

Hypothesizing that Putative Dopaminergic, Melatonin, Benzodiazepine Reward Circuitry Receptor(s) Activator Provides Sleep Induction Benefits

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Abstract

The issue of insomnia is a global phenomenon which requires additional in-depth research. Insomnia especially in alcohol-dependent patients, for example, may lead to suicide. It is noteworthy that childhood sleep problems predict the onset of drinking in boys. We now know that while there are multi-faceted reasons for sleep problems and disturbances (e.g. sleep drive homeostasis, circadian rhythm physiology, and genetic influences), the scientific community has not been able to deliver an appropriate solution. Some benefit has been noted with cognitive behavioral therapy, but it has minimal effects in patients relapsing from drugs especially alcohol, cocaine and opiates. While there are a number of pharmaceutical drugs developed to treat insomnia, most have associated side effects and even addiction liability. We do know that benzodiazepines hijack the midbrain dopamine system leading to addiction. Finally, it has been proposed that dopamine D2 receptors are involved in rapid eye movement sleep, suggesting as proposed herein that dopaminergic activation is a worthwhile mechanism to explore in the future. The concepts presented herein on potential nutrigenomic therapy warrants further in-depth analysis. In this regard we hypothesize based on both literature review and empirical data that a putative dopaminergic, melatonin, benzodiazepine reward circuitry receptor(s) activator provides sleep induction benefits.

Keywords: Insomnia; Reward circuitry; Reward Deficiency Syndrome (RDS); Melatonin; Benzodiazepines; Nutrigenomics; Rapid-eye movement; Sleep

Introduction

Considering the benefits provided by typical hypnotic and non-hypnotic medication for the treatment of chronic insomnia such as barbiturates, benzodiazepines, as well as Zolpidem, versus the risk of both abuse liability and toxicity is a challenging calculation. The calculation is confounded by the paucity of evidence-based data on the hypnotic efficacy of sleep inducing pharmacological and non pharmacological treatments for chronic insomnia. While inducing sleep, many hypnotic-type medications may also induce potential abuse liability for the patient and other side effects. For example, benzodiazepines, prescription drugs remedying anxiety and insomnia, are recreationally abused; the number of individuals abusing the benzodiazepines is on the rise [1]. Importantly, the mechanism of benzodiazepine activation of midbrain dopamine neurons is well-known, with the mesocorticolimbic reward system affected by benzodiazepine [1].

Others have suggested that non-pharmacological approaches can facilitate sleep and reduce sleep disruption without the specter of side effects and may be a satisfactory regimen in the potential of regaining restorative sleep patterns. In this hypothesis paper, we attempt to show certain neurological mechanisms involved in normal sleep patterns may provide a blueprint to the development of a non-pharmacological treatment for chronic insomnia.

Insomnia Definition and Prevalence

Sleep disorders affect one fifth of Americans [2] and manifest in impaired function or excessive sleepiness due to reduced sleep quality [3]. For persons with sleep disorders, quality of life is greatly affected, for example, attention is reduced, concentration limited, memory negatively affected, reasoning and problem solving skills decreased, and reaction time to emotional and physical pain worsened in persons with insomnia compared to matched controls [4]. Classified by the International Classification of Sleep Disorders (ICSD) as a dyssomnia [5], insomnia is the chief sleep disorder [6].

A condition which negatively affects the ability of an individual to fall asleep or maintain desirable sleep duration or quality, insomnia has

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Received December 12, 2013; **Accepted** January 23, 2014; **Published** January 25, 2014

Citation: Blum K, Berman MO, Downs BW, Braverman ER, Kreuk F, et al. (2014) Hypothesizing that Putative Dopaminergic, Melatonin, Benzodiazepine Reward Circuitry Receptor(s) Activator Provides Sleep Induction Benefits. J Sleep Disorders Ther 3: 153. doi:10.4172/2167-0277.1000153

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several risk factors. Age and gender have been implicated as risk factors for insomnia, with the elderly more likely to experience insomnia and women more likely to experience difficulties sleeping than men [7]. Older individuals have trouble maintaining sleep, while falling asleep is the primary sleep issue in younger individuals [8]. 95% of adults had experienced insomnia in 1979, according to a Gallup poll survey, indicating that most people are vulnerable to some instances of sleep disorder [8].

The range of adults with chronic insomnia, ~10% to 15%, and the range of adults with transient insomnia, 25% to 35%, can be explained by the variable diagnostic measures and differing definitions in the study of sleep disorders [7]. Recent changes in the definitions of insomnia now reflect perceptions of sleep problems in patients and include the effect poor quality sleep has on daily function [8]. The constantly evolving definitions in the study of sleep disorders limit the potential for determining the scope of the problem. However, comprehensive surveys in large cohorts provide opportunities to measure this scope—one third of all people experiencing sleep issues annually, half of which seek medical advice for the issue, with only 15% of people actually reported as having sleep disorders [8]. To effectively treat a sleep disorder, the differences between sleep disorders must be understood fully and undoubtedly, such that diagnosis is accurate and treatment is pointed and geared specifically to each respective condition.

According to a 1995 report from the National Sleep Foundation, in a primary care population study, only 6% of insomniacs had gone to their physician specifically for this complaint. Additionally, insomnia in psychiatric patients is under-recognized [9]. While insomnia has been investigated in depth, insomnia is still not completely understood, the study hindered by inconsistent diagnostic criteria and variable definitions.

Insomnia and Sleep Disorder Comorbidities

Primary sleep disorders, not accompanied by other conditions, occur in some cases; however, many sleep disorders occur concomitantly with other medical and/or psychiatric conditions [10]. Latest sleep surveys indicate that of the general adult population, insomnia affects 10% to 17%, and increased rates of insomnia occur in patients with psychiatric conditions [11]. In example, Okuji et al. [11] determined that 69% of patients with mood disorder spectrum, 63% of patients with anxiety disorder, and 50% of patients with an ICD-10 schizophrenia spectrum complained of insomnia.

It is well known that insomnia commonly occurs concomitantly with depression, and it is generally thought of as a symptom in mood disorder [12]. Some studies, however, have claimed that depression and insomnia are disorders distinct in etiology and of genetic influences [13]. Utilizing a 15,000 subject European cohort and longitudinal study, in 40% of cases insomnia occurred before depression and in 56% of cases insomnia occurred before recurrent depression [13]. Insomnia has been implicated as a risk factor for depression. Individuals with a history of insomnia have four times the risk for depression as those that do not [14]. Moreover, the Breslau et al. [14] study also found that prior insomnia history significantly correlated with substance use disorder (S.U.D.), smoking, and risk for anxiety. Finally, following successful treatment for depressive symptoms, as measured with the Hamilton Rating Scale for Depression (HAM-D) scores, patients still reported sleeping difficulties [14].

Many of the symptoms that occur in insomniacs also occur in other sleep disorders; furthermore, sleep disorders, in general, are associated with a myriad of additional co morbidities. For example, the relationship

of sleep and suicide has been investigated. A 1997 study conducted by Ağargün determined that persons with the worst quality of sleep, as measured through the Pittsburgh Sleep Quality Index (PSQI), consequently scored the highest suicide subscale scores, indicating an inverse relationship between suicide and sleep quality [15].

In regards to stress, numerous anxiety disorder patients report problems falling and staying asleep; in support, polysomnographic tests of panic disorder patients indicate a reduced efficiency in sleep patterns when compared to normal controls—with increased time awake and increased time before falling asleep [16]. Interestingly, REM sleep measures do not differ significantly nor does sleep architecture for panic disorder patients and normal subjects [16]. For patients with generalized anxiety disorder, 60% to 70% complain that they have issues sleeping; polysomnographs of these patients showed an increase in the time it took to fall asleep as well as a reduction in ability to maintain sleep [16]. Similarly, the REM sleep measures and sleep architecture were not significantly different from controls. Obsessive-compulsive disorder (OCD) patients, though reporting poor sleep, did not show significant difference from controls; patients with social phobias have not been shown to differ in sleep parameters from controls [16].

More recently, utilizing a cohort of 375,653 US adults (≥ 18 years of age) in a 2013 study, Liu et al. [17] investigated the relationship between chronic disease and insufficient sleep. Controlling for various demographics and adjusting for covariates, a significant positive relationship ($p < 0.0001$) was observed between six chronic diseases and insufficient sleep [17]. These relationships were modestly explained by frequent mental distress; the relationships between both high blood pressure and diabetes and insufficient sleep were modestly explained by obesity [17]. While the relationship between insufficient sleep and chronic diseases has been investigated, the comprehensive cause-and-effect relationship is impossible to infer from such studies; thus, relationships between these conditions remains unclear [7].

Post-traumatic Stress disorder (PTSD) has also been associated with degradation in sleep quality, 70% to 91% of patients with PTSD have reported issues falling to and maintaining sleep, and 19% to 71% of patients report nightmares, dependent on PTSD severity and physical aggression exposure [18]. The studies relating sleep patterns of PTSD patients and controls are presently inconclusive; however, for PTSD patients the system of REM sleep control seems to be dysregulated [18]. Interestingly, PTSD patients are more predisposed to sleep disordered breathing (SDB) and disorders involving movement during sleep; these comorbidities have been implicated as playing roles in the sleep deficiencies of PTSD patients [18].

Other conditions associated with insomnia are Chronic Obstructive Pulmonary Diseases, Obstructive Sleep Apnea, and Restless Leg Syndrome (RLS).

Insomnia and Sleep Disorder Management

Sleep disorders are presently managed with pointed and treat-to-target techniques depending on condition, with the type and etiology of the condition influencing ideal management [19]. The initial treatment regimen for sleep disorders involves improving sleep hygiene; this is completed by utilizing routine strategies to promote a healthy and silent sleep situation, reducing caffeine or alcohol consumption prior to bed, adhering to a non-disruptive exercise schedule, limiting exposure to stimulants, and employing wind-down sessions prior to sleep [20].

Determined through a comprehensive 59 trial meta-analysis, sleep induction and sleep maintenance have both been improved by non-

pharmacological treatments for insomnia [21]. In these studies, sleep restriction therapy and stimulus control therapy were associated with the strongest evidence [21]. Moreover it was found that an average of 5 hours of intervention was shown to reduce time of onset latency and time awake after sleep onset [21].

Furthermore, cognitive behavioral therapy is utilized to treat insomnia and nightmares in PTSD patients by utilizing specialized strategies such as the imagery rehearsal therapy (IRT), a technique in which alternate positive endings are imagined and discussed for nightmares of the patient between a therapist and the patient [18]. While there have been only a few studies on the matter, significant reductions in insomnia and nightmares have been demonstrated through IRT therapy in PTSD patients [18]. Some uncontrolled experiments implicate continuous positive airway pressure as also improving sleep quality, with reduction in nightmare incidence, insomnia and other PTSD symptoms [18]. Continued research is necessary to determine the value of behavioral therapies for sleep disorders.

Additional sleep disorder treatment techniques include behavioral therapy such as biofeedback, as well as light therapy, chronotherapy, and pharmacotherapy, using sedatives and/or hypnotics [19,22-24]. Relaxation therapy, stimulus control therapy [25], sleep restriction therapy [26], and cognitive behavioral therapy (CBT) [27] are other interesting non-pharmacological techniques utilized to treat sleep disorders.

Pharmacotherapeutic Intervention

In the search for a drug which induces sleep without the usual hypnotic-abuse liability and toxicity has been a real challenge for the pharmaceutical industry. Griffiths et al. [28] evaluated 19 hypnotic drugs for both abuse liability and toxicity and found that Phenobarbital has the highest abuse liability and toxicity and Trazodone (a non-approved anti-insomniac drug) while having no abuse liability potential does have significant toxicity [28]. However, one drug, ramelteon, was found not to have any abuse liability or toxicity. This is quite interesting considering that this substance does not bind to the typical GABA receptor. Unlike all other hypnotic drugs used to treat insomnia, ramelteon is a melatonin receptor agonist acting at MT1 MT2 receptors located at/in the superchiasmatic nucleus, which affects the circadian sleep-wake cycle. The MT1 receptor seems to be associated with direct promotion of sleep. This receptor is believed to play a role in helping to quiet down arousal and allow sleepiness to take over. The MT2 receptor seems to be acting primarily with respect to the reinforcement of the whole 24-hour cycle. Ramelteon has negligible affinity for the MT3 receptors, which are widely distributed throughout the body, or for other major neurotransmitter receptors such as GABA, histamine, opioid, dopamine, or acetylcholine. A recent PubMed search revealed a total of 1,138 papers regarding pharmacological and non-pharmacological treatment of chronic insomnia of which 755 were pharmacological.

Hypothesis

It is hypothesized that measurement of various genetic mutations through gene expression, single nucleotide polymorphisms, as well as additional phenotypic and genetic diagnostics, with the interest of changing the makeup and creation of nutritional supplements, will shift the diagnostic, stratification, prognostic, and treatment paradigm for sleep in humans. Furthermore, mesolimbic neurochemical reward circuitry manipulation inducing dopamine release at the Nucleus accumbens will offer benefits in stress and pain relief, both major

factors in sleep processes [29]. Specifically, the present theoretical notion includes proprietary algorithms that combine genetic mutations into index values, referred to as Genoscores, to represent specific pre-defined formulations. We hereby propose that a number of experiments be performed to further our scientific credibility. The experiments will include both genetic and non-genetic subjects and the formulations will include both “one-size-fits all” as well as DNA-based customized formulations to induce sleep. The trials will also include comparisons with known FDA approved sleep medications. The protocol will consist of a double-blind randomized placebo-controlled cross-over study. The measurement scales will include one of the following instruments: Fatigue Severity Scale (FSS); Stanford Sleepiness Scale (SSS); Epworth Sleepiness Scale (ESS) and/or Chalder Fatigue Scale (CFS) or Empirical Sleepiness & Fatigue Scales developed by Bailes and associates.

EZ-Sleep™

EZ-sleep™ is a unique formula and method to safely and naturally induce effective sleep. This novel technology contrasts with existing tactics to manipulate three important pathways in sleep induction. Moreover we are hypothesizing that EZ-Sleep™, a putative dopaminergic, melatonin, benzodiazepine reward circuitry receptor(s) activator, may become an important front-line non-pharmacological treatment for chronic insomnia. We further hypothesize that utilization of this nutraceutical may result in significant reduction of hypnotic medication abuse and toxicity liability thereby increasing benefit over risk.

Rationale

This novel approach utilizes synergistic nutraceutical components to exploit symbiotic mechanisms stimulating metabolism and healthy sleep through:

1. Pleasure mechanisms that effect stress
2. The metabolic and immunological mechanisms that effect sleep induction.
3. The neuroendocrine system that affects circadian rhythm

Importantly, these three systems are homeostatic and compensatory, intimately interactive and interdependent in ensuring optimal sleep and metabolic function. This novel nutraceutical technology optimizes sleep mechanisms especially those tied to stress. Table 1 lists the ingredients in EZ-Sleep™. A careful review of the existing literature reveals that the ingredients in EZ-Sleep™ should lead to enhance sleep function. In the arsenal of nutrients, EZ-Sleep™ primarily contains sleep inducing ingredients.

Ingredients & Scientific Explanation

EZ-Sleep™ complex: stress reduction components

Manipulation of pleasure mechanisms that effect stress is exploited by some of the ingredients of EZ-Sleep™, especially through promotion of dopamine release at the Nucleus accumbens, stimulating stress reduction and pain reduction.

In humans, an imaging study by Hilker and associates (2006) found that marked striatal dopamine depletion was demonstrated in patients with REM sleep behavior disorder utilizing functional MRI [30]. Dopamine is also involved in other sleep disorders including Restless Leg syndrome (RLS). A neurological disorder affecting 1-10% of the population, RLS induces urges to move ones extremities in an effort to address paraesthetic sensations [31]. RLS symptoms are heightened when going to sleep in the evening and interrupt/delay desired sleeping

Supplement Facts
Serving Size: 1 Tablet, 45 minutes before bedtime without food
Serving per container: 60
Amount per Serving
Vitamin B6 (as Pyridoxine HCL, Pyridoxal-5-Phosphate)
Calcium (as hydroxycitrate)
Magnesium (as magnesium citrate and oxide) (aspartate is better!)
Manganese (ascorbate)
Potassium (as hydroxycitrate)
Synaptamine Proprietary Complex
Chromium picolinate
DL-phenylalanine (D-PhenEze™)
L-Glutamine
Rhodiola rosea Extract (3%)‡ (RhodiGen™)
Grifonia simplicifolia Extract (5-HTP)
**EZ Sleep™ Proprietary Calming blend
Passiflora incarnata L. Extract Δ (EM103 Passiflora incarnata)
Protykin (50% trans-resveratrol)
Melatonin
* Daily Value not established.
**Chamomile, Valerian, and Hops Flower (33 mg each)
TOTAL MGs

Table 1: Ingredients of EZ-Sleep™: the putative dopaminergic, melatonin, benzodiazepine reward circuitry receptor(s) activators that enable sleep induction benefits.

and waking times. While the etiopathogenesis of RLS remains unknown, a dopaminergic system is hypothesized to play an important role in RLS manifestation-the use of dopamine agonists in treatment, such as 2005 FDA approved ropinirole, offer valuable therapeutic solutions to RLS [31].

Dopaminergic involvement of sleep and wakefulness is very complex, and exact mechanisms are still unclear. The various receptors of dopamine (D1-D5) all have very distinct properties and may interact at different sleep processes. While dopamine agonists seem to induce sleep interaction of dopamine at various dopamine receptor sites, there may be differential sleep induction and wakefulness depending on the dopamine receptor targeted. For example, recent hypotheses implicate D3 receptor involvement in pramipexole stimulated sleep increase and locomotor activity reduction [32]. Furthermore, high dose pramipexole stimulated postsynaptic D2 receptor activation has been hypothesized to increase motor behavior and wakefulness [32]. REM latency has been increased in rats that were administered a dopamine D4 receptor antagonist (L-741,741), and these results suggest a role for D4 receptors in the regulation of wake and sleep [33].

Lima et al. [34] following animal experimentation, proposed that blockage of dopaminergic D2 receptors produce a decrease of REM but not of slow wave sleep in rodents after REM sleep deprivation [34]. This work suggests that in regards to sleep and wake state maintenance and regulation, dopamine acts as a key substance [34].

While there is sufficient evidence for serotonergic involvement in stress induced insomnia and SSRI's may work in certain instances, long term treatment of insomnia with these agents have been somewhat disappointing, in spite of significant animal work suggestive of serotonin involvement in sleep disorders.

The serotonergic synthesis inhibitor para-chlorophenylalanine, p-CPA, pretreatment has been studied in a murine model, utilizing young male Charles Foster rats subjected to acute immobilization stress, to investigate their resultant sleep-wake patterns [35]. Three groups of rats, subjected to (i) acute immobilization stress, (ii) p-CPA

pretreatment and acute immobilization stress, and (iii) neither p-CPA pretreatment nor acute immobilization stress, were monitored in their sleep quality and resultant wakefulness [35]. As a result, p-CPA pretreatment successfully reversed the detrimental effects following acute immobilization stress, including changes in total sleep time and total time of REM sleep [35]. Other work from the laboratory of Geller and Blum initially showed that p-CPA caused an enhancement of stress related conflict in rats [36].

The following ingredients promote stress manipulation through synergistic and symbiotic mechanisms.

Passiflora incarnate: Passionflower is the name of several plants stemming from the Passiflora genus [37]. The origin of Passiflora is in the tropical and subtropical regions of the western hemisphere, and there are over 40 different species in the genus. First transported by Spanish conquerors from Mexico to Europe in the sixteenth century, Passionflower has been utilized as a calming tea remedying menstrual pain, conjunctivitis, hemorrhoids, diarrhea, colic, dysentery, skin eruptions, and muscle spasms and is now a worldwide medical herb. The inclusion of Passionflower in sleep inducing formulas exploits its effect on the central nervous system (CNS) and its stress reduction effects [38]. When in a comfortable sleep environment a reduction in stress should be associated with sleepiness.

A problem with Passionflower is its identity since a number of alkaloids have been sold under its name; however, *Passiflora incarnate* (P. incarnata) stands out as the most important, being the most consistently effective. The total alkaloid content of P. incarnata, as listed on the U.S. Agricultural Research Service's ethno botanical database, is 100 to 900 ppm, and it has a 1.2% to 3.9% total flavonoid content. In P. incarnata, there are twenty flavonoids, amongst them gynocardine and cyanogenic glycoside, as well as six alkaloids, and some researchers have attributed the sedative effects from P. incarnata to the alkaloids: Harmane and relatives, harmol and harmaline. In contrast, other researchers have attributed CNS bioactivity to flavonoids such as luteolin, apigenin, or their glycosides, stating that the alkaloid content of P. incarnata is not high enough to cause CNS effects.

Most recently, a highly anxiolytic, tri substituted benzoflavone moiety has been isolated from a P. incarnata extract. P. incarnata extract has effectively restored the libido of older male rats [39]; restored fertility and libido previously compromised by tetra hydro cannabinol, nicotine and alcohol addiction [40]; and compared to oxazepam, double-blind randomized studies have indicated that Passiflora extract has been proven to be a fairly effective means for managing generalized anxiety [39]. Interestingly, other double-blind randomized controlled trials have suggested the potential for Passiflora extract as a valuable adjuvant for managing opiate withdrawal [41]. In a mice model, Passiflora has been shown to decrease benzodiazepine dependence. Moreover, the sedative effects of P. incarnata have been verified in numerous pharmacological investigations. EZ-Sleep™ was formulated with information from Euro med (source of dried aerial EM103 P. incarnata parts, cut or fragmented). Separated leaves have been demonstrated as affording the highest possible CNS results, and excluding the flowers, the usage of all aerial parts may prove to be the best method for maximizing bioactive EM103 P. incarnata plant parts. Passiflora preparation standardization has been studied actively, in special regard to its relation on anxiolytic activity.

It was suggested in the early 1970's, by one of us (KB), that serotonin was a biological substrate of stress. Through injections of p-CPA, a serotonin chemical synthesis depletor in rodents, the initiation of stress

in rodents was attenuated. Other researchers have also recognized and shown serotonin and dopamine involvement in the production of stress in humans and other animals. By comparing skin conductance levels in a double-blind randomized controlled human trial, stress levels have been shown to be reduced by amino acid and enkephalinase inhibition therapy. These results support *Passiflora* extract use for anxiety disorder treatments, especially for serotonin mediated disorders. Interestingly, this is homologous to a *Passiflora* extract phyto constituent indole.

The genus *Passiflora* comprises about 500 species [37]. The substance *Passiflora incarnata* and its benzoflavone isolate binds to the benzodiazepine receptor [42]. As such, it has many biological effects including promotion of sleep, anxiolytic activity [43], anti-alcohol and opiate craving activity [40], promotion of sexual appetite [39], and hypnotic activity [44].

11.1.2 DL-Phenylalanine (validated via FTIR verified reference standard D-PhenEze™): DL-phenylalanine (DLPA) inhibits the breakdown of the opioid peptides and has been shown to reduce stress in a double blind placebo controlled study. DLPA has been found to reduce stress by anti-craving reward mechanism.

D-phenylalanine inhibits the enzyme enkephalinase, which metabo-lizes or breaks down enkephalins, thereby increasing enkephalins availability and, most likely, increasing dopamine availability at reward sites (under stressful conditions especially) [45-47].

Furthermore, L-phenylalanine is utilized to stimulate dopamine production and/or increase brain reward neither area nor epinephrine levels. A significant problem with L-phenylalanine is potential competition with other amino-acids, i.e. blood born L-tyrosine and L-tryptophan at the large neutral amino-acid brain carrier system. However, for the first time, other data has demonstrated synthesis and release responses to several dopaminergic agents may be stemming from synaptosomal dopamine, a product of the hydroxylation of phenylalanine. Dopamine created from 14C-phenylalanine in the Caudate nucleus of a rat through synaptosomal preparation was increased and concomitantly stimulated by Cogentin and Amphetamine. A net increase in dopamine also occurs due to amfoelic acid. In this regard, synaptosomal particles are potential components that can synthesize dopamine from L-phenylalanine; synthesis from L-phenylalanine potentially under regulatory control by synaptosomal particles.

L-Tyrosine: L-tyrosine is utilized to increase dopamine levels in the brain as an amino-acid synthesis promoter, direct precursor. L-tyrosine is used for repletion of metabolized neurotransmitters (i.e. dopamine).

EZ Sleep™ Proprietary Calming Blend: The following ingredients constitute the calming blend to promote sleep: Chamomilia flower, hops flower, valerian root extract, Jamaican dogwood extract, valanic acid, and kava kava. Chamomile extract leads to a significant decrease in sleep latency in rats [48]. Kava Kava reduced generalized anxiety disorder in humans [49,50]. A combination of Valerian-Hops is used as a sleep aid [51]. Binding affinities were observed for this combination of serotonin receptor subtypes including 5-HT7 that promotes sleep. Valerian and valanic acid are partial agonists of the 5-HT5A receptor, a substrate involved in insomnia. Valanic acid enhances the sedative effects of Valerian. Trends toward increase in slow-wave sleep and lack of effect on REM sleep were observed in 1994. There have been studies on Hops that show a sedative effect [52].

Pyridoxal-5-phosphate: Pyridoxal-5-phosphate is the active ingredient of vitamin B₆, important as a co-factor in neurotransmitter

production and gastrointestinal amino acid absorption improvement.

Calcium: Calcium promotes release of neurotransmitters. Many metabolic events require calcium, and calcium nutrient inclusion is therefore proposed by the authors to promote sleep. Calcium in a number of species induces a sleep-like state [53,54].

EZ-Sleep™ complex: sleep induction enhancement components

While stress-reduction plays an important role in enabling sleep induction, other components of EZ-Sleep™ directly promote sleep induction through various other mechanisms. Most of the hypnotic drugs on the market are central nervous depressants acting at the gamma- aminobutyric acid (GABA)_A receptor. In this regard, wisdom dictates that only a few hypnotic-like drugs have been approved to treat insomnia, but not beyond short term therapy because of the abuse liability. The benzodiazepine hypnotics are only approved for short term use, as are zolpidem immediate-release (Ambien) and zaleplon (Sonata) the non-benzodiazepine agents that act at the same benzodiazepine-activated GABA_A receptor complex. The following ingredients make use of the GABA complex and serotonergic mechanisms to aid sleep induction.

L-Glutamine: L-glutamine, a precursor amino-acid for GABA, is utilized to increase GABA levels in the brain at anxiety associated receptors. L-glutamine maintains balance in case of D-phenylalanine over-inhibition. The inhibitory action of GABA on brain function is tied to integrated sleep processes [55]. GABA shuts off the neurotransmitters that induce wakefulness. Chronic excess of GABA in the brain induces increased slow-wave sleep [56]. Studies have shown that Adenosine A2A receptor agonist induced sleep by inhibiting the histaminergic system through increasing GABA release in the tuberomammillary nucleus [57]. GABA is linked to the benzodiazepine receptor. The sedative hypnotic benzodiazepine-GABA receptor agonist (BzRas) Zaleplon induces a long-term anti-insomnia effect in older patients [58]. The GABA_A receptor is the target for most widely prescribed sleep medications [59]. The stimulation of the benzodiazepin-GABA site induces sedation, hypnosis, and anxiolytic activity.

Grifoniasimplicifolia Extract, 5-HTP (optional): 5-HTP is an amino acid precursor to brain serotonin. Serotonin levels rise during sleep stages. Sleep is a problem with age and many old people complain about insomnia. It is known that age induces a decrease in serotonergic receptors. The serotonin precursor 5-HTP causes a reversal of insomnia by para-chlorophenylalanine induced serotonin brain depletion [60]. While Serotonin-2A and 2C receptor gene polymorphisms may associate with sleep problems in Japanese patients, these polymorphisms did not associate with apnea [61]. However, both age and BMI did associate. Sleep apnea syndrome is associated with serotonin transporter gene polymorphism [62]. While the 5-HT2A receptor may be involved in insomnia (whereby antagonists may be helpful), 5-HT7 promotes REM sleep [63,64]. Injection of a 5-HT1A -receptor agonist directly into the dorsal midbrain promotes sleep.

Utilizing brain micro dialysis, lateral hypothalamus serotonin release was examined following systemic administration of 5-hydroxy-1-tryptophan in an in vivo rat model [65]. A long lasting, dose-dependent and immediate increase in dialysates 5-HT is observed with the administration of 5-HTP. The 5-HTP- induced response of 5-HT was significantly attenuated and levels of basal 5-HT decreased significantly, when calcium was not included in the perfusion medium, thereby limiting exocytosis.

Chromium Salts (Nicotinate and Picolinate): Chromium is a

tryptophan enhancing substance, which increases the brain content of serotonin. Serotonin is involved in the natural sleep process [66]. Brain serotonin production has been shown to be promoted by an oxygen-coordinated chromium nicotinate. Picolinate, another chromium salt, effects the production of serotonin. Since brain serotonin is important as a sleep neurotransmitter, the EZ-sleep™ formula will contain this salt [67].

Rhodiola rosea Extract (3%) (validated via FTIR verified reference standard RhodiGen™): As demonstrated in several clinical trials with double-blind placebo controls, *Rhodiola rosea* (*R. rosea*) positively enhances mood, reduces stress and has no detectable toxicity levels. *R. rosea* extract positively influences the higher nervous system, improving memory and attention span. Where lower dopamine and serotonin brain levels are observed, it is hypothesized that *R. rosea* can potentially act as a COMT inhibitor. COMT activity has been decreased by 60% and neurotransmitter levels by 30% by *R. rosea*. This phenomenon will assist in sleep induction. Moreover, the plant adaptogen *R. rosea* promotes positive effects on sleep [68]. *R. rosea* has a positive effect on paradoxical sleep deprivation [69]. *R. rosea* improves endurance exercise in healthy young adults [70]. *R. rosea* reduces stress and improves sleep [71]. *R. rosea* improves mental capacity in a double-blind study [72]. *R. rosea* was effective in improving sleep quality in young men living in high altitudes [73].

Manganese (ascorbate) (ManganEze™): Manganese is found in a large variety of minerals, sea and fresh water, marine and land plants, and animals [74]. Manganese is an essential trace element, human requirements being estimated at between 3 and 9 mg per day. 15 studies have described the adverse mood effects of Manganese (Mn) overexposure, specifically in six dimensions of mood: (i) irritability, nervousness and anxiety; (ii) emotional disturbance; (iii) psychotic experiences; (iv) sleep disturbance, lack of vigor and fatigue; (v) aggression hostility; (vi) compulsive and/or impulsive behavior [75]. 1:15 studies utilized standardized measures of mood. When the Brief Symptom Inventory (BSI) and Profile of Moods State (POMS) standardized mood scales were used to evaluate low Mn levels of exposure and its consequence on mood, results indicated that older men with higher Mn levels showed significant disturbances on four of the six mood dimensions relative to men with lower Mn levels, including irritability, nervousness and anxiety; aggression hostility; and emotional disturbance [75]. The POMS and BSI are useful standardized mood scales for the assessment of Mn/mood effects [75]. However, optimal doses produce health benefits. Mn has hypnotic-like effects and as such, enhances alcohol-induced sleeping time in mice. There are no human studies directly involving the effects of Mn on sleep performance, but it has been considered as a sedative inducing nutrient for years.

EZ-Sleep™ complex: neuroendocrine circadian rhythm manipulation components

Circadian rhythm, created by molecular mechanisms, is considered a biological property universal to the majority of living things on earth; in which, the regulation of clock genes through a transcription feedback loop is vital to all studied species [76]. The clock genes observed in insects and mammals have been remarkably alike, indicating genetic level, evolutionary circadian rhythm conservation [76]. Homeostasis and circadian rhythms work concomitantly to regulate arousal and sleep in mammals; however, the underlying genetic pathway through which sleep is regulated is not readily understood. Similarities in the molecular arousal regulation pathways between insects and mammals have been discovered; in example, dopamine has been implicated as a key player in the regulation of arousal and sleep-like behavior in ants [76].

Interestingly there is strong evidence for the interaction of melatonin and dopamine D2 receptor. Both the melatonin and dopaminergic systems regulate the light/dark cycles in the animal as well as in the human [77].

Acknowledged to play a role in numerous mammalian brain regions such as the retina, hypothalamus, and nigrostriatal system, the presence of a dopamine-melatonin association is of particular interest. For example, in C57BL/6 mice nigrostriatal damage is caused by the effect of melatonin on 1 methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine [78]. In C57BL/6 mice, however, the interaction between striatal dopamine and melatonin rhythmic production is not readily understood [77].

Work utilizing the C57BL/6 mice model has investigated circadian rhythm variations in striatal dopamine levels and pineal production of melatonin [78]. This work has indicated the possibility for a series of significant dopamine and melatonin interactions. In mice controls, melatonin has a narrow circadian rhythm peak at midnight, striatal dopamine reaches a low-point at midnight, and 3,4-dihydroxyphenylacetic acid (DOPAC) levels, a primary dopamine metabolite, increase shortly after a decrease in striatal dopamine levels [78]. Following pineal gland removal, the cyclic changes in dopamine and DOPAC levels were less pronounced; however, administration of melatonin over a 6 day period to pinealectomized mice dose-dependently repaired this rhythm [78]. This suggests a potential murine linkage between pineal melatonin secretion and dopamine circadian rhythm [78].

Ramelteon, approved by the Food and Drug Administration (FDA) in 2005, is presently the only medication utilized for long-term insomnia treatment and works by exploiting the soporific property of melatonin; it works as a melatonin receptor agonist [79]. The efficacy of ramelteon is not presently known, although findings have been promising; the efficacy will rely on the results of additional placebo-controlled trials [79]. The effectiveness of melatonin and ramelteon in treating insomnia requires further attention, as present data on the topic is based on studies with several limitations, and there have been only three control trials for ramelteon [79]. It is important to note that sleep maintenance has not been shown to improve with zolpidem controlled-release or eszopiclone, a GABAA agonist. In fact, according to Johnson and Griffiths (2005) subjective comparisons have characterized the hypnotic effect of ramelteon relative to the benzodiazepine and non-benzodiazepine GABA_A active agents as “more subtle” and “less prominent” [28]. Furthermore, post-sleep questionnaires have indicated that ramelteon's hypnotic effect may be experienced as less robust than could be expected from polysomnography data [80].

The following EZ-Sleep™ ingredients affect circadian rhythms, promoting improved sleep quality and improved duration.

Melatonin: Existing as a hormone, endogenous melatonin is secreted by the pineal gland and linked to circadian rhythm [81]. A study of melatonin in the 1970's and 1980's revealed sedative/hypnotic effects of this compound [82,83]. In a recent meta-analysis of 16 studies by Buscemi et al. [84]. It has been concluded that while melatonin may not be effective in primary sleep disorder treatment, it is potentially useful in short term DSPS treatment [84]. The use of melatonin for a short period, 3 months or less, has been implicated as safe.

The pineal gland hormone melatonin improves sleep quality [85]. A recent meta-analysis reveals melatonin treatment significantly reduced sleep onset latency and increased total sleep duration [86]. Melatonin secretion helps regulate sleep and circadian rhythms [87]. Beta-Methyl-6 chloromelatonin significantly decreases sleep latency in insomnia

[88]. Melatonin improves sleep behavior in children with epilepsy [89]. While one study was negative with respect to the effectiveness in melatonin versus placebo with regard to sleep deprivation of winter depression, other studies are positive in terms hypnotic actions [90]. It seems that the effects of melatonin on sleep works best in patients that have abnormal sleep patterns compared to health individuals [91, 92].

Magnesium (ligand? aspartate?) (MagNezyum™): Chronic stress reduces intracellular magnesium [93]. Aging effects sleep and magnesium reverses these age-related effects and promotes sleep [94]. EEG blood magnesium levels are under strong genetic control, whereas brain magnesium levels are not [95]. Optimal levels of magnesium are required for normal sleep regulation [96].

INGREDIENT	DOSE	FINDING
Pyridoxine HCL Pyridoxal 5-Phosphate	20 mg (20% PHCL; 80% P-5-P	Catalyst for synthesis of neurotransmitters
Chromium ^{a,b}	400 mcg	Chromium is a tryptophan enhancing substance, which increases the brain content of serotonin. Serotonin is involved in the natural sleep process [66].
DL-phenylalanine ^{c,d,e,f}	2000 mg	DLPA inhibits the breakdown of the opioid peptides and has been shown to reduce stress in a double blind placebo controlled study. DLPA has been found to reduce stress by anti-craving reward mechanism.
L-Glutamine ^{g,h,i,j,k}	150 mg	L-Glutamine is the precursor amino-acid for GABA. The inhibitory action of GABA on brain function is tied to integrated sleep processes [55]. GABA shuts off the neurotransmitters that induce wakefulness. Chronic excess of GABA in the brain induces increased slow-wave sleep [56]. Studies have shown that Adenosine A2A receptor agonist induced sleep by inhibiting the histaminergic system through increasing GABA release in the tuberomammillary nucleus [57]. GABA is linked to the benzodiazepine receptor. The sedative hypnotic benzodiazepine–GABA receptor agonist (BzRas) Zaleplon induces a long-term anti-insomnia effect in older patients [58]. The GABAA receptor is the target for most widely prescribed sleep medications [59]. The stimulation of the benzodiazepin –GABA site induces sedation, hypnosis, and anxiolytic activity.
Grifoniasimplicifolia Extract (5-HTP) ^{l,m,n,o,p,q,r,s,t,u}	100 mg	5-HTP is an amino acid precursor to brain serotonin. Serotonin levels rise during sleep stages. Sleep is a problem with age and many old people complain about insomnia. It is known that age induces a decrease in serotonergic receptors. The serotonin precursor 5-HTP causes a reversal of insomnia by para-chlorophenylalanine induced serotonin brain depletion [60]. While Serotonin-2A and 2C receptor gene polymorphisms may associate with sleep problems in Japanese patients, these polymorphisms did not associate with apnea [61]. However, both age and BMI did associate. Sleep apnea syndrome is associated with serotonin transporter gene polymorphism [62]. While the 5-HT2A receptor may be involved in insomnia (whereby antagonists may be helpful), 5-HT7 promotes REM sleep [63,64]. Injection of a 5-HT1A –receptor agonist directly into the dorsal midbrain promotes sleep.
Melatonin	10 mg	The pineal gland hormone melatonin improves sleep quality [85]. A recent meta-analysis reveals melatonin treatment significantly reduced sleep onset latency and increased total sleep duration [86]. Melatonin secretion helps regulate sleep and circadian rhythms [87]. Beta-Methyl-6 chloromelatonin significantly decreases sleep latency in insomnia [88]. Melatonin improves sleep behavior in children with epilepsy [89]. While one study was negative with respect to the effectiveness in melatonin versus placebo with regard to sleep deprivation of winter depression, other studies are positive in terms hypnotic actions [90]. It seems that the effects of melatonin on sleep works best in patients that have abnormal sleep patterns compared to health individuals [91,92].
Rhodiola rosea	100 mg	The plant adaptogen rhodiola rosea promotes positive effects on sleep [68]. Rhodiola rosea has a positive effect on paradoxical sleep deprivation [69]. Rhodiola rosea improves endurance exercise in healthy young adults [70]. Rhodiola rosea reduces stress and improves sleep [71]. Rhodiola rosea improves mental capacity in a double-blind study [72]. Rhodiola was effective in improving sleep quality in young men living in high altitudes [73].
Passion Flower	300 mg	The genus Passiflora comprises about 500 species [37]. The substance Passifloraincarnita and its benzoflavob isolate binds to the benzodiazepine receptor [42]. As such, it has many biological effects including promotion of sleep, anxiolytic activity [43], anti-alcohol and opiate craving activity [40], promotion of sexual appetite [39], and hypnotic activity [44].
Calming Blend		
(The following ingredients constitute the calming blend to promote sleep: Chamomilia flower, hops flower, valerian root extract, Jamaican dogwood extract, valanic acid, and kava kava)	200 mg	Chamomiles extract lead to a significant decrease in sleep latency in rats [48]. Kava Kava reduced generalized anxiety disorder in humans [49,50]. A combination of Valarian–Hops is used as a sleep aid [51]. Binding affinities were observed for this combination of serotonin receptor subtypes including 5-HT7 that promotes sleep. Valarian and Valanic acid are partial agonists of the 5-HT5A receptor a substrate involved in insomnia. Valanic acid enhances the sedative effects of Valarian. Trends toward increase in slow-wave sleep and lack of effect on rapid eye movement (REM) sleep were observed in 1994. There have been studies on Hops that show a sedative effect [52].
Magnesium	270 mg	Chronic stress reduces intracellular magnesium [93]. Aging effects sleep and magnesium reverses these age-related effects and promotes sleep [94]. EEG blood magnesium levels are under strong genetic control, whereas brain magnesium levels are not [95]. Optimal levels of magnesium are required for normal sleep regulation [96].
Calcium	555 mg	Calcium in a number of species induces a sleep-like state [53, 54].
Manganese ascorbate	13.25 mg	Manganese is found in a large variety of minerals, sea and fresh water, marine and land plants, and animals [74]. Manganese is an essential trace element, human requirements being estimated at between 3 and 9 mg per day. 15 studies have described the adverse mood effects of Manganese (Mn) overexposure, specifically in six dimensions of mood: (i) irritability, nervousness and anxiety; (ii) emotional disturbance; (iii) psychotic experiences; (iv) sleep disturbance, lack of vigor and fatigue; (v) aggression hostility; (vi) compulsive and/or impulsive behavior [75]. 1:15 studies utilized standardized measures of mood. When the Brief Symptom Inventory (BSI) and Profile of Moods State (POMS) standardized mood scales were used to evaluate low Mn levels of exposure and its consequence on mood, results indicated that older men with higher Mn levels showed significant disturbances on four of the six mood dimensions relative to men with lower MN levels, including irritability, nervousness and anxiety; aggression hostility; and emotional disturbance [75]. The POMS and BSI are useful standardized mood scales for the assessment of Mn/mood effects [75]. However, optimal doses produce health benefits. Mn has hypnotic-like effects and as such, enhances alcohol sleeping time in mice. There are no human studies directly involving the effects of Mn on sleep performance, but it has been considered as a sedative inducing nutrient for years.

Table 2: Clinical support for ingredients of EZ-Sleep™: the relative dosage and scientific findings in clinical support of various ingredients to be utilized in the EZ-Sleep™ formula.

EZ-Sleep™ complex: additional components

The final components of EZ-Sleep™ are supplements and proprietary complexes involved in antioxidant support and sleep mechanism facilitation.

Protykin (50%): Protykin is an extract of *Polygonum cuspidatum* which supplies antioxidant and hormone support.

Potassium

Synaptamine Proprietary Complex: Table 2 lists the relative dosages and summarizes the clinical support for the ingredients of EZ-Sleep™.

Conclusion

The issue of insomnia is a global phenomenon which requires additional in-depth research. Insomnia especially in alcohol-dependent patients, for example, may lead to suicide. It is noteworthy that childhood sleep problems predict the onset of drinking in boys [97]. We now know that while there are multifaceted reasons for sleep problems and disturbances (e.g. sleep drive homeostasis, circadian rhythm physiology and genetic influences), the scientific community has not been able to deliver an appropriate solution. Some benefit has been noted with cognitive behavioral therapy, but it has minimal effects in patients relapsing from drugs especially alcohol, cocaine and opiates. While there are a number of pharmaceutical drugs developed to treat insomnia, most have associated side effects and even addiction liability. We do know that benzodiazepines hijack the midbrain dopamine system leading to addiction. Finally, Lima et al. [34] proposed that dopamine D2 receptors are involved in rapid eye movement sleep, suggesting as we have proposed herein that dopaminergic activation is one mechanism worthwhile exploring in the future [34]. The concepts presented herein on potential nutrigenomics therapy warrants further in-depth analysis [98-105].

Acknowledgement

The writing of this paper was supported in part by funds from the National Institutes of Health, NIAAA (RO1-AA07112 and K05-AA00219) and the Medical Research Service of the US Department of Veterans Affairs (MOB). TS is partially supported by SAHMSA grants as well. The writing of this paper was funded in-part by a grant awarded to Kenneth Blum and Eric R. Braverman from Life Extension Foundation, Ft. Lauderdale, Florida to PATH Foundation NY.

Conflicts of Interest

Kenneth Blum, PhD, holds US and foreign patents on nutraceutical complex. Kenneth Blum, Bernard W. Downs, Margaret Madigan are owners and employees of IGENE and Impact Genomics. There are no other conflicts.

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