature ranging from 0.01 to 0.38°C [118].

### Cortisol

Studies have demonstrated that the presence of insomnia and its severity is related to the hypersecretion of cortisol [123-125]. Similar hyperactivation of the hypothalamic-pituitary-adrenal (HPA) axis has been reported in patients with depression. Therefore, it would be right to consider cortisol as a risk factor for both insomnia and depression. It could be that both conditions results from a common pathology; also there is no evidence to indicate which of the

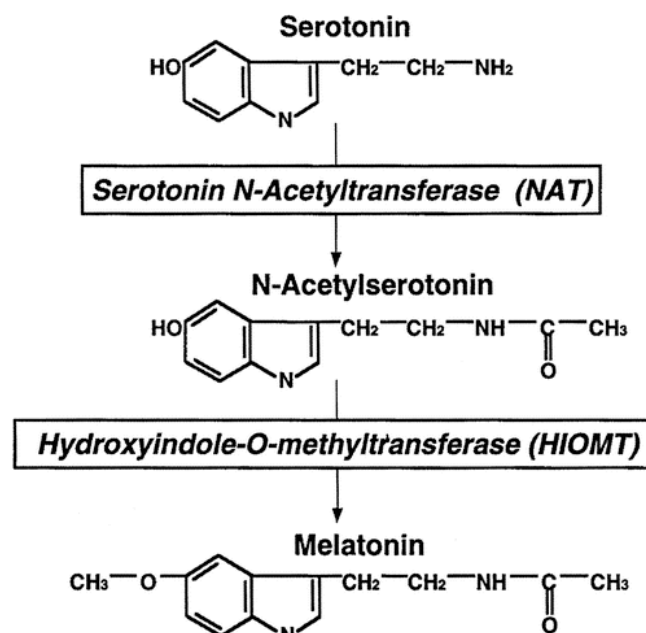


Fig. (2). Synthesis of melatonin from serotonin.

conditions appear first. Finally, this supports the notion that medications working on the HPA axis (e.g. corticotrophin-releasing hormone antagonists) may be effective for treating both the disorders. In most studies, insomnia and poor sleep were consistently found to be associated with elevated evening cortisol levels [126, 127]. Slow wave sleep and REM sleep were also decreased, which may be related to increased cortisol concentrations and/or an increased body temperature [128].

Cortisol, which plays many important regulatory roles in human physiology, can be measured from most bodily fluids, including saliva [129-131]. In people with adequate sleep and healthy body weight, salivary cortisol concentrations peak within 30–45 min after awakening and decline steadily throughout the day forming a trough after 12 h of awakening [132, 133]. The awakening response (i.e. the morning spike in cortisol levels) has been reported to be absent or attenuated after complete overnight sleep deprivation because of the absence of the sleep-to-wake transition, while partial sleep loss has been reported to amplify the cortisol response to the sleep-to-wake transition [134]. Laboratory studies have examined the impact of sleep loss on endocrine patterns primarily in men [135]. Sustained elevations of cortisol in the afternoon/evening after acute sleep loss, under conditions of controlled caloric intake, have been linked to a decrease in circulating leptin (a hormone produced by adipocytes that suppresses appetite) and increases in ghrelin (a hormone that promotes food intake), changes that are associated with increases in subjective ratings of hunger, particularly for calorie- and carbohydrate-rich foods [17, 136].

### SLEEP AND ITS INFLUENCE ON OBESITY, DIABETES MELLITUS AND CARDIO VASCULAR DISEASE

Consistent with the laboratory findings, there is evidence from cross-sectional population studies that self-reported chronic short sleep is positively correlated with higher body

mass indices (BMIs) and larger waist:hip ratios [17, 137, 138]. However, the interpretations have been subjected to serious criticism. Although epidemiological data have linked short sleep to increased body weight in both men and women (at least, cross-sectionally), the limited information available on women includes few epidemiological studies of both sexes that included hormone sampling [139]. It was observed that self-reported short sleep was associated with decreased leptin levels in a single morning sample and a flattening of the daily cortisol pattern [140]. One study involving five women and six men who had an imposed 14 days of either 8.5 or 5.5 h in bed, reported no significant effect on leptin or ghrelin levels, in contrast to previous studies of acute sleep restriction in men [141]. A large-scale epidemiological study of adolescents reported a weak association between body mass index (BMI) and self-reported short sleep in males, but none in females [142]. Thus, there is a need for studies of the effects of acute sleep restriction on endocrine function in women and for consideration of possible sex differences [143].

Epidemiological reports appearing recently have provided evidence that habitual sleep duration is prospectively and independently associated with mortality and with common diseases such as type 2 diabetes and heart disease [144, 145]. The relationship is typically a U-shaped curve where the lowest risk is found at about 7–8 h of sleep per night with the odds rising for shorter and longer sleepers. There are, however, other studies reporting non-U-shaped associations between sleep duration and mortality [146]. Although there are few proposed mechanisms for how longer sleep duration might be harmful, some experimental evidence exists to suggest short sleep may be causing morbidity. Short-term sleep restriction appears to impair glucose regulation and, if these effects continue over the long term, sleep restriction could also lead to obesity *via* changes in the hunger hormones leptin and ghrelin [147, 148].

The two most commonly reported associations between sleep duration and obesity/disease/mortality. The first is the U-shaped association (grey line) where sleep durations that are longer or shorter than about 7–7.5 h/night were associated with greater obesity. This leads to the optimal dose theory of habitual sleep duration. The other pattern is a negative linear pattern where the longest sleep durations are associated with the least likelihood and the lowest sleep durations are associated with the greatest likelihood of obesity/ disease/mortality, *ceteris paribus*. This suggests the more sleep is better theory of habitual sleep duration.

Recent studies have linked hormones associated with energy balance such as ghrelin and leptin with sleep. In both experimental and epidemiological studies, restricted or inadequate sleep is associated with altered levels of ghrelin and leptin, spurring the theory that poor sleep may disrupt endocrine regulation of energy balance, promoting weight gain [18]. Chronic insomnia is associated with obesity and prospectively predicts weight gain. No known study to date has evaluated nocturnal levels of ghrelin and leptin in primary insomnia patients. Ghrelin and leptin signal the brain regarding bodily state of energy balance promoting either satiety or hunger. Sleep processes are also related to ghrelin. A number of studies have shown that ghrelin levels

rise at night, although experimental sleep deprivation is reported to blunt night-time ghrelin levels, in such cases ghrelin increases in daytime levels were observed especially in the following afternoon and evening. Conversely, ghrelin administration increases non-REM sleep in humans. Leptin is a hormone secreted primarily by adipocytes the levels are low in large adipose deposits and *vice versa* and thereby signals the hypothalamus regarding the degree of fat stores in the body. In sleep deprivation the leptin level decreases during daytime but in healthy human volunteers on the other hand it increases and stimulates appetitive behaviors. Ghrelin levels rise between 0100 h and 0300 h during sleep and stimulates the nocturnal rise in growth hormone. Intravenous administration of ghrelin before bedtime can increase non-REM sleep in men, although sleep propensity and the timing of administration are important. Ghrelin administered in the early morning (after 400 h) did not affect sleep levels during the following day. Similarly, in a community-dwelling sample of men and women from the Wisconsin Sleep Cohort Study, increased morning levels of ghrelin were associated with less sleep time [18].

## SUMMARY

This paper has demonstrated how the quantity and quality of sleep can influence food intake and also how food and nutrients can influence sleep and the risk of obesity, diabetes mellitus, coronary arterial disease and hypertension. The potential for shift work to influence the pathogenesis of non-communicable diseases through chronobiological and related fast (convenience) foods is discussed. Also of importance is ‘when we eat’. Nutrient content such as high protein and carbohydrates meals can influence well-being and affect moods, attention and concentration among normal adult subjects with respect to age and gender. Specifically, how nutrition impacts on physical performance, sleep and fatigue, and the sleep disorders is discussed as are ‘stimulants’ such as caffeine and alcohol. The effect of individual dietary components such as tryptophan, vitamins, iron, calcium and magnesium on sleep induction or otherwise is discussed. Herbs such as passionflower, chamomile, lemon balm, valerian, hops, kava kava and lavender are discussed in the context of medicinal properties and sleep benefit. Finally, the pivotal role of hormones such as melatonin, progesterone, cortisol, estrogen, serotonin, etc. on Central Nervous-Enteric Nervous system interactions and sleep are discussed in relation to the pathogenesis of many diseases such as cancer, diabetes, gastrointestinal and cardiovascular diseases.

## CONFLICT OF INTEREST

Declared none.

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## REFERENCES

- [1] Rosenbaum L, Lamas D. Facing a “Slow-Motion Disaster”-The UN Meeting on Noncommunicable Diseases. US: New England Journal of Medicine 2011.
- [2] Singh RB, Sharma JP, Vargova V, *et al.* Association of inflammation, heavy meals, magnesium, nitrite, and coenzyme Q10 deficiency and circadian rhythms with risk of acute coronary syndromes. World Heart J 2011; 2: 219-28.

- [3] Boggild H, Knutsson A. Shift work, risk factors and cardiovascular disease. *Scand J Work Environ Health* 1999; 25(2): 85-99.
- [4] Kivimäki MM, Virtanen M, Elovainio A, Kouvonen A, Väänänen A, Vahtera J. Work stress in the etiology of coronary heart disease—a meta-analysis. *Scand J Work Environ Health* 2006; 32(6): 431.
- [5] Spiegel K, Tasali E, Penev P, Van Cauter E. Brief communication: sleep curtailment in healthy young men is associated with decreased leptin levels, elevated ghrelin levels, and increased hunger and appetite. *Ann Intern Med* 2004; 141(11): 846-50.
- [6] Anjum B, Tewari S, Jain V, et al. 24-Hour chronomics of ambulatory blood pressure monitoring in rotating night shift workers and controls. *World Heart J* 2011; 4.
- [7] Feige B, Gann H, Brueck R, et al. Effects of alcohol on polysomnographically recorded sleep in healthy subjects. *Alcohol Clin Exp Res* 2006; 30(9): 1527-37.
- [8] Froy O. Metabolism and circadian rhythms—implications for obesity. *Endocrine Rev* 2010; 31(1): 1-24.
- [9] Gale JE, Cox HI, Qian J, Block GD, Colwell CS, Matveyenko AV. Disruption of circadian rhythms accelerates development of diabetes through pancreatic beta-cell loss and dysfunction. *J Biol Rhythms* 2011; 26(5): 423-33.
- [10] Morikawa Y, Nakagawa H, Miura K, et al. Shift work and the risk of diabetes mellitus among Japanese male factory workers. *Scand J Work Environ Health* 2005; 31(3): 179-83.
- [11] Pan A, Schernhammer ES, Sun Q, Hu FB. Rotating night shift work and risk of type 2 diabetes: two prospective cohort studies in women. *PLoS Medicine* 2011; 8(12): e1001141.
- [12] Suwazono Y, Sakata K, Okubo Y, et al. Long-term longitudinal study on the relationship between alternating shift work and the onset of diabetes mellitus in male Japanese workers. *JOEM* 2006; 48(5): 455.
- [13] Van Cauter E. Sleep disturbances and insulin resistance. *Diabetic Med* 2011; 28: 1455-62.
- [14] Van Cauter E, Spiegel K, Tasali E, Leproult R. Metabolic consequences of sleep and sleep loss. *Sleep Med* 2008; 9: S23-8.
- [15] Van Dongen A, Boot CRL, Merkus SL, Smid T, Van Der Beek AJ. The effects of shift work on body weight change—a systematic review of longitudinal studies. *Scand J Work Environ Health* 2011; 37(4): 263-75.
- [16] Lo SH, Lin LY, Hwang JS, Chang YY, Liao CS, Wang JD. Working the night shift causes increased vascular stress and delayed recovery in young women. *Chronobiol Int* 2010; 27(7): 1454-68.
- [17] Taheri S, Lin L, Austin D, Young T, Mignot E. Short sleep duration is associated with reduced leptin, elevated ghrelin, and increased body mass index. *PLoS Med* 2004; 1(3): 210.
- [18] Spiegel K, Tasali E, Penev P, Cauter E. Brief communication: sleep curtailment in healthy young men is associated with decreased leptin levels, elevated ghrelin levels, and increased hunger and appetite. *Ann Intern Med* 2004; 141(11): 846.
- [19] Porter J, Horne J. Bed-time food supplements and sleep: effects of different carbohydrate levels. *Electroencephalogr Clin Neurophysiol* 1981; 51(4): 426-33.
- [20] Lieberman H, Spring B, Garfield G. The behavioral effects of food constituents: strategies used in studies of amino acids, protein, carbohydrate and caffeine. *Nutr Rev* 1986; 44(s3): 61-70.
- [21] Spring B, Maller O, Wurtman J, Digman L, Cozolino L. Effects of protein and carbohydrate meals on mood and performance: Interactions with sex and age. *J Psychiatr Res* 1983; 17(2): 155-67.
- [22] Afaghi A, O'Connor H, Chow C. High-glycemic-index carbohydrate meals shorten sleep onset. *Am J Clin Nutr* 2007; 85(2): 426.
- [23] Roth T, Hajak G, Ustün T. Consensus for the pharmacological management of insomnia in the new millennium. *Int J Clin Pract* 2001; 55(1): 42.
- [24] Sproule B, Busto U, Buckle C, Herrmann N, Bowles S. The use of non-prescription sleep products in the elderly. *Int J Geriatr Psychiatr* 1999; 14(10): 851-7.
- [25] Van Cauter E, Polonsky KS, Scheen AJ. Roles of circadian rhythmicity and sleep in human glucose regulation. *Endocr Rev* 1997; 18: 716-38.
- [26] Bruni O, Ferri R, Miano S, Verrillo E. L-5-Hydroxytryptophan treatment of sleep terrors in children. *Eur J Pediatr* 2004; 163(7): 402-7.
- [27] Johnson J. A comparative study of the bedtime routines and sleep of older adults. *J Community Nurs* 1991; 8(3): 129-36.
- [28] Driver H, Shulman I, Baker F, Buffenstein R. Energy content of the evening meal alters nocturnal body temperature but not sleep. *Physiol Behav* 1999; 68(1-2): 17-23.
- [29] Fagioli I, Baroncini P, Ricour C, Salzarulo P. Decrease of slow-wave sleep in children with prolonged absence of essential lipids intake. *Sleep* 1989; 12(6): 495-9.
- [30] Nedeltcheva A, Kessler L, Imperial J, Penev P. Exposure to recurrent sleep restriction in the setting of high caloric intake and physical inactivity results in increased insulin resistance and reduced glucose tolerance. *J Clin Endocrinol Metab* 2009; 94(9): 3242.
- [31] Cheruku SR, Montgomery-Downs HE, Farkas SL, Thoman EB, Lammi-Keefe CJ. Higher maternal plasma docosahexaenoic acid during pregnancy is associated with more mature neonatal sleep-state patterning. *Am J Clin Nutr* 2002; 76(3): 608.
- [32] Van Cauter E, Blackman J, Roland D, Spire J, Refetoff S, Polonsky K. Modulation of glucose regulation and insulin secretion by circadian rhythmicity and sleep. *J Clin Invest* 1991; 88(3): 934.
- [33] Edwards S, Montgomery I, Colquhoun E, Jordan J, Clark M. Spicy meal disturbs sleep: an effect of thermoregulation? *Int J Psychophysiol* 1992; 13(2): 97-100.
- [34] Husain AM, Yancy WS Jr, Carville ST, Miller PP, Westman EC. Diet therapy for narcolepsy. *Neurology* 2004; 62(12): 2300-2.
- [35] Davis J, Alderson N, Welsh R. Serotonin and central nervous system fatigue: nutritional considerations. *Am J Clin Nutr* 2000; 72(2): 573S.
- [36] Fernstrom J, Fernstrom M. Exercise, serum free tryptophan, and central fatigue. *J Nutr* 2006; 136(2): 553S.
- [37] Davis J, Bailey S. Possible mechanisms of central nervous system fatigue during exercise. *Med Sci Sports Exerc* 1997; 29(1): 45.
- [38] Maes M, Mihaylova I, Leunis J. In chronic fatigue syndrome, the decreased levels of omega-3 poly-unsaturated fatty acids are related to lowered serum zinc and defects in T cell activation. *Neuroendocrinol Lett* 2005; 26(6): 745-51.
- [39] Bell I. Sciences, specific food factors in postprandial sleepiness and sleep in normal young adults. Palo Alto, CA: Stanford University 1977.
- [40] Kiloh L, Garside R. The independence of neurotic depression and endogenous depression. *Br J Psychiatry* 1963; 109(461): 451.
- [41] Crisp A, Stonehill E, Fenton G. The relationship between sleep, nutrition and mood: a study of patients with anorexia nervosa. *Br Medical J* 1971; 47(546): 207.
- [42] Berger R, Phillips N. Energy conservation and sleep. *Behav Brain Res* 1995; 69(1-2): 65-73.
- [43] Dewasmes G, Duchamp C, Minaire Y. Sleep changes in fasting rats. *Physiol Behav* 1989; 46(2): 179-84.
- [44] Michalsen A, Schlegel F, Rodenbeck A, et al. Effects of short-term modified fasting on sleep patterns and daytime vigilance in non-obese subjects: results of a pilot study. *Ann Nutr Metab* 2000; 47(5): 194-200.
- [45] Roky R, Chapotot F, Hakkou F, Bencheikroun M, Buguet A. Sleep during Ramadan intermittent fasting. *J Sleep Res* 2001; 10(4): 319-27.
- [46] Morgan L, Arendt J, Owens D, et al. Effects of the endogenous clock and sleep time on melatonin, insulin, glucose and lipid metabolism. *J Endocrinol* 1998; 157(3): 443.
- [47] Novak C, Kotz C, Levine J. Central orexin sensitivity, physical activity, and obesity in diet-induced obese and diet-resistant rats. *Am J Physiol Endocrinol Metab* 2006; 290(2): E396.
- [48] Atkinson G, Davenne D. Relationships between sleep, physical activity and human health. *Physiol Behav* 2007; 90(2-3): 229-35.
- [49] Shilo L, Sabbah H, Hadari R, et al. The effects of coffee consumption on sleep and melatonin secretion. *Sleep Med* 2002; 3(3): 271-73.
- [50] Halson S. Nutrition, sleep and recovery. *Eur J Sport Sci* 2008; 8(2): 119-26.
- [51] Birketvedt G, Florholmen J, Sundsfjord J, et al. Behavioral and neuroendocrine characteristics of the night-eating syndrome. *JAMA* 1999; 282(7): 657.
- [52] Stunkard A, Grace W, Wolff H. Night eating syndrome. In: Christopher GF, Kelly D, Eds. *Eating disorders and obesity. A comprehensive handbook*. NY: Guilford Press 2002; pp. 183-8.
- [53] Manni R, Ratti M, Tartara A. Nocturnal eating: prevalence and features in 120 insomnia referrals. *Sleep* 1997; 20(9): 734-8.
- [54] Auger R. Sleep-related eating disorders. *Psychiatry (Edgmont)* 2010; 3(11): 64.

- [55] Schenck CH, Mahowald M. Review of nocturnal sleep-related eating disorders. *Int J Eat Disord* 1994; 15(4): 343-56.
- [56] Lauer C, Krieg J. Sleep in eating disorders. *Sleep Med Rev* 2004; 8(2): 109-18.
- [57] Uchiyama M, Okawa M, Shibui K, *et al.* Altered phase relation between sleep timing and core body temperature rhythm in delayed sleep phase syndrome and non-24-hour sleep-wake syndrome in humans. *Neurosci Lett* 2000; 294(2): 101-4.
- [58] Taylor E, Briner R, Folkard S. Models of shiftwork and health: an examination of the influence of stress on shiftwork theory. *Human Factors. J Hum Fact Ergon Soc* 1997; 39(1): 67-82.
- [59] Roehrs T, Roth T. Sleep, sleepiness, and alcohol use. *Alcohol Res Health* 2001; 25(2): 101-9.
- [60] Arnedt W, Munt M. Simulated driving performance following prolonged wakefulness and alcohol consumption: separate and combined contributions to impairment. *J Sleep Res* 2000; 9(3): 233-41.
- [61] Roehrs T, Yoon J, Roth T. Nocturnal and next day effects of ethanol and basal level of sleepiness. *Hum Psychopharm Clin Exp* 1991; 6(4): 307-11.
- [62] Hindmarch I, Rigney U, Stanley N, Quinlan P, Rycroft J, Lane J. A naturalistic investigation of the effects of day-long consumption of tea, coffee and water on alertness, sleep onset and sleep quality. *Psychopharmacology* 2000; 149(3): 203-16.
- [63] PorkkaHeiskanen T, Kalinchuk AV. Adenosine as a sleep factor. *Sleep Biol Rhythms* 2011; 9: 18-23.
- [64] Bonnet MH, Arand D. Caffeine use as a model of acute and chronic insomnia. *Sleep* 1992; 15(6): 526-36.
- [65] Landolt HP, Werth E, Borbély AA, Dijk DJ. Caffeine intake (200 mg) in the morning affects human sleep and EEG power spectra at night. *Brain Res* 1995; 675(1-2): 67-74.
- [66] Luciano M, Zhu G, Kirk K, *et al.* "No Thanks, It Keeps Me Awake": The Genetics of coffee-attributed sleep disturbance. *Sleep* 2007; 30(10): 1378.
- [67] Markus C, Jonkman L, Lammers J, Deutz N, Messer M, Rigtering N. Evening intake of  $\alpha$ -lactalbumin increases plasma tryptophan availability and improves morning alertness and brain measures of attention. *Am J Clin Nutr* 2005; 81(5): 1026.
- [68] Dollander M. Etiology of adult insomnia. *Encephale* 2002; 28: 493-502.
- [69] Landolt HP, Rétey JV, Tönz K, *et al.* Mid Caffeine attenuates waking and sleep electroencephalographic markers of sleep homeostasis in humans. *Neuropsychopharmacology* 2002; 27(5): 843-51.
- [70] Markus CR, Jonkman LM, Lammers JHCM, Deutz NEP, Messer MH, Rigtering N. Evening intake of  $\alpha$ -lactalbumin increases plasma tryptophan availability and improves morning alertness and brain measures of attention. *Am J Clin Nutr* 2005; 81(5): 1026.
- [71] Lien E. Infant formulas with increased concentrations of  $\alpha$ -lactalbumin. *Am J Clin Nutr* 2003; 77(6): 1555S.
- [72] Morin C, Koetter U, Bastien C, Ware J, Wooten V. Valerian-hops combination and diphenhydramine for treating insomnia: a randomized placebo-controlled clinical trial. *Sleep* 2005; 28(11): 1465-71.
- [73] Meoli A, Rosen C, Kristo D, *et al.* Oral nonprescription treatment for insomnia: an evaluation of products with limited evidence. *J Clin Sleep Med* 2005; 1(2): 173-87.
- [74] Baldewicz T, Goodkin K, Feaster D, *et al.* Plasma pyridoxine deficiency is related to increased psychological distress in recently bereaved homosexual men. *Psychosomatic Med* 1998; 60(3): 297.
- [75] Morley J, Glick Z, Rubenstein L. Nutrition and behavior. In: Morkey JE, Thomes DR, Eds. *Geriatric nutrition: A comprehensive review*. The Netherlands: CRC Press 2007; p. 271.
- [76] Jones B. Basic mechanisms of sleep-wake states. In: Kryger MH, Roth T, Dement WC, Eds. *Principles and practice of sleep medicine*. Philadelphia: WB Saunders 1994; p. 145-62.
- [77] Kin K, Uchiyama M, Okawa M. Topics on treatment of insomnia: melatonin, vitamin B12, and bright light therapy. *Jpn J Psychiatr Treat* 1999; 14(4): 411-20.
- [78] Honma K, Kohsaka M, Fukuda N, Morita N, Honma S. Effects of vitamin B12 on plasma melatonin rhythm in humans: Increased light sensitivity phase-advances the circadian clock? *Cell Mol Life Sci* 1992; 48(8): 716-20.
- [79] Ohta T, Ando K, Iwata T, *et al.* Treatment of persistent sleep-wake schedule disorders in adolescents with methylcobalamin (vitamin B12). *Sleep* 1991; 14(5): 414.
- [80] Chan P, Huang TY, Chen YJ, Huang WP, Liu YC. Randomized, double-blind, placebo-controlled study of the safety and efficacy of vitamin B complex in the treatment of nocturnal leg cramps in elderly patients with hypertension. *J Clin Pharmacol* 1998; 38: 1151-4.
- [81] Kryger M, Otake K, Foerster J. Low body stores of iron and restless legs syndrome: a correctable cause of insomnia in adolescents and teenagers. *Sleep Med* 2002; 3(2): 127-32.
- [82] Mizuno S, Mihara T, Miyaoka T, Inagaki T, Horiguchi J. CSF iron, ferritin and transferrin levels in restless legs syndrome. *J Sleep Res* 2005; 14(1): 43-7.
- [83] Earley C. Restless legs syndrome. *New Engl J Med* 2003; 348(21): 2103.
- [84] Skomro R, Ludwig S, Salamon E, Kryger M. Sleep complaints and restless legs syndrome in adult type 2 diabetics. *Sleep Med* 2001; 2(5): 417-22.
- [85] Allen R, Earley C. Restless legs syndrome: a review of clinical and pathophysiological features. *J Clin Neurophysiol* 2001; 18(2): 128.
- [86] Zucconi M, Ferini-Strambi L. Epidemiology and clinical findings of restless legs syndrome. *Sleep Med* 2004; 5(3): 293-9.
- [87] Tarquini B. Iron metabolism: clinical chronobiological aspects. *Chronobiologia* 1978; 5(3): 315-6.
- [88] O'keeffe S, Gavin K, Lavan J. Iron status and restless legs syndrome in the elderly. *Age Ageing* 1994; 23(3): 200.
- [89] Barry A. Observations on the treatment of eclampsia. *Ir J Med Sci (1926-1967)* 1942; 17(11): 603-6.
- [90] Mark R. Observations on arthritis deformans and calcium metabolism. *J Metab Res* 1923; 1: 135.
- [91] De Santo R, Esposito M, Cesare C, *et al.* High prevalence of sleep disorders in hemodialyzed patients requiring parathyroidectomy. *J Renal Nutr* 2008; 18(1): 52-5.
- [92] Virga G, Stanic L, Mastro Simone S, Gastaldon F, da Porto A, Bonadonna A. Hypercalcemia and insomnia in hemodialysis patients. *Nephron* 2000; 85(1): 94-5.
- [93] Durlach J, Pagès N, Bac P, Bara M, Guiet-Bara A. Biorhythms and possible central regulation of magnesium status, phototherapy, darkness therapy and chronopathological forms of magnesium depletion. *Magnes Res* 2002; 15(1-2): 49.
- [94] David Seaman D. Magnesium deficiency, inflammation and nervous system hyperexcitability. *Dynamic Chiropractic* 2003; 21(7): 1-6.
- [95] Papadopol V, Tuchendria E, Palamaru I. Magnesium and some psychological features in two groups of pupils (magnesium and psychic features). *Magnesium Res* 2001; 14(1-2): 27-32.
- [96] Saeed S, Bloch R, Antonacci D. Herbal and dietary supplements for treatment of anxiety disorders. *Am Fam Physician* 2007; 76(4): 549-56.
- [97] Soulimani R, Younos C, Jarmouni S, Bousta D, Misslin R, Mortier F. Behavioural effects of *Passiflora incarnata* L. and its indole alkaloid and flavonoid derivatives and maltol in the mouse. *J Ethnopharmacol* 1997; 57(1): 11-20.
- [98] Akhondzadeh S, Naghavi H, Vazirian M, Shayeganpour A, Rashidi H, Khani M. Passionflower in the treatment of generalized anxiety: a pilot double blind randomized controlled trial with oxazepam. *J Clin Pharm Ther* 2001; 26(5): 363-7.
- [99] Hadley S, Petry J. Valerian. *Am Fam Physician* 2003; 67(8): 1755-8.
- [100] Stevinson C, Ernst E. Valerian for insomnia: a systematic review of randomized clinical trials. *Sleep Med* 2000; 1(2): 91-9.
- [101] Bent S, Padula A, Moore D, Patterson M, Mehling W. Valerian for sleep: a systematic review and meta-analysis. *Ame J Med* 2006; 119(12): 1005-12.
- [102] Rodenbeck A, Simen S, Cohrs S, *et al.* Alterations of the sleep stage structure as a feature for GABAergic effects of a valerian-hop preparation in patients with psychophysiological insomnia. *Somnologie-Berlin* 1998; 2: 26-31.
- [103] Gardiner P, Kemper K. Insomnia: herbal and dietary alternatives to counting sheep. *Contemp Pediatr-Montvale* 2002; 19(2): 69-89.
- [104] Nathan M, Scholten R. The complete german commission E monographs: Therapeutic guide to herbal medicines. *Ann Intern Med* 1999; 130(5): 459.
- [105] Musser S. Kava (Piper methysticum). *Encyclopedia of dietary supplements* 2005; p. 373.
- [106] Wheatley D. Medicinal plants for insomnia: a review of their pharmacology, efficacy and tolerability. *J Psychopharmacol* 2005; 19(4): 414.

- [107] Kennedy D, Little W, Scholey A. Attenuation of laboratory-induced stress in humans after acute administration of *Melissa officinalis* (Lemon Balm). *Psychosom Med* 2004; 66(4): 607.
- [108] Eisenberg D, Davis R, Ettner S, *et al.* Trends in alternative medicine use in the United States, 1990-1997: results of a follow-up national survey. *JAMA* 1998; 280(18): 1569.
- [109] Gyllenhaal C, Merritt S, Peterson S, Block K, Gochenour T. Efficacy and safety of herbal stimulants and sedatives in sleep disorders. *Sleep Med Rev* 2000; 4(3): 229-51.
- [110] Blumenthal M. The complete German Commission E monographs: therapeutic guide to herbal medicines. 1998: Thieme Medical Pub.
- [111] Diego M, Jones N, Field T, *et al.* Aromatherapy positively affects mood, EEG patterns of alertness and math computations. *Int J Neurosci* 1998; 96(3): 217-24.
- [112] Hardy M, Kirk-Smith M, Stretch D. Replacement of drug treatment for insomnia by ambient odour. *Lancet* 1995; 346(8976): 701.
- [113] Chu C, Kemper K. Lavender (*Lavandula* spp.). Longwood Herbal Task Force. Available from: <http://www.mep.edu/herbal>, 2005.
- [114] Wood JD, Alpers DH, Andrews PL. Fundamentals of neurogastroenterology. *Gut* 1999; 45 (Suppl 2): II6-16.
- [115] George O, Vallée M, Le Moal M, Mayo W. Neurosteroids and cholinergic systems: implications for sleep and cognitive processes and potential role of age-related changes. *Psychopharmacology* 2006; 186(3): 402-13.
- [116] Miller E. Hormonal changes and insomnia in perimenopause and postmenopause. *Medscape Internal Med* 2005; 7(1): 1-5.
- [117] Morin A, Jarvis C, Lynch A. Therapeutic options for sleep-maintenance and sleep-onset insomnia. *Pharmacotherapy* 2007; 27(1): 89-110.
- [118] Atkinson G, Drust B, Reilly T, Waterhouse J. The relevance of melatonin to sports medicine and science. *Sports Med* 2003; 33(11): 809-31.
- [119] Jan J, O'Donnell M. Use of melatonin in the treatment of paediatric sleep disorders. *J Pineal Res* 1996; 21(4): 193-9.
- [120] Ross C, Morris B, Whitehouse W. Melatonin treatment of sleep-wake cycle disorders in children and adolescents. *Dev Med Child Neurol* 1999; 41(12): 850.
- [121] Smits M, Nagtegaal E, van der Heijden J, Coenen A, Kerkhof G. Melatonin for chronic sleep onset insomnia in children: a randomized placebo-controlled trial. *J Child Neurol* 2001; 16(2): 86.
- [122] Tjon Pian Gi C, Broeren J, Starreveld J, Versteegh FA. Melatonin for treatment of sleeping disorders in children with attention deficit/hyperactivity disorder: a preliminary open label study. *Eur J Pediatr* 2003; 162(7): 554-5.
- [123] Vgontzas A, Chrousos G. Sleep, the hypothalamic-pituitary-adrenal axis, and cytokines: multiple interactions and disturbances in sleep disorders. *Endocrinol Metab Clin* 2002; 31(1): 15-36.
- [124] Vgontzas A, Tsigos C, Bixler E, *et al.* Chronic insomnia and activity of the stress system: a preliminary study. *J Psychosom Res* 1998; 45(1): 21-31.
- [125] Hatzinger M. Neuropeptides and the hypothalamic-pituitary-adrenocortical (HPA) system: review of recent research strategies in depression. *World J Bio Psychiatry* 2000; 1(2): 105-11.
- [126] Rodenbeck A, Huether G, Rütger E, Hajak G. Interactions between evening and nocturnal cortisol secretion and sleep parameters in patients with severe chronic primary insomnia. *Neurosci Lett* 2002; 324(2): 159-63.
- [127] Vgontzas A, Zoumaki M, Bixler E, *et al.* Impaired nighttime sleep in healthy old versus young adults is associated with elevated plasma interleukin-6 and cortisol levels: physiologic and therapeutic implications. *J Clin Endocrinol Metab* 2003; 88(5): 2087.
- [128] Moussamih R, Aadil S. Physiological and chronobiological changes during Ramadan intermittent fasting. *Ann Nutr Metab* 2004; 48: 296-303.
- [129] Dorn L, Lucke J, Loucks T, Berga S. Salivary cortisol reflects serum cortisol: analysis of circadian profiles. *Ann Clin Biochem* 2007; 44(3): 281.
- [130] Edwards S, Evans P, Hucklebridge F, Clow A. Association between time of awakening and diurnal cortisol secretory activity. *Psychoneuroendocrinol* 2001; 26(6): 613-22.
- [131] Van Cauter E, Polonsky KS, Scheen AJ. Roles of circadian rhythmicity and sleep in human glucose regulation. *Endocr Rev* 1997; 18(5): 716-38.
- [132] Davis K, Parker K, Montgomery G. Sleep in infants and young children:: Part one: normal sleep. *J Pediatr Health Care* 2004; 18(2): 65-71.
- [133] Sachar E, Halbreich U, Asnis G, Swami R, Nathan M, Halpern F. Neurotransmitter regulation of cortisol secretion in depression: Studies of the response to dextroamphetamine. 1980: Elsevier-North-Holland Biomedical Press.
- [134] Riemann D, Klein T, Rodenbeck A, *et al.* Nocturnal cortisol and melatonin secretion in primary insomnia. *Psychiatry Res* 2002; 113(1-2): 17-27.
- [135] Drake C, Roehrs T, Roth T. Insomnia causes, consequences, and therapeutics: an overview. *Depress Anxiety* 2003; 18(4): 163-76.
- [136] Chapat J, Després J, Bouchard C, Tremblay A. Short sleep duration is associated with reduced leptin levels and increased adiposity: Results from the Québec family study. *Obesity* 2007; 15(1): 253-61.
- [137] Taheri S. The link between short sleep duration and obesity: we should recommend more sleep to prevent obesity. *Br Med J* 2006; 91(11): 881.
- [138] Knutson K, Spiegel K, Penev P, Van Cauter E. The metabolic consequences of sleep deprivation. *Sleep Med Rev* 2007; 11(3): 163-78.
- [139] Seicean A, Redline S, Seicean S, *et al.* Association between short sleeping hours and overweight in adolescents: results from a US Suburban High School survey. *Sleep Breath* 2007; 11(4): 285-93.
- [140] Kumari M, Badrick E, Ferrie J, Perski A, Marmot M, Chandola T. Self-reported sleep duration and sleep disturbance are independently associated with cortisol secretion in the Whitehall II study. *J Clin Endocrinol Metab* 2009; 94(12): 4801.
- [141] Nedeltcheva A, Kilkus J, Imperial J, Kasza K, Schoeller D, Penev P. Sleep curtailment is accompanied by increased intake of calories from snacks. *Am J Clin Nutr* 2009; 89(1): 126.
- [142] Knutson K. Sex differences in the association between sleep and body mass index in adolescents. *J Pediatr* 2005; 147(6): 830-4.
- [143] Antonina Ombade OMB, Benjamin R. Impact of acute sleep restriction on cortisol and leptin levels in young women. *Physiol Behav* 2010; 99: 651-6.
- [144] Patel S, Ayas N, Malhotra M, *et al.* A prospective study of sleep duration and mortality risk in women. *Sleep* 2004; 27(3): 440-4.
- [145] Kojima M, Wakai K, Kawamura T, *et al.* Sleep patterns and total mortality: a 12-year follow-up study in Japan. *J Epidemiol* 2000; 10(2): 87.
- [146] Amagai Y, Ishikawa S, Gotoh T, *et al.* Sleep duration and mortality in Japan: the Jichi medical school cohort study. *J Epidemiol* 2004; 14(4): 124-8.
- [147] Mullington J, Chan J, Van Dongen H, *et al.* Sleep loss reduces diurnal rhythm amplitude of leptin in healthy men. *J Neuroendocrinol* 2003; 15(9): 851-4.
- [148] Spiegel K, Knutson K, Leproult R, Tasali E, Cauter E. Sleep loss: a novel risk factor for insulin resistance and Type 2 diabetes. *J Appl Physiol* 2005; 99(5): 2008.

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