IRB Protocol No. 35933
Version Date: 11/10/2015

Efficacy of Trazodone vs. Cognitive Behavioral Therapy in Patients with Chronic Insomnia associated with Objective Short Sleep Duration

Principal Investigator: Alexandros N. Vgontzas, M.D.
Department of Psychiatry

Table of Contents

Sections

1.0 Introduction

Insomnia is the most common sleep disorder and is associated with significant morbidity and mortality. Female gender, middle-age, physical and mental health problems, and heredity have been reported as risk factors for the development of insomnia. Despite the fact that over the past two decades insomnia has been the focus of extensive research, its pathophysiology remains obscure and most commonly available treatments for this disorder are associated with good outcomes in subjective sleep quality but poor outcomes in objective sleep duration. Furthermore, the criteria for diagnosing insomnia is only based on subjective reports, and the decision on how to treat it is frequently a challenge to the clinician.

A. Chronic insomnia is associated with emotional and physiological hyperarousal – Insomnia is considered to be the most common sleep disorder (NIH, 2005). Its prevalence varies considerably based on the definition used. While one-fourth to one-third of the general population reports a complaint of difficulty falling and/or staying asleep (US Department of HEW, 1970; Karacan et al, 1976; Bixler et al, 1979; Mellinger et al, 1985; Klink and Quan, 1987; Klink et al, 1992; Dodge et al, 1995; Foley et al, 1995; US Department of DHHS, 1996), about ten percent present chronic complaints and seek medical help for insomnia (Ancoli-Israel and Roth, 1999; Ford and Kamerow, 1989). Insomnia is more common among women, middle-aged and older adults, and patients with medical or psychiatric disorders. Despite the evidence that insomnia has significant public health implications, including impaired occupational performance, increased absenteeism at work, higher health care costs, and quality of life (NIH, 2005; Basta et al, 2007; Buysse et al, 2006; Simon and Von Korff, 1997; Chevalier et al, 1999), the connection of insomnia to significant medical morbidity, i.e., cardiometabolic and neurocognitive risks, and mortality has been just recently reported (Vgontzas et al, 2009a; Vgontzas et al, 2009b; Vgontzas et al, 2010; Fernandez-Mendoza et al, 2010).

The diagnosis of insomnia, according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV TR), is based solely on the subjective complaints of difficulty initiating or maintaining sleep, early awakening, and interrupted or non-restorative sleep, that are associated with clinically significant impairment in daytime function, for which no identifiable cause i.e. other sleep disorder, psychiatric disorder, medical condition, is attributed (American Psychiatric Association, 2000.). There are no objective measures that are useful in the diagnosis, differential diagnosis, severity assessment, or therapeutic response of insomnia (NIH, 2005; Basta et al, 2007; Buysse et al, 2006; Chesson et al, 2000). Such a gap increases the uncertainty in terms of diagnostic priorities and treatment guidelines.

Insomnia is associated with both emotional and physiological hyperarousal (Kales and Kales, 1984; Kales et al, 1983; Bonnet and Arand, 2003; Bonnet and Arand, 1995; Bonnet and Arand, 2006). Insomniacs tend to be anxious, ruminative, and depressed while physiologically they have significantly increased rectal temperature, heart rate, vasoconstriction, increased skeletal muscle movement before and during sleep, increased metabolic rate and inability to fall asleep during the day despite the subjective feeling of

fatigue, extreme at times (Kales and Kales, 1984; Kales et al, 1983; Bonnet and Arand, 2003; Bonnet and Arand, 1995; Bonnet and Arand, 2006; Stepanski et al, 1988; Edinger et al, 2001). These characteristics are different than those found in healthy subjects after sleep deprivation, i.e., severe objective sleepiness, decreased metabolic rate, etc. (Bonnet and Arand, 2003; Bonnet and Arand, 1995; Vgontzas et al, 1999; Vgontzas et al, 2004; Vgontzas et al, 2007). Furthermore, data from the quantitative EEG analysis, neuroimaging and neurocognitive function suggest that insomnia is a disorder of physiological hyperarousal and not a disorder of sleep loss (Merica et al, 1998; Perlis et al, 2001; Nofzinger et al, 2004; Fernandez-Mendoza et al, 2010; Fulda and Schulz, 2001).

Until several years ago, few studies had assessed the activity of the stress system (e.g., cortisol levels) in insomniacs and their results were inconsistent. The majority of these studies reported no difference between "poor" sleepers and normal individuals in the levels of 24-h cortisol and 17-hydorxysteroid excretion (Frankel et al, 1973; Johns et al, 1971; Adam et al, 1986). A preliminary study by our group investigated possible association between chronic insomnia and the activity of the stress system by measuring urinary free cortisol (UFC), catecholamines, and growth hormone (GH) and found that 24-h UFC levels, norepinephrine, and catecholamine metabolites were positively correlated with polysomnographic indices of sleep disturbance, i.e., total wake time (TWT) or percent stage 1 sleep (Vgontzas et al, 1998).

In a subsequent controlled study 24-h serial adrenocorticotropic hormone (ACTH) and cortisol levels were significantly higher in insomniacs compared to normal sleepers (Vgontzas et al, 2001). Within the 24-h period the greatest elevations were observed in the evening and during the first half of the night. Furthermore, within the group of insomniacs, the sub-group with high degree of objective sleep disturbance (%TST <70) had higher amount of cortisol compared to the subgroup with low degree of sleep disturbance. The group of insomniacs with high sleep efficiency was not different in terms of cortisol levels from normal controls. Based on these two studies, we concluded that in chronic insomnia 1) the activity of the stress system is directly proportional to the degree of objective sleep disturbance, and 2) polysomnographic measures can provide a reliable index of the biological impact and severity of chronic insomnia (Vgontzas et al, 2001).

These findings were confirmed by several studies (Rodenbeck et al, 2003; Rodenbeck et al, 2002; Irwin et al, 2003) but not all (Riemann et al, 2002; Varkevisser et al, 2005). It appears that the difference between these two groups of studies is the degree of polysomnographically documented sleep disturbance. For example, in the study by Rodenbeck et al. (2002), the correlation between area under the curve (AUC) of cortisol and % sleep efficiency was 0.91, suggesting that high cortisol levels are present in those insomniacs with an objective short sleep duration. In contrast, in the study by Riemann in which no cortisol differences were observed between insomniacs and controls, the objective sleep of insomniacs was very similar to that of controls, i.e., sleep efficiency of 88.2% vs. 88.6% (Riemann et al, 2002). Furthermore, in a study that applied constant routine conditions, all indices of physiological arousal were increased but not to a significant degree due to lack of power and not careful selection of controls (Varkevisser

et al, 2005; Bonnet, 2005). Interestingly, in this study a visual inspection of cortisol data suggested an elevation of cortisol values of 15% to 20% in the insomnia group, a difference which is similar to that reported in our study and is considered of clinical significance (Varkevisser et al, 2005).

Collectively, these findings suggest that chronic insomnia with concomitant objective sleep disturbance is a state of physiological hyperarousal which puts the individual into a high risk of significant medical morbidity.

B. Chronic insomnia is associated with significant medical morbidity– Many studies have established that insomnia is highly comorbid with psychiatric disorders and is a risk factor for the development of depression, anxiety, and suicide (NIH, 2005; Basta et al, 2007; Buysse et al, 2006; Ford and Kamerow, 1989; Breslau et al, 1996; Ohayon et al, 2002). However, in contrast to the other most common sleep disorder, i.e., sleep apnea, chronic insomnia has not been linked with significant medical morbidity, e.g., cardiovascular disorders. Few studies that have examined the association of chronic insomnia with hypertension have reported modest and inconsistent effects of little or no clinical significance (Phillips and Mannino, 2007; Suka et al, 2003; Janson et al, 2001; Bixler et al, 2002). As we discussed in the previous section, most, but not all, studies have reported that chronic insomnia is associated with an overall hypersecretion of ACTH and cortisol, suggesting an activation of the hypothalamic-pituitary-adrenal (HPA) axis in these patients (Vgontzas et al, 1998; Vgontzas et al, 2001; Rodenbeck et al, 2003; Rodenbeck et al, 2002; Riemann et al, 2002; Varkevisser et al, 2005). This association is strong in those insomniacs with evidence of objective poor sleep.

Given the well-established association of hypercortisolemia with significant medical morbidity, i.e., hypertension, diabetes, metabolic syndrome, osteoporosis, and others (80), we examined the joint effects of insomnia and short sleep duration on the risk of medical morbidity, i.e., hypertension, diabetes, and neurocognitive deficits, and mortality in a general population sample of 1,741 men and women randomly selected from Central Pennsylvania (Penn State Cohort) (Bixler et al, 1998; Bixler et al, 2001). In the first study, the highest risk of hypertension was in insomniacs with < 5 hour sleep duration group (OR = 5.0), and the second highest in insomniacs who slept 5-6 hours (OR = 3.5) when compared to the normal sleeping and ≥ 6 hour sleep duration group (Vgontzas et al, 2009a). In the second study, we examined the joint association of insomnia and objective short sleep duration on the risk for diabetes. A significantly increased risk for diabetes was observed in the group of the most severe insomniacs, i.e., insomnia with objective sleep duration < 5 hours (Vgontzas et al, 2009b). In the third study, significant neurocognitive deficits were observed only in insomniacs with < 6 hours as compared to controls or insomniacs with ≥ 6 hours (Fernandez-Mendoza et al, 2010). In our fourth study, we reported that objective short sleep duration (< 6 hours) in male insomniacs predicts mortality over a period of 14 years of follow-up (Vgontzas et al, 2010). Finally, in the same cohort, we examined the differential psychological profile of insomniacs with objective short and normal sleep duration (Fernandez-Mendoza et al, 2011). This latter study revealed that insomniacs with normal seep duration present with

sleep misperception (i.e., the tendency to underestimate sleep duration) and anxious-ruminative and poor coping resources personality traits.

Based on these studies, we have recently suggested that objective sleep duration in chronic insomnia is a marker of the biological severity of the disorder.

C. Subtypes of chronic insomnia based on its biological severity – The field of sleep disorders medicine has attempted to define subgroups within insomnia based on etiology (i.e., primary vs. secondary), age of onset (i.e., childhood vs. adult), and objective sleep findings (American Academy of Sleep Medicine, 2005). Although for years sleep specialists suggested that the sleep lab was of no use in the evaluation of insomnia (NIH, 2005), the previously published data on the association of insomnia combined with objective short sleep duration with the stress system (Vgontzas et al, 1998; Vgontzas et al, 2001; Rodenbeck et al, 2003; Backhaus et al, 2006; Shaver et al, 2002; Irwin et al, 2003), the autonomic system (Bonnet and Arand, 1997; Stepanski et al, 1994; Bonnet and Arand, 1995), and with medical morbidity (Vgontzas et al, 2009a; Vgontzas et al, 2009b; Fernandez-Mendoza et al, 2010) and mortality (Vgontzas et al, 2010), have led us to suggest two subtypes of chronic insomnia.

The first subtype is associated with physiological hyperarousal, i.e., short sleep duration, activation of the stress system (Vgontzas et al, 1998; Vgontzas et al, 2001; Rodenbeck et al, 2003; Backhaus et al, 2006; Shaver et al, 2002), and significant medical sequelae, e.g., hypertension (Vgontzas et al, 2009a), type 2 diabetes (Vgontzas et al, 2009b), neurocognitive deficits (Fernandez-Mendoza et al, 2010) and increased mortality (Vgontzas et al, 2010), whereas the second subtype is not associated with physiological hyperarousal, i.e., normal sleep duration, normal activity of the stress system (Vgontzas et al, 1998; Vgontzas et al, 2001; Shaver et al, 2002), and lack of significant medical sequelae (Vgontzas et al, 2009a; Vgontzas et al, 2009b; Vgontzas et al, 2010; Fernandez-Mendoza et al, 2010), but with sleep misperception and an anxious-ruminative, poor coping skills profile (Fernandez-Mendoza et al, 2011).

Thus, our proposed subtyping of chronic insomnia suggests that physiological hyperarousal may play a primary role in the phathophysiology of insomnia with objective short sleep duration, whereas psychological factors might be primary in insomnia with normal sleep duration. Our findings on these proposed subtypes may have a significant impact on how we diagnose and treat insomnia. Currently, the diagnosis of insomnia is only based on subjective complaints (American Psychiatric Association, 2000). The introduction of objective measures of sleep in the evaluation of insomnia may be of relevance for the practicing physician in terms of prioritizing intervention based on severity. In fact, we have also proposed that these 2 subtypes may respond differentially to treatment approaches. Insomniacs with objective short sleep duration may respond better to treatments that primarily aim at decreasing physiological hyperarousal (e.g., hypercortisolemia) and increasing sleep duration, such as medication or other biological treatments (Rodenbeck et al, 2003), whereas insomniacs with normal sleep duration may respond better to treatments that primarily aim at decreasing cognitive-emotional

hyperarousal (e.g., rumination) and altering sleep misperception, such as psychological treatment (Morin and Espie, 2003).

However, whether insomnia with objective short sleep duration responds better to pharmacological rather than to psychological treatment has not yet been examined.

D. Treatment of chronic insomnia – Most sleep specialists advocate a multidimensional approach for the treatment of insomnia that includes education on sleep hygiene, psychotherapy including behavioral methods and cognitive behavioral therapy (CBT), and medication including hypnotics, sedative antidepressants, or over-the-counter medications.

The list of behavioral and cognitive techniques is long, and the latest American Academy of Sleep Medicine (AASM) paper on "Practice Parameters for the Psychological and Behavioral Treatment of Insomnia" lists seven methods for which there is no evidence for the superiority or specificity of one method in comparison to another one (Morgenthaler et al, 2006; Morin et al, 2006). According to the AASM committee, it is well established that CBT improves subjective measures of sleep in insomnia (Morgenthaler et al, 2006; Morin et al, 2006). However, only 11 studies out of the 37 systematically reviewed by the AASM practice parameters committee used objective sleep data to study the effects of CBT and their results could not prove that CBT is effective in improving objective sleep duration (Morgenthaler et al, 2006; Morin et al, 2006). Moreover, the most recent published studies (2004-2010) do not provide evidence supporting a clinically significant effect of CBT on extending objective sleep duration, either measured with PSG (Siversten et al, 2006a; Siversten et al, 2006b; Krystal and Edinger, 2010) or with actigraphy (Siversten et al, 2006a; Espie et al, 2007; Edinger et al, 2007; Edinger et al, 2009), with just one uncontrolled study being the exception (Cervena et al, 2004). Furthermore, these recent studies demonstrate once again (Morgenthaler et al, 2006; Morin et al, 2006) that most studies examining the effect of CBT for insomnia have been comprised of samples of chronic insomniacs with a rather "normal" (≥ 6 hours) objective sleep duration (Okajima et al, 2010).

Very little evidence currently guides practitioners in terms of selecting behavioral or pharmacologic treatments for a specific patient, much less the specific treatment within these broad categories. Sleep–wake regulation is complex, and the number of neurotransmitters and neuromodulators involved is large. This creates a number of viable targets for insomnia therapy. The long standing reliance on benzodiazepine receptor agonists is likely to give way to a greater variety of treatments, including those affecting targets such as histamine, orexin, and serotonin receptors (Buysse, 2010). Hypnotics appear to be effective but only short-term, while the administration of sedative antidepressants such as trazodone, although widely used by the practicing physician (Morlock et al, 2006), is not supported by systematic studies including efficacy, tolerance, and side effects (Mendelson, 2005). Trazodone is a sedative triazolopyridine antidepressant, which possesses antidepressant and also anxiolytic and hypnotic activities (Al-Yassiri et al, 1981; McCall, 2010).

More importantly, the effectiveness of the available treatment options has not been evaluated in terms of the severity of the disorder or biological indices of known

clinical significance (such as the degree of objective sleep disturbance). The data on the association of objective short sleep duration in insomnia with hypercortisolemia (Vgontzas et al, 1998; Vgontzas et al, 2001; Rodenbeck et al, 2003; Rodenbeck et al, 2002; Riemann et al, 2002; Varkevisser et al, 2005) and high risk for medical morbidity (Vgontzas et al, 2009a; Vgontzas et al, 2009b; Vgontzas et al, 2010; Fernandez-Mendoza et al, 2010) provide the basis for a guided approach in the treatment of insomnia, which can be useful to the general practitioner. Because insomnia associated with objective short sleep duration is associated with HPA axis activation, the use of medication that down regulates the HPA axis, such as trazodone, may be a promising tool in the pharmacological approach. In support of this argument are the results of a small study from Germany that showed that a small dose of a sedative antidepressant (doxepin) was effective in improving sleep and normalizing plasma cortisol secretion in primary insomniacs (Rodenbeck et al, 2003). Recent studies have also shown that doxepin is effective in increasing objective sleep duration in chronic insomniacs (Rodenbeck et al, 2003; Krystal et al, 2010; Roth et al, 2010; Scharf et al, 2008; Roth et al, 2007; Hajak et al, 2001). In contrast, insomnia associated with "normal" sleep duration, normal activity of the HPA axis, and lack of significant medical morbidity may respond better to psychotherapeutic interventions. In support of this hypothesis are the several studies on CBT effectiveness that included insomniacs with an average objective sleep duration of 6 hours or more and reported improved sleep efficiency (better consolidation of sleep) but no significant lengthening of sleep duration (Edinger et al, 2001; Jacobs et al, 2004; Morin et al, 2004; Sivertsen et al, 2006a; Edinger et al, 2007a;Sivertsen et al, 2006b; Espie et al, 2007; Edinger et al, 2009; Krystal and Edinger, 2010; Okajima et al, 2010). In this project, we will focus on the more severe group and we will test whether a sedative antidepressant (trazodone) is more effective in insomnia with objective short sleep duration than CBT.

Collectively, the above reviewed studies show that chronic insomnia with objective short sleep duration is a state of hyperarousal associated with hyperactivity of the stress system and significant medical sequelae and suggest that sedative antidepressants may have better beneficial effects than CBT in improving insomnia with objective short sleep duration.

2.0 Objectives

Little is known about the pathophysiology of chronic insomnia whereas the currently available treatments are either partially effective and/or associated with poor outcome in objective measures of nighttime sleep.

Accumulating evidence points to the possibility that chronic insomnia is a state of physiological and emotional hyperarousal. In individuals with chronic insomnia, objective short sleep duration is associated with hyperactivity of the stress system (e.g., hypercortisolemia) and with increased risk of significant medical sequelae, such as cardiometabolic and neurocognitive disorders. It appears that objective measures of sleep may be a reliable index of the biological severity of the disorder. Finally, CBT, the current recommended first-line treatment for chronic insomnia is associated with improvement of subjective sleep quality whereas it does not appear to significantly

improve objective sleep duration. Interestingly, most studies examining the efficacy and/or effectiveness of CBT have been conducted in chronic insomniacs with a rather "normal" (> 6 hours) sleep duration.

Sedative antidepressants, such as trazodone, are widely used by the practicing physician to treat chronic insomnia. However, there is a lack of studies that have examined their efficacy, tolerance, and side effects. Several studies have reported that sedative antidepressants may reduce cortisol levels and/or increase objective sleep duration in chronic insomniacs. As yet, there have not been controlled studies to examine the effects of trazodone versus CBT on severe chronic insomnia, i.e., those with objective short sleep duration.

The primary hypothesis to be tested is that trazodone improves both subjectively and objectively chronic insomnia with objective short sleep duration. Specifically, in this study, we will assess the following specific aim/hypothesis: to examine the effects of trazodone vs. CBT in chronic insomniacs with objective short sleep duration. Specifically, we hypothesize that trazodone will be more effective than CBT in improving both subjectively and objectively chronic insomnia. To test this hypothesis, we propose a pilot, 3-month randomized trial of trazodone compared to CBT in 24 male and female patients with chronic insomnia with objective short sleep duration.

A. Primary outcomes: we hypothesize that **trazodone** will result in a greater improvement of objective sleep duration (assessed by PSG and actigraphy) and subjective nighttime sleep than CBT in insomniacs with objective short sleep duration.

B. Secondary outcomes: we hypothesize that **trazodone** compared to CBT will result in a greater improvement of daytime fatigue, cortisol, inflammatory markers, and insulin sensitivity in insomniacs with objective short sleep duration.

The accomplishment of the above-described objectives will create the basis for the development of novel and specific treatments for chronic insomnia, and improve our understanding of the pathophysiology of this heterogeneous disorder.

3.0 Study Design and Methods

1. Rationale – Current treatments for chronic insomnia are either partially effective and/or associated with poor outcomes in objective measures of nighttime sleep. Specifically, CBT, the most widely used therapeutic modality, is not associated with a satisfactory and clinically significant increase in objective sleep duration (Okajima et al, 2010). Furthermore, it is not known whether CBT can reverse the activation of the stress system, i.e., hypercortisolemia, associated with insomnia with objective short sleep duration. Sedative antidepressants, such as trazodone, have been shown in several studies to increase objective sleep duration and/or decrease cortisol levels (McCall, 2010). The goal of this interventional study is to assess the effect of trazodone vs. CBT in patients with chronic insomnia with objective short sleep duration.

All subjects will be randomly assigned into either a trazodone or a CBT group. The group assignment will be decided by our statistician so that the investigators

involved with subject recruitment and screening remain blind to the randomization process.

4.0 Inclusion and Exclusion Criteria

Study Population – A total of 70 men and women will be screened for inclusion in this study. 24 men and women with chronic insomnia will be enrolled to receive study therapy over a 3-month period. This study will focus on adult men and women (30- 60 years old) with a chronic complaint of insomnia and concomitant objective short sleep duration, based on both clinical and polysomnographic criteria. All subjects will meet the Research Diagnostic Criteria (RDC) for insomnia (Edinger et al, 2004) and will demonstrate < 6 hours of sleep, as assessed by polysomnography (Table 1). In addition, they should meet the criteria for duration for more than one year because this is the population that is associated with hypercortisolemia and medical morbidity as shown in our previous experimental and epidemiological studies.

Table 1. Research diagnostic criteria (RDC) for insomnia.

Insomnia disorder
A. The individual reports one or more of the following sleep related complaints: 1. difficulty initiating sleep, 2. difficulty maintaining sleep, 3. waking up too early, or 4. sleep that is chronically non-restorative or poor in quality.
B. The above sleep difficulty occurs despite adequate opportunity and circumstances for sleep.
C. At least one of the following forms of daytime impairment related to the nighttime sleep difficulty is reported by the individual: 1. fatigue/malaise; 2. attention, concentration, or memory impairment; 3. social/vocational dysfunction or poor school performance; 4. mood disturbance/irritability; 5. daytime sleepiness; 6. motivation/energy/initiative reduction; 7. proneness for errors/accidents at work or while driving; 8. tension headaches, and/or GI symptoms in response to sleep loss; and 9. concerns or worries about sleep.

Our participants will be middle-aged adults since objective sleep duration significantly correlates with age in an inverse manner. We will not exclude insomniacs with minor forms of anxiety or depression, i.e., dysthymic disorder, since these conditions are highly comorbid in chronic insomniacs (Buysse et al, 1993; Kales and Kales, 1984; Buysse et al, 1994a; Buysse et al 1994b). However, insomniacs with a current diagnosis of a major mental disorder, i.e., schizophrenia, major depression, will be excluded from the study because these conditions are associated with the primary outcome variables of this study. In addition, we will exclude subjects with morbid obesity (BMI > 39) because, at this level, obesity is frequently associated with frequent sleep pathology, i.e., apnea, EDS, and significant medical morbidity (Vgontzas et al, 1994; Vgontzas et al, 1998).

Participants with an apnea/hypopnea index (A/HI) > 5 or periodic limb movements > 5 per hour of sleep will be excluded from the study. Also, subjects with a primary disorder of EDS, e.g., narcolepsy, or subjects with a history of shift work or circadian disorder will be excluded from the study (Vgontzas and Kales, 1999; Roehrs et al, 2005; Boggild and Knutsson, 1999) (Table 2).

Table 2. Inclusion/exclusion criteria.

Inclusion	Exclusion
Chronic insomnia (RDC) with a duration ≥ 1 year	Major mental illness
Objective short sleep duration (< 6h)	Substance abuse/dependence
BMI < 39	Sleep apnea (apnea/hypopnea index ≥ 5)
Age range: 30-60	PLMD (periodic limb movements ≥ 5)
Equal number of men and women	Objective normal sleep duration (≥6h)
	Primary disorders of EDS, i.e., narcolepsy
	Shift work or circadian disorders
	Diabetes, chronic renal failure, hepatic insufficiency, chronic heart failure
	Current use of hypnotics or sleep inducing sedative antidepressants

RDC = research diagnostic criteria; PLMD = periodic limb movements disorder

Subjects treated for diabetes or suffering from chronic renal failure or hepatic insufficiency or chronic heart failure will be excluded from the study. Also, because of the known effects of steroids on sleep, subjects on those medications will be excluded from the study. A family history of diabetes will be recorded during the medical history and physical examination and controlled within our analyses. Also, the potential effects of other medications or substances, such as alcohol or smoking, will be controlled within our analyses. Subjects with a diagnosis of substance abuse or dependence will be excluded from the study due to the potential effects of these substances on sleep and metabolism. Patients should be free of hypnotic use or sedative antidepressants administered at bedtime to improve sleep for one month before entering the study. Finally, patients using psychotropic medications, i.e., SSRI, who do not meet the criteria for a current major psychiatric disorder, and have continuous complaints of insomnia, will be included in the study. This is because a large portion of insomniacs consist of depressed individuals whose depression improved but still they have complaints of chronic insomnia. Potential confounding effects of medication on some of the outcome measures, i.e., objective sleep duration, will be dealt with in the analysis

Women and Minority Inclusion – In this project, we will include middle-aged men and women 30- 60 because they represent the majority of patients with insomnia in the general and clinic population. Women who are pregnant or breastfeeding will not be enrolled in the study. We plan to recruit about 21% of subjects belonging in minority groups. The racial and ethnic distribution shown in the Targeted/Planned Enrollment Table reflects the general demographics of our region. Minorities will be recruited from our clinics as well as through advertisements in papers with large groups of minority readers, such as Harrisburg, PA and Lebanon, PA.

Inclusion of Children – The prevalence and clinical characteristics of insomnia in children is not well established. In fact, current literature indicates that the etiology, clinical and sleep laboratory characteristics of insomnia in children are different than that in adults, i.e., bed-resistance, family dynamics, absence of sleep-related worry, etc. Most importantly, there is not sufficient evidence to use pharmacologic treatment in childhood insomnia.

5.0 Recruitment and Consent Process

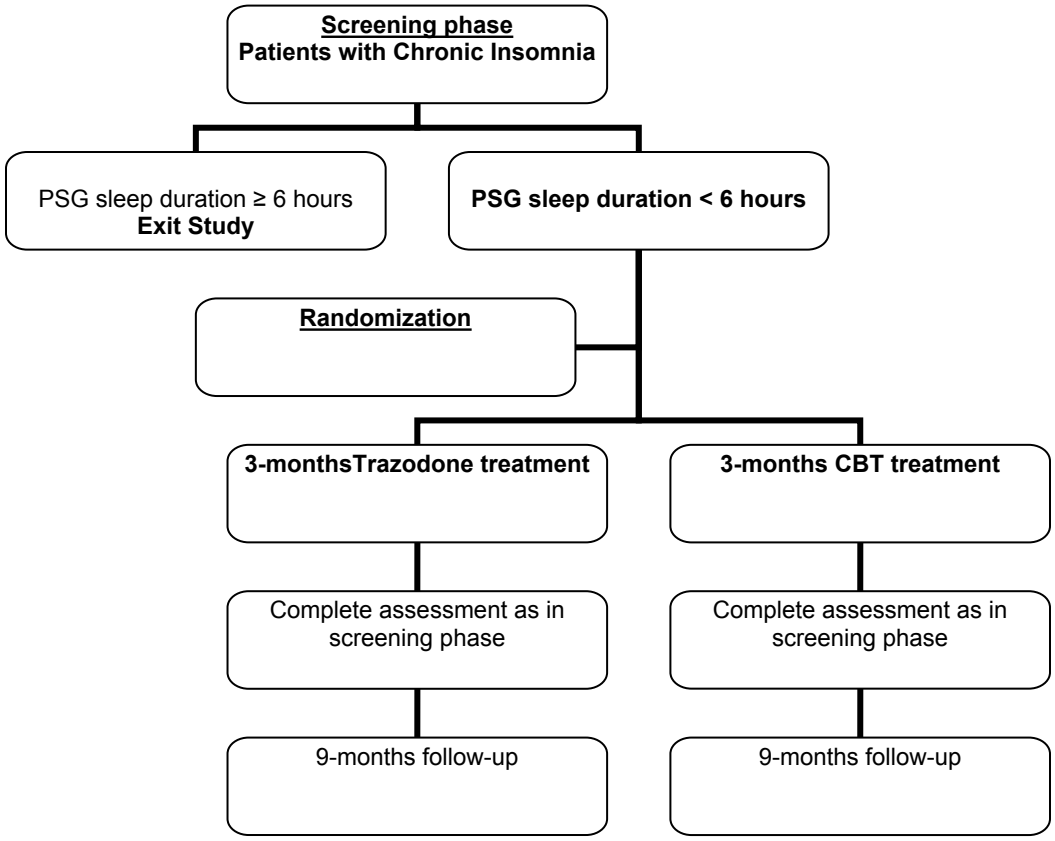
When potential participants respond to an advertisement, a structured phone script or online script and interview is used to explain study procedures and determine eligibility. A member of the research team will then offer eligible participants the opportunity to participate in the study by scheduling a visit and sending a copy of the consent form for thorough review prior to the visit. At the time of the visit, the participant signs the consent form and is enrolled in the study. Potential participants may also be identified by clinicians in the Sleep Disorders Clinic and offered information about the study.

6.0 Study Procedures

Screening phase

The subjects' diagnoses of insomnia and other sleep disorders will be established by a clinical sleep history conducted by a clinical psychiatrist or psychologist who practices sleep medicine. The subjects that meet the research diagnostic criteria (RDC) for insomnia will be included in the study (see Table 1). The subjects' sleep patterns will be assessed via a sleep diary and actigraphy (for two weeks) prior to their visit to the sleep lab. Each subject will be monitored continuously for eight hours for one night in the sleep unit of the GCRC according to standard techniques (Rechtschaffen and Kales, 1986; Iber et al, 2007.). The first night will serve as a screening night for the presence of sleep apnea or periodic limb movements, and an adaptation night to control for "first night" effects. Prior to or during their visit to the sleep unit, the participants will be assessed for psychiatric disorders using a Structured Clinical Interview for DSM-IV, the Mini International Neuropsychiatric Interview (MINI ; Sheehan et al, 2006).

Figure 1. Screening phase, randomization of patients with insomnia.



Randomized Clinical Trial of Trazodone vs. CBT

a. Baseline measures – Following the screening night, the subjects that will enter the randomized trial will be monitored in the sleep laboratory continuously for 8 hours for 2 consecutive nights according to standard techniques (Rechtschaffen A, Kales A, 1968) (Table 3). Following the first night in the sleep laboratory, the participants will be admitted to GCRC for a complete semi-structured medical history and physical examination. Blood, urine and saliva will be collected and an electrocardiogram (EKG) will be performed. A pregnancy test will be performed on females of child bearing age. Following the second night in the sleep laboratory, daytime sleepiness and fatigue, nighttime sleep quality and quantity, and mood will be assessed subjectively with standardized self-reported questionnaires.

b. Randomization Scheme for Intervention – Subjects will be randomly assigned by our statistician into either a trazodone or a CBT program. Between the two intervention groups, we will attempt to have similar BMI, gender, and age distributions. If a patient is randomized and enters the randomization trial, then the patient will be considered enrolled in the study.

c. Completion of Study Visit – After 3 months on trazodone or CBT, the patients will undergo a repeat of the baseline evaluation as noted below (Table 3). This will include a complete physical examination, 2-night, 8-hour polysomnography, two-week

actigraphy & sleep diary, blood, urine, and saliva collection, and subjective measures of nighttime sleep and daytime functioning.

d. Once patients have completed 3 months of study, they will be followed-up again 6 months later. The same procedures performed during the baseline and post treatment phase will be repeated.

Table 3. Study design of randomized trial of trazodone vs. CBT

	Screening	Baseline	CBT Weekly Visits	Trazodone Monthly Visits	3 months	9 months
Structured Clinical Interview (MINI)	X					
Polysomnography & Video Recording						
1 night	X					
2 nights		X			X	X
Actigraphy						
2 weeks	X	X			X	X
Pregnancy Test	X	X				
Biomarkers						
Urinalysis		X			X	X
Urine Drug Screen		X			X	X
Blood Count		X			X	X
Blood Chemistries		X			X	X
Lipid Panel		X			X	X
Thyroid		X			X	X
Saliva cortisol		X			X	X
Blood Inflammation		X			X	X
Blood Insulin sensitivity		X			X	X
Medical history & physical exam.		X			X	X
EKG		X			X	X
Subjective Measures						
Post Sleep Assessment	X	X			X	X
Sleep diary	X	X	X	X	X	X
PSQI		X			X	X
ISI		X	X	X	X	X
PSAS		X			X	X
APS		X			X	X
FIRST		X			X	X
POMS-F		X			X	X
MFI		X			X	X
ESS		X			X	X
SSS	X	X			X	X
BDI-II		X			X	X
BAI		X			X	X
HAD-S		X			X	X
DBAS		X			X	X

d. Intervention Design – The CBT protocol used in this project will include evidence-based, behavioral and cognitive techniques; it will consist of what is called a "multimodal CBT treatment" covering sleep hygiene, stimulus control, sleep restriction, and cognitive therapy (Perlis et al, 2005).

A session-by-session schedule of the CBT treatment program is presented in Table 4. The 1st intervention session will present a conceptual cognitive-behavioral model of insomnia (Perlis et al, 2005) and the patient will receive sleep hygiene instructions. A brief presentation of the cognitive-behavioral model of insomnia proposed by Perlis et al (2005) will be explained to the patients and will serve as the basis to present all clinical procedures that will be used during treatment. The role of sleep-related behaviors and habits will be addressed, and a standard handout with sleep hygiene instructions will be given to the patient at the end of the session (Perlis et al, 2005). The 2nd session will introduce stimulus control and sleep restriction therapies, which have shown to be strongly efficacious in insomnia (Perlis et al, 2005). The goals of these therapies are: to reduce activities incompatible with sleep and develop positive associations of good sleep with the bedroom, increase sleep-wake specificity by avoiding napping in the day and getting up if wakeful at night, increase sleep efficiency by spending less time in bed and build up the natural sleep drive, and establish regular sleep habits and keep to a consistent pattern from night to night throughout the week. Because stimulus control and sleep restriction involves getting up from bed and going to other room, sessions 3rd and 4th will focus on addressing difficulties associated with these techniques. The 5th session will introduce the cognitive therapy component. Cognitive therapy is a psychotherapeutic method designed to change a person's beliefs, expectations, appraisals, and attributions (Morin, 1993; Perlis et al, 2005). In the context of insomnia, cognitive therapy seeks to change sleep expectations, catastrophic beliefs about the causes and consequences of insomnia, and beliefs about sleep-promoting practices. This intervention is predominantly verbal in nature and is more time consuming to implement in-session than behavioral procedures described in previous sessions. In fact, the 6th session will focus on cognitive restructuring, i.e., changing the patient's dysfunctional concerns and beliefs about sleep and insomnia. The 7th session will give end to the cognitive restructuring component but will also address difficulties associated with all clinical procedures described. The 8th session will integrate all clinical procedures as to improve long-term adherence, relapse prevention and will also include a post-treatment assessment, as presented in Table 3.

Table 4. A session-by-session schedule of the CBT program

Session	New/Review*	Content	Duration
1	N	Conceptual model and sleep hygiene	50 min
2	N	Setting up sleep restriction and stimulus control, Set prescription for sleep restriction	50 min
3	R	Sleep restriction and stimulus control treatment gains and compliance	50 min
4	R	Sleep restriction and stimulus control treatment gains and compliance	50 min
5	N	Cognitive therapy	50 min
6	R	Cognitive therapy	50 min
7	R	Cognitive therapy, sleep restriction, and stimulus control gains and compliance	50 min
8	N	Discuss relapse prevention Post-treatment assessment	50 min

* New/Review refers to the introduction of a new clinical component vs. a review of the outcomes and adherence of previously introduced components.

This **CBT protocol** is designed to be implemented over a period of 12 weeks, with consultation sessions held on a weekly basis (Perlis et al, 2005). There will be 2 sessions devoted to baseline evaluation, along with a 2-week baseline sleep diary and actigraphy monitoring period, followed by 8 therapy sessions. This number of sessions is needed to present a conceptual behavioral model of insomnia, describe all clinical procedures and their rationale, provide enough time for patients to experiment with those procedures at home, and to problem-solve difficulties encountered during home practice. Clinical sessions will be held weekly, to ensure continuity between sessions. The treatment program described here has been validated according to specific parameters (Perlis et al, 2005). Individual therapy sessions will last approximately for 50 minutes. Each therapy session is highly structured and covers a different aspect of treatment. Although their specific content varies on the technique presented/used, most sessions are structured according to the agenda outlined in Table 5.

Table 5. CBT session agenda

- Review sleep diary.
- Evaluate compliance with clinical procedures and homework assignment.
- Identify problems during home practice and strategies for promoting treatment adherence.
- Introduce new treatment component and its rationale.
- Present didactic material supporting this component.
- Review homework assignments for the upcoming week.

The very first item of the agenda is to review the sleep diary for the previous week. This provides a clear message to the patient that self-monitoring is expected and is an essential component of therapy. The next step is to check the extent to which the patient has complied with previous recommendations. After problem solving adherence issues, a new treatment component is introduced. Each procedure is described along with its rationale and objectives. Handouts will always be provided to consolidate the new information presented during the session. The final item on the agenda is to review homework assignment for the upcoming week giving a written summary to the patient.

The **trazodone group** will receive a standard handout on sleep hygiene instructions and subsequent biweekly and monthly visits to check treatment effectiveness, adherence and possible side-effects, if they occur, and also follow-up review of sleep hygiene practices. All patients will receive a standard dose of trazodone 50 mg. in their first visit and will be followed-up with 2 additional biweekly visits. During these biweekly visits, doses will be adjusted according to drug effectiveness and possible side-effects. Consecutive visits will be scheduled monthly and will focus on assessing treatment effectiveness, adherence and possible side-effects and need to adjust medication doses.

Techniques

1. Medical History and Physical Examination

Each subject will have a complete medical history and physical examination using a semi-structured format and a battery of clinical tests, including complete blood count, liver function test, urinalysis, lipid panel, thyroid indexes, and electrocardiography. Pre-menopausal women will also have a pregnancy test performed. Blood pressure will be measured in the morning and in the evening using a pneumoelectric microprocessor-controlled instrument. The recorded blood pressure will be the average of 3 consecutive readings during a 5-minute period following 10 minutes of rest in the supine position. Anthropometric measures will include height, weight, neck size, and waist and hip measurements according to standard procedures. Specifically, neck size is measured at the superior border of the cricothyroid membrane with the subject in the upright position. Waist is measured at or 1 cm above the umbilical midline and hip at the widest area around the buttocks.

2. Objective assessment of Nighttime Sleep

a. Polysomnography – Each subject will be monitored continuously for eight hours for 2 consecutive nights (adaptation night and one baseline night) according to standard techniques (Rechtschaffen A, Kales A, 1968). Also, to improve the accuracy and reliability of our nighttime sleep measures, the subjects' typical sleep time at home will be assessed objectively via actigraphy for two weeks before the sleep laboratory recordings (see below) and during the sleep lab recordings. Respiration will be monitored throughout the night by thermocouples at the nose and mouth (Salter Labs) and nasal cannula/pressure and by thoracic strain gauges. We will use both thermocouples and nasal cannula because it has been reported that the pressure signal identifies transient elevated upper airway resistance not detected conventionally (Iber et al, 2007). An apnea/hypopnea index ≥ 5 will be used to define the presence of sleep apnea.

b. Actigraphy – An actigraphy monitor (ActiGraph GT3X) will be placed on the wrist of the nondominant hand of subjects. The subjects will be asked to keep an actigraphy log for two week periods in which they note daily time to bed, time out of bed, or times when the device is removed (e.g., taking a bath, swimming).

3. Subjective assessment of Nighttime Sleep and Arousal

a. Post-sleep Assessment – Throughout the study, subjects will complete a post-sleep questionnaire upon awakening each morning in the sleep lab and will estimate time to fall asleep, number of nightly awakenings, total sleep time, soundness and quality of sleep, and morning sleepiness.

b. Sleep Diary – A 2-week sleep log or diary will be used for assessment of the subjects' perceived sleep patterns at the screening phase, at the onset of the study, during the intervention period, at the end of the intervention and at follow-up.

c. Sleep Quality – The Pittsburg Sleep Quality Index (PSQI) will be used for assessment of the subjects' overall sleep quality at the onset of the study, at the end of the intervention and at follow-up (Buysse et al, 1989).

d. Insomnia Severity – The Insomnia Severity Index (ISI) will be used for assessment of the subjects' overall perceived insomnia severity at the onset of the study, during the intervention period, at the end of the intervention and at follow-up (Bastien et al, 2001).

e. Pre-sleep Arousal – The Pre-Sleep Arousal Scale (PSAS) will be used for assessment of the subjects' perceived pre-sleep cognitive and somatic arousal at the onset of the study, at the end of the intervention and at follow-up (Nicassio et al, 1985).

f. Arousability – The Arousability Predisposition Scale (APS) will be used for assessment of the subjects' perceived overall tendency to present high levels of cognitive and emotional arousal at the onset of the study, at the end of the intervention and at follow-up (Coren, 1988).

g. Stress-related Insomnia – The Ford Insomnia Response to Stress Test (FIRST) will be used for assessment of the subjects' overall perceived likelihood of having sleep disturbances in association with specific and common stressful events at the onset of the study, at the end of the intervention and at follow-up (Drake et al, 2004).

4. Assessment of Daytime Functioning

a. Sleepiness and Fatigue – Subjects will estimate degree of sleepiness/alertness after awakening in the sleep lab with a 10-cm analog scale that ranges from "extremely sleepy" to "not sleepy" and the Stanford Sleepiness Scale (SSS) (MacLean et al, 1992). The Epworth Sleepiness Scale (ESS) will be used for assessment of the subjects' overall sleepiness at the onset of the study, at the end of the intervention and at follow-up (Johns, 1991). The Fatigue subscale of the Profile of Mood States (POMS-F) (McNair et al, 1971.), and the Multidimensional Fatigue Inventory (MFI) (Smets et al, 1995) will be used for assessments of the subjects' overall fatigue at the onset of the study, at the end of the intervention and at follow-up.

b. Mood – The Beck Depression Inventory-II (BDI-II) will be used for assessment of the subjects' overall severity of depressive symptoms at the onset of the study and at the end of the intervention (Beck et al, 1996). The Beck Anxiety Inventory (BAI) will be used for assessment of the subjects' overall severity of anxious symptoms (somatic component) at the onset of the study, at the end of the intervention and at follow-up (Osman et al 1997). The Anxiety subscale of the Hospital Anxiety and Depression Scale (HAD-S) will be used for assessment of the subjects' overall severity of anxious symptoms (cognitive component) at the onset of the study, at the end of the intervention and at follow-up (Zigmond and Snaith, 1983).

c. Cognition – The Dysfunctional Beliefs and Attitudes about Sleep scale (DBAS) will be used for assessment of the subjects' sleep cognitions (i.e., causal attributions of insomnia, perceived consequences of insomnia, sleep requirements expectations, control and predictability of sleep, and beliefs about sleep-promoting practices) at the onset of the study, at the end of the intervention and at follow-up (Espie et al 2000).

5. Assessment of the Stress System, Inflammation, and Insulin Resistance

a. Stress System – We propose to sample saliva at five time points during the day, i.e. 8:00 before breakfast, 12:00 before lunch, 3:00 pm, 6:00 pm, and 9:00 pm. It has been demonstrated that five samples are adequate to examine circadian variation of cortisol secretion (Pervanidou et al, 2007a; Pervanidou et al, 2007b). No food or exercise would be allowed at least half an hour before sample collection. Each sample will be collected by having the participant place a cotton swab in his or her mouth for 2 minutes or chew it for 1 minute. These samples will be collected on Day 2 of the baseline and follow-up phases (3 and 9 months) of the study. The cotton swab will then be placed inside a plastic tube and kept in the refrigerator at 0-4ºC. Salivary cortisol will be extracted from the cotton by centrifuging the plastic tubes and cotton at 100g for 8 minutes to separate the saliva into the outer tube. The cotton will be removed and all samples will be stored at -85ºC.

b. Inflammation Markers– TNFα, TNFr1 and IL-6 will be measured in two single serum samples on Day 2(evening and morning pre- and post-sleep recording) because their concentration varies during the 24-hour sleep-wake cycle. Blood will be collected during the baseline and follow-up phases (3 and 9 months) of the study. Serum TNFα, TNFr1, and IL-6 will be measured by ELISA (R&D Systems, Minneapolis, MN) (Vgontzas et al, 2004; Vgontzas et al, 2007; Vgontzas et al, 1997; Vgontzas et al, 2004; Vgontzas et al, 2008).

c. Insulin Sensitivity – Whole-body insulin sensitivity can be measured with the euglycemic insulin clamp technique, which measures insulin resistance (IR) directly and is considered the "gold standard". However, the intensity, complexity and risks of the method make it unsuitable for large studies such as ours. The use of a fasting glucose to insulin (G/I) ratio is the simplest and easiest way technically and appears to provide a reasonable estimate of tissue sensitivity to insulin in large samples. Many studies have shown that simple indices of insulin sensitivity derived from fasting glucose and insulin levels, such as homeostasis model assessment (HOMA) (Ip et al, 2002; Punjabi et al, 2002) and Quantitative Insulin Sensitivity Check Index (QUICKI), are simple, accurate methods for assessing insulin sensitivity in large studies (Quon, 2001; Katz et al, 2000). The reliability of the G/I ratio is expected to be very good in our study given that overnight fasting is well-controlled within the sleep lab environment. Blood samples will be collected on day 2 (evening and morning pre-and post-sleep recording) during the baseline and follow-up phases (3 and 9 months) of the study.

7.0 Risks and Discomforts

Protection of Human Subjects

1. The data to be collected from each subject include: medical history and physical examination; sleep EEG and respiration; actigraphy; and self-reported questionnaires and scales.

2. The venous puncture is associated with minor discomfort and a risk of a bruise at the site of the venous puncture.

3. Potential risks include the risk of study-related procedures. There is a minimal risk associated with the discomfort of having standard clinical EEG past electrodes applied to the scalp. Rarely, we have had an individual who has had a mild allergic reaction to the tape applied over electrodes. This risk is minimized by using hypoallergenic tape.

4. There are a few potential risks associated with trazodone. Trazodone is a sedative triazolopyridine antidepressant, habitually used for the treatment of depression and insomnia because it possesses antidepressant and also anxiolytic and hypnotic activities (Al-Yassiri et al, 1981; McCall, 2010). Pharmacologically, it is a serotonin antagonist and reuptake inhibitor; it is a blocker of postsynaptic serotonin receptors 5-HT1A, 5-HT1C, and 5-HT2, as well as postsynaptic α1-adrenergic receptors. It has a peak serum concentration of 1-2 hours and an elimination half-life of about 5-9 hours. When prescribed as an antidepressant, i.e., to alleviate major depression, the usual doses of trazodone are ≥ 150 mg daily. Daytime doses of trazodone at 100 mg have been found to impair critical flicker fusion and choice reaction time 1-4 hours later in only two studies (Burns et al, 1986; Warrington et al, 1984). Bedtime doses of trazodone at 100 mg have been found to lower blood pressure and impair critical flicker fusion the next morning in one study (Saletu-Zyhlarz et al, 2001). One study mentioned in a recent review found orthostatic hypotension and priapism as a side effect of bedtime trazodone administration (James and Mendelson, 2004). When prescribed as a hypnotic, it is habitually used at low-doses (i.e., 50 mg daily at bedtime). The vast majority of studies have shown that trazodone improves subjective sleep quality and increases objective total sleep time, percent of stages 3 and 4, and sleep efficiency, and decreases the percent of stage 1, number of awakenings, and stage shifts, as assessed by PSG (Burns et al, 1986; Saletu-Zyhlarz et al, 2001; James and Mendelson, 2004; Dording et al, 2002; Nierenberg et al, 1994; Haffmans, 1999; Walsh et al, 1998; Montgomery et al, 1983; Yamadera et al, 1998; Ware and Pittard, 1990; Kaynak et al, 2004; Zavesicka et al, 2008). There are no controlled studies or clinical reports of major side-effects with low-dose trazodone when administered at bedtime in insomniacs. The most common side effect of low-dose trazodone when administered at bedtime may be minimal morning sedation, based on clinical experience. Common risks of trazodone given at higher doses include headache, dry mouth, blurred vision, dizziness, fatigue, nausea and suicidal thoughts in children, adolescents and young adults with depression.

5. There are a few potential risks associated with CBT. When individuals start the sleep scheduling component they are asked to restrict their time in bed and in some instances their sleep duration. This procedure may cause some residual daytime sleepiness that might interfere with daytime functioning. The patient will be warned of this possible effect and will be asked not to get into risky behaviors if feeling excessively sleepy (e.g., driving). Another possible side-effect of CBT may be the frustration felt by the patient due to a lack of achievement of expected goals. CBT is a goal-oriented, homework-based psychotherapy and in some cases the patient may be delayed to respect to the planned objectives which may cause some frustration. However, we do not anticipate any major side-effects to occur.

8.0 Benefits

Risk to Benefit Ratio Only – In our opinion, these studies will provide significant new information in regard to the underlying mechanism of chronic insomnia and will lay the foundation for new treatments for a disorder that affects a large proportion of the general population. In addition, trazodone may hold the benefit of improving sleep duration in chronic insomnia, and a long-term reduction in the risk of developing cardiometabolic and/or psychiatric problems. The benefit to others may be validation of trazodone as the basis for treatment of a common sleep disorder with significant medical sequelae. Data obtained in this study can be used to design larger multi-center trials testing these findings. We believe that overall, the risks of these experiments are small compared to the importance of the knowledge that will be obtained.

9.0 Reporting of Adverse Events and Unanticipated Problems Involving Risks to Participants or Others

The PI will report all adverse events or unanticipated problems to the IRB/HSPO according to established guidelines.

10.0 Study Withdrawal/Discontinuation

Taking part in this research study is voluntary. The participants do not have to participate in this research. If they choose to take part, they have the right to stop at any time. If they decide not to participate or if they decide to stop taking part in the research at a later date, there will be no penalty or loss of benefits to which they are entitled and just need to notify the primary investigator that they wish to discontinue.

The research investigators may also discontinue any participant. Possible reasons for this are: continuing the research would be harmful, they did not follow the instructions of the study doctor, or they experience serious side effects.

11.0 Statistical Analysis of the Study

Analysis

a. Sample Size Calculation – This is a pilot study to collect preliminary data using two interventions, i.e., trazodone or CBT, with unknown effects for chronic insomnia with objective short sleep duration. Based on our previous experience with interventional studies, we suggest that 10 subjects per group will be adequate to detect a difference of 20 minutes in objective sleep duration between the two treatment interventions. To allow for an anticipated 20% attrition rate, 24 subjects will be assigned to a study intervention to ensure complete data from 20 participants. The results of this study will allow the establishment of sample size for any future studies. Our statistical consultant in this study is Dr. Duanping Liao.

b. Analytic Plan

Specific Aim 1: Examine the Effect of Trazodone vs. CBT for the Primary Outcome Variables (objective and subjective sleep duration) in Patients with Chronic Insomnia with Objective Short sleep Duration

Throughout the analysis, we will compare the differences (end of the interventional study baseline) between the two groups of the outcome of interest (e.g., total sleep time).

Total Sleep Time, Polysomnography: Both at baseline and the end of the intervention, polysomnography will be measured for 2 consecutive nights. We will calculate the time-specific difference from the baseline to the end of intervention. Then, we will compare the two treatment conditions with respect to the overall mean change across all time points ("difference of difference") using the two-sample t-test. Alternatively, repeated measures analysis of variance (ANOVA) will be used to compare treatment conditions with respect to polysomnographic total sleep time changes from baseline. The time and treatment condition main effects as well as interaction between time and treatment condition will be tested. Adjustments for multiple comparisons across different time points and between intervention groups will be performed. Potential confounders and interaction between treatment condition and confounder will also be examined. In the event that the distribution of polysomnographic total sleep time are not consistent with the assumptions of normality required for ANOVA, attempts will be made to find suitable transformation.

Total Sleep Time, Actigraphy: Both at baseline and the end of the intervention, actigraphy will be measured for 2 weeks. We will calculate the time-specific difference from the baseline to the end of intervention. Then, we will compare the two treatment conditions with respect to the overall mean change across all time points ("difference of difference") using the two-sample t-test. Alternatively, repeated measures analysis of variance (ANOVA) will be used to compare treatment conditions with respect to actigraphic total sleep time changes from baseline. The time and treatment condition main effects as well as interaction between time and treatment condition will be tested. Adjustments for multiple comparisons across different time points and between intervention groups will be performed. Potential confounders and interaction between treatment condition and confounder will also be examined. In the event that the distribution of actigraphic total sleep time are not consistent with the assumptions of normality required for ANOVA, attempts will be made to find suitable transformation.

Total Sleep Time, sleep diary: Both at baseline and the end of the intervention, subjective sleep duration will be measured with a 2-week sleep log. We will calculate the time-specific difference from the baseline to the end of intervention. Then, we will compare the two treatment conditions with respect to the overall mean change across all time points ("difference of difference") using the two-sample t-test. Alternatively, repeated measures analysis of variance (ANOVA) will be used to compare treatment conditions with respect to subjective total sleep time changes from baseline. The time and treatment condition main effects as well as interaction between time and treatment

condition will be tested. Adjustments for multiple comparisons across different time points and between intervention groups will be performed. Potential confounders and interaction between treatment condition and confounder will also be examined. In the event that the distribution of subjective total sleep time are not consistent with the assumptions of normality required for ANOVA, attempts will be made to find suitable transformation.

Specific Aim 2: Examine the Effect of Trazodone vs. CBT on the Secondary Outcome Variables (insomnia severity, daytime functioning, stress, inflammation and insulin sensitivity) in Patients with Chronic Insomnia with Objective Short sleep Duration

Subjective sleep quality and insomnia severity: Both at baseline and the end of the intervention, self-reported sleep quality (PSQI) and insomnia severity (ISI) will be measured. We will calculate the time-specific difference from the baseline to the end of intervention. Then, we will compare the two treatment conditions with respect to the overall mean change across all time points ("difference of difference") using multivariate repeated measures analysis of variance (MANOVA) to compare treatment conditions with respect to all measures of subjective sleep quality and insomnia severity changes from baseline. The time and treatment condition main effects as well as interaction between time and treatment condition will be tested. Adjustments for multiple comparisons across different time points and between intervention groups will be performed. Potential confounders and interaction between treatment condition and confounder will also be examined. In the event that the distribution of subjective sleep quality and insomnia severity measures are not consistent with the assumptions of normality required for MANOVA, attempts will be made to find suitable transformation.

Sleepiness, fatigue, and mood: Both at baseline and the end of the intervention, self-reported sleepiness (ESS), fatigue (POMS-F and MFI) and mood (BDI-II, BAI, and HAD-S) will be measured. We will calculate the time-specific difference from the baseline to the end of intervention. Then, we will compare the two treatment conditions with respect to the overall mean change across all time points ("difference of difference") using multivariate repeated measures analysis of variance (MANOVA) to compare treatment conditions with respect to all measures of sleepiness, fatigue, and mood changes from baseline. The time and treatment condition main effects as well as interaction between time and treatment condition will be tested. Adjustments for multiple comparisons across different time points and between intervention groups will be performed. Potential confounders and interaction between treatment condition and confounder will also be examined. In the event that the distribution of sleepiness, fatigue, and mood measures are not consistent with the assumptions of normality required for MANOVA, attempts will be made to find suitable transformation.

Stress, inflammation, and insulin sensitivity: Both at baseline and the end of the intervention, saliva cortisol, TNFα, TNFr1, IL-6, and the fasting glucose to insulin ratio (G/I) will be measured. We will calculate the time-specific difference from the baseline to the end of intervention. Then, we will compare the two treatment conditions with respect to the overall mean change across all time points ("difference of difference")

using multivariate repeated measures analysis of variance (MANOVA) to compare treatment conditions with respect to all measures of stress, inflammation and insulin sensitivity changes from baseline. The time and treatment condition main effects as well as interaction between time and treatment condition will be tested. Adjustments for multiple comparisons across different time points and between intervention groups will be performed. Potential confounders and interaction between treatment condition and confounder will also be examined. In the event that the distribution of stress, inflammation and insulin sensitivity measures are not consistent with the assumptions of normality required for MANOVA, attempts will be made to find suitable transformation.

12.0 Privacy and Confidentiality Considerations

All research records that are reviewed, stored, and analyzed at The Milton S. Hershey Medical Center (HMC) and Penn State College of Medicine (PSU) will be labeled with a code number. The list that matches the participant's name with the code number will be kept in a locked file in the PI's office. The research records will be kept in password-protected computer files and in file cabinets in locked rooms. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.

13.0 Data and Safety Monitoring Plan

This study involves low risk to subjects as it involves a low-dose sedative antidepressant treatment, a CBT program, and polysomnography.

Oversight for the conduct of the study will be provided by the PI, Alexandros Vgontzas, MD. He will ensure that all eligibility criteria and consent requirements are met prior to a subject's participation in the study and that all study procedures and adverse event reporting occur according to the IRB approved protocol.

All data forms and study specific information will be kept in locked file cabinets and in a password protected computer database with access limited to the PI and clinical research team. Any presentation or publication of the data will be done in aggregate fashion without identifiers.

All adverse events will be documented and reported by the PI to the IRB according to HSPO policies and procedures.

The PI will review cumulative adverse events, early termination of study participation, and accrual every six months and report any issues requiring modification of the study or alteration of the risk: benefit ratio to the IRB immediately. A summary of adverse events, study progress and protocol modifications will be included for IRB review in the continuing review report.

14.0 Compensation

Participants will be compensated in the amount of $400 upon completion of the study. Partial compensation will be given ($25 for each night spent in the sleep laboratory, $10 for each visit of treatment session, each monthly visit including initial visit to obtain actigraphy watch and sleep log.

15.0 Drugs, Biologics, or Devices

Trazodone is a sedative triazolopyridine antidepressant, habitually used for the treatment of depression and insomnia because it possesses antidepressant and also anxiolytic and hypnotic activities (Al-Yassiri et al, 1981; McCall, 2010). Pharmacologically, it is a serotonin antagonist and reuptake inhibitor; it is a blocker of postsynaptic serotonin receptors 5-HT1A, 5-HT1C, and 5-HT2, as well as postsynaptic α1-adrenergic receptors. It has a peak serum concentration of 1-2 hours and an elimination half-life of about 5-9 hours. When prescribed as an antidepressant, i.e., to alleviate major depression, the usual doses of trazodone are ≥ 150 mg daily. When prescribed as a hypnotic, it is habitually used at low-doses (i.e., 50 mg daily at bedtime). The effects of trazodone on sleep have been evaluated in a variety of subjects, including patients with insomnia and depression and normal controls. In general, most studies have shown that trazodone improves subjective sleep quality and increases objective total sleep time, percent of stages 3 and 4, and sleep efficiency, and decreases the percent of stage 1, number of awakenings, and stage shifts, as assessed by PSG (Burns et al, 1986; Saletu-Zyhlarz et al, 2001; James and Mendelson, 2004; Dording et al, 2002; Nierenberg et al, 1994; Haffmans, 1999; Walsh et al, 1998; Montgomery et al, 1983; Yamadera et al, 1998; Ware and Pittard, 1990; Kaynak et al, 2004; Zavesicka et al, 2008).

16.0 Records and Study Monitoring

Not Applicable.

17.0 Facilities

General Clinical Research Center & Sleep Lab

18.0 References

Adam K, Tomeny M, Oswald I. Physiological and psychological differences between good and poor sleepers. J Psychiatric Res 1986;20:301-316.

American Academy of Sleep Medicine. The International Classification of Sleep Disorders (ICSD-2): diagnostic and coding manual. 2nd ed. Westchester: American Academy of Sleep Medicine; 2005.

American Psychiatric Association. Diagnostic and statistical manual of mental disorders, text revision. 4th ed. Washington, DC: American Psychiatric Association;2000.

Ancoli-Israel S, Roth T. Characteristics of insomnia in the United States: results of the 1991 National Sleep Foundation Survey I. Sleep 1999;1:S347-S353.

Backhaus J, Junghanns K, Born J, Hohaus K, Faasch F, Hohagen F. Impaired declarative memory consolidation during sleep in patients with primary insomnia: influence

of sleep architecture and nocturnal cortisol release. Biol Psychiatry 2006;60:1324-30.

Basta M, Chrousos GP, Vela-Bueno A, Vgontzas AN. Chronic insomnia and the stress system. Sleep Med Clin 2007;2:279-291.

Bastien CH, Vallières A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. Sleep Med 2001;2(4):297-307.

Beck AT, Steer RA, Ball R, Ranieri W. Comparison of Beck Depression Inventories -IA and -II in psychiatric outpatients. J Pers Assess 1996;67(3):588-97.

Bixler EO, Vgontzas AN, Lin HM, et al. Prevalence of sleep-disordered breathing in women. Effects of gender. Am J Respir Crit Care Med 2001;163:608-613.

Bixler EO, Vgontzas AN, Lin HM, Vela-Bueno A, Kales A. Insomnia in Central Pennsylvania. J Psychosom Res 2002;53:589-592.

Bixler EO, Vgontzas AN. Ten Have T, Tyson K, Kales A. Effects of age on sleep apnea in men: I. Prevalence and severity. Am J Respir Crit Care Med 1998;157:144-148.

Bixler, EO, Kales A, Soldatos CR, Kales JD, Healey S. Prevalence of sleep disorders in the Los Angeles metropolitan area. Am J Psychiatry 1979;136:1257-1262.

Boggild H, Knutsson A. Shift work, risk factors and cardiovascular disease. Scand J Work Environ Health 1999;25:85-99.

Bonnet MH, Arand DL. 24-hour metabolic rate in insomniacs and matched normal sleepers. Sleep 1995;18(7):581-588.

Bonnet MH, Arand DL. Consequences of Insomnia. Sleep Med Clin 2006;1:351-358.

Bonnet MH, Arand DL. Insomnia, metabolic rate and sleep restoration. J Intern Med 2003;254:23-31.

Bonnet MH, Arand DL. Physiological activation in patients with sleep state misperception. Psychosom Med 1997;59:533-40.

Bonnet MH. Hyperarousal as the basis for insomnia: effect size and significance. Sleep 2005;28:1500-1501.

Breslau N, Roth T, Rosenthal L, Andreski P. Sleep disturbance and psychiatric disorders: a longitudinal epidemiological study of young adults. Biol Psychiatry 1996;39:411-418.

Burns M, Hoskowitz H, Jaffe J. A comparison of the effects of trazodone and amitriptyline on skills performance by geriatric subjects. J Clin Psychiatry 1986; 47:252–254.

Buysse DJ, Ancoli-Israel S, Edinger JD, Lichstein KL, Morin CM. Recommendations for a standard research assessment of insomnia. Sleep 2006;29:1155-1173.

Buysse DJ, Reynolds CF 3rd, Hauri PJ, Roth T, Stepanski EJ, Thorpy MJ, Bixler EO, Kales A, Manfredi RL, Vgontzas AN, et al. Diagnostic concordance for DSM-IV sleep disorders: a report from the APA/NIMH DSM-IV field trial. Am J Psychiatry 1994b;151:1351-1360.

Buysse DJ, Reynolds CF 3rd, Kupfer DJ, Thorpy MJ, Bixler E, Manfredi R, Kales A, Vgontzas A, Stepanski E, Roth T, et al. Clinical diagnoses in 216 insomnia patients using the International Classification of Sleep Disorders (ICSD), DSM-IV and ICD-10 categories: a report from the APA/NIMH DSM-IV Field Trial. Sleep 1994a;17:630-637.

Buysse DJ, Reynolds CF III, Hauri PJ, Roth T, Stepanski EJ, Thorpy MJ et al. Diagnostic concordance for insomnia patients among sleep specialists using proposed DSM-IV, proposed ICD-10, and ICSD diagnostic systems: report from the APA/NIMH DSM-IV field trial. In: Widiger TA, et al editors. DSM-IV Sourcebook, volume 4.Washington, DC: American Psychiatric Association; p: 869-889.

Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index (PSQI): A new instrument for psychiatric research and practice. Psychiatry Res 1989;28(2):193-213.

Buysse DJ. Overview of treatment considerations. In: Sateia MJ and Buysse DJ editors. Insomnia: diagnosis and treatment. Colchester, UK: Informa Healthcare; p: 256-259

Cervena K, Dauvilliers Y, Espa F, Touchon J, Matousek M, Billiard M, Besset A. Effect of cognitive behavioural therapy for insomnia on sleep architecture and sleep EEG power spectra in psychophysiological insomnia. J Sleep Res 2004;13(4):385-93.

Chesson A Jr, Hartse K, Anderson WM, Davila D, Johnson S, Littner M, Wise M, Rafecas J. Practice parameters for the evaluation of chronic insomnia. An American Academy of Sleep Medicine Report Standards of Practice Committee of the American Academy of Sleep Medicine. Sleep 2000;23:237-241.

Chevalier H, Los F, Boichut D, Bianchi M, Nutt DJ, Hajak G, et al. Evaluation of severe insomnia in the general population : results of a European multinational survey. J Psychopharmacol 1999:13:S21-S24.

Coren S. Prediction of insomnia from arousability predisposition scores: scale development and cross-validation. Behav Res Ther 1988;26:415–20.

Dodge R, Cline MG, Quan SF. The natural history of insomnia and its relationship to respiratory symptoms. Arch Intern Med 1995;155:1797-1800.

Dording C, Mischoulon D, Petersen T, et al. The pharmacologic management of SSRI-induced side effects: A survey of psychiatrists. Ann Clin Psychiatry 2002; 14:143–147.

Drake C, Richardson G, Roehrs T, Scofield H, Roth T. Vulnerability to stress-related sleep disturbance and hyperarousal. Sleep 2004;27:285–91.Edinger JD, Bonnet MH, Bootzin RR, Doghramji K, Dorsey CM, Espie CA, Jamieson AO, McCall WV, Morin CM, Stepanski EJ; American Academy of Sleep Medicine Work Group. Derivation of research diagnostic criteria for insomnia: report of an American Academy of Sleep Medicine Work Group. 2004;27:1567-1596.

Edinger JD, Glenn DM, Bastian LA, Marsh GR, Daile D, Hope V, et al. Sleep in laboratory and sleep at home II: comparisons of middle-aged insomnia sufferers and normal sleepers. Sleep 2001;24(7):761-70.

Edinger JD, Olsen MK, Stechuchak KM, Means MK, Lineberger MD, Kirby A, Carney CE. Cognitive behavioral therapy for patients with primary insomnia or insomnia associated predominantly with mixed psychiatric disorders: a randomized clinical trial. Sleep 2009; 32(4):499-510.

Edinger JD, Wohlgemuth WK, Radtke RA, Coffman CJ, Carney CE. Dose-response effects of cognitive-behavioral insomnia therapy: a randomized clinical trial. Sleep 2007;30:203-212.

Edinger JD, WohlgemuthWK, Radtke RA, Marsh GR, Quillian RE. Cognitive behavioral therapy for treatment of chronic primary insomnia. JAMA 2001;285:1856-1864.

Espie CA, Inglis SJ, Harvey L, Tessier S. Insomniacs' attributions. psychometric properties of the Dysfunctional Beliefs and Attitudes about Sleep Scale and the Sleep Disturbance Questionnaire. J Psychosom Res 2000;48(2):141-8.

Espie CA, MacMahon KM, Kelly HL, Broomfield NM, Douglas NJ, Engleman HM, McKinstry B, Morin CM, Walker A, Wilson P. Randomized clinical effectiveness trial of nurse-administered small-group cognitive behavior therapy for persistent insomnia in general practice. Sleep 2007;30(5):574-84.

Fernandez-Mendoza J, Calhoun S, Bixler EO, Pejovic S, Karataraki M, Liao D, Vela-Bueno A, Ramos-Platon MJ, Sauder KA, Vgontzas AN. Insomnia with objective short sleep duration is associated with deficits in neuropsychological performance: a general population study. Sleep 2010;33(4):459-65.

Fernandez-Mendoza J, Calhoun SL, Bixler EO, Karataraki M, Liao D, Vela-Bueno A, Ramos-Platon MJ, Sauder KA, Basta M, Vgontzas AN. Sleep Misperception and Chronic Insomnia in the General Population: Role of Objective Sleep Duration and Psychological Profiles. Psychosom Med 2011; in press

Foley DJ, Monjan AA, Brown SL, Simonsick EM, Wallace RB, Blazer DG. Sleep complaints among elderly persons: an epidemiologic study of three communities. Sleep 1995;18(6):425-432.

Ford DE, Kamerow DB. Epidemiologic study of sleep disturbances and psychiatric disorders. JAMA 1989;262:1479-1484.

Frankel BL, Buchbinder R, Coursey R, Snyder F. Sleep patterns and psychological test characteristics of chronic primary insomniacs. Sleep Res 1973;2:149.

Fulda S, Schulz H. Cognitive dysfunction in sleep disorders. Sleep Med 2001;5:423-445.

Haffmans PMJ. The effects of trazodone on sleep disturbances included by brofaromine. Eur Psychiatry 1999; 14:167–171.

Hajak G, Rodenbeck A, Voderholzer U, Riemann D, Cohrs S, Hohagen F, Berger M, Rüther E. Doxepin in the treatment of primary insomnia: a placebo-controlled, double-blind, polysomnographic study. J Clin Psychiatry 2001;62(6):453-63.

Iber C, Ancoli-Israel S, Chesson AL Jr, Quan SF. The AASM Manual for the Scoring of Sleep and Associated Events: Rules Terminology and Technical Specifications. American Academy of Sleep Medicine: Westchester, IL, 2007.

Ip MSM, Lam B, Ng MMT, Lam WK, Tsant KWT, Lam KSL. Obstructive sleep apnea is independently associated with insulin resistance. Am J Respir Crit Care Med 2002;165:670-676.

Irwin M, Clark C, Kennedy B, Christian Gillin J, Ziegler M. Nocturnal catecholamines and immune function in insomniacs, depressed patients, and control subjects. Brain Behav Immun 2003;17:365-72.

Jacobs GD, Pace-Schott EF, Stickgold R, Otto MW. Cognitive behavior therapy and pharmacotherapy for insomnia. Arch Intern Med 2004;164:1888-1896.

James S, Mendelson W. The use of trazodone as a hypnotic: A critical review. J Clin Psychiatry 2004; 65:752–755.

Janson C, Lindberg E, Gislason T, Elmasry A, Boman G. Insomnia in men – a 10-year prospective population based study. Sleep 2001;24:425-430.

Johns MW, Gay TJA, Masterton JP, Bruce DW. Relationship between habits, adrenocortical activity and personality. Psychosom Med 1971;33:499-508.

Johns MW.A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 1991;14(6):540-5.

Kales A, Caldwell AB, Soldatos CR, Bixler EO, Kales JD. Biopsychobehavioral correlates of insomnia II. Pattern specificity and consistency with the Minnesota Multiphasic Personality Invetory. Psychosomatic Med 1983;45:341-345.

Kales A, Kales JD. Evaluation and treatment of insomnia. New York: Oxford University Press, 1984.

Karacan I, Thornby JI, Anch M, Holtzer CE, Warheit GJ, Schwab JJ, et al. Prevalence of sleep disturbances in a primarily urban Florida county. Arch Gen Psychiatry 1976;10:239-244.

Katz A, Nambi SS, Mather K, et al. Quantitative insulin sensitivity check index: a simple, accurate method for assessing insulin sensitivity in humans. J Clin Endocrinol Metab 2000;85:2402-2410.

Kaynak H, Kaynak D, Gözükirmizi E, Guilleminault C. The effects of trazodone on sleep in patients treated with stimulant antidepressants. Sleep Med 2004;5(1):15-20.

Klink M, Quan SF, Kaltenborn WT, Lebowits MD. Risk factors associated with complaints of insomnia in a general adult population. Arch Intern Med 1992;152:1634-1637.

Klink M, Quan SF. Prevalence of reported sleep disturbances in a general adult population and their relationship to obstructive airways diseases. Chest 1987;91:540-546.

Kripke DF, Garfinkel L, Wingard DL, Klauber MR, Marler MR. Mortality associated with sleep duration and insomnia. Arch Gen Psychiatry 2002;59:131-136.

Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. Arch Neurol 1989; 46(10):1121-3.

Krystal AD, Durrence HH, Scharf M, Jochelson P, Rogowski R, Ludington E, Roth T. Efficacy and Safety of Doxepin 1 mg and 3 mg in a 12-week Sleep Laboratory and Outpatient Trial of Elderly Subjects with Chronic Primary Insomnia. Sleep 2010;33(11):1553-61.

Krystal AD, Edinger JD. Sleep EEG predictors and correlates of the response to cognitive behavioral therapy for insomnia. Sleep 2010;33(5):669-77.

MacLean AW, Fekken GC, Saskin P, Knowles JB. Psychometric evaluation of the Stanford Sleepiness Scale. J Sleep Res 1992;1(1):35-39.

McCall WV. Off-label use of prescription medications for insomnia: sedating antidepressants, antipsychotics, anxiolytics, and anticonvulsants. In: Sateia MJ and Buysse DJ editors. Insomnia: diagnosis and treatment. Colchester, UK: Informa Healthcare; p: 397-409

McNair DM, Lorr M, Droppleman LF. Profile of Mood States Manual. San Diego: Educational and Industrial Testing Services; 1971.

Mellinger GD, Balter MB, Uhlenhuth EH. Insomnia and its treatment. Prevalence and correlates. Arch Gen Psychiatry 1985;42:225-232.

Mendelson WB. A review of the evidence for the efficacy and safety of trazodone in insomnia. J Clin Psychiatry 2005;66:469-476.

Merica H, Blois R, Gaillard JM. Spectral characteristics of sleep EEG in chronic insomnia. Eur J Neurosci 1998;10:1826-1834.

Montgomery I, Oswald I, Morgan K, et al. Trazodone enhances sleep in subjective quality but not in objective duration. Br J Clin Pharmacol 1983; 16:139–144.

Morgenthaler T, Kramer M, Alessi C, Friedman L, Boehlecke B, Brown T, Coleman J, Kapur V, Lee-Chiong T, Owens J, Pancer J, Swick T; American Academy of Sleep Medicine. Practice parameters for the psychological and behavioral treatment of insomnia: an update. An american academy of sleep medicine report. Sleep 2006;29:1415-1419.

Morin CM, Bastien C, Guay B, Radouco-Thomas M, Leblanc J, Vallières A. Randomized clinical trial of supervised tapering and cognitive behavior therapy to facilitate benzodiazepine discontinuation in older adults with chronic insomnia. Am J Psychiatry 2004;161:332-342.

Morin CM, Bootzin RR, Buysse DJ, Edinger JD, Espie CA, Lichstein KL. Psychological and behavioral treatment of insomnia:update of the recent evidence (1998-2004). Sleep 2006;29:1398-1414.

Morin CM, Espie CA. Insomnia: A Clinician's Guide to Assessment and Treatment. Springer: NY, 2003.

Morin CM. Insomnia: Psychological Assessment and Management. The Guilford Press: NY, 1993.

Morin CM. Measuring outcomes in randomized clinical trials of insomnia treatments. Sleep Med Rev 2003;7:263-279.

Morlock RJ, Tan M, Mitchell DY. Patient characteristics and patterns of drug use for sleep complaints in the United States: analysis of National Ambulatory Medical Survey data, 1997-2002. Clin Ther 2006;28:1044-1053.

National Institutes of Health. NIH state of the science statement on manifestations and management of chronic insomnia in adults. J Clin Sleep Med 2005;1:412-421.

Nicassio PM, Mendlowitz DR, Fussell JJ, Petras L. The phenomenology of the pre-sleep state: the development of the pre-sleep arousal scale. Behav Res Ther 1985;23(3):263-71.

Nierenberg A, Adler LA, Peselow E, et al. Trazodone for antidepressant-associated insomnia. Am J Psychiatry 1994; 151:1069–1072.

Nofzinger EA, Buysse DJ, Germain A, Price JC, Miewald JM, Kupfer DJ. Functional neuroimaging evidence for hyperarousal in insomnia. Am J Psychiatry 2004;161:2126-2129.

Ohayon MM. Epidemiology of insomnia: what we know and what we still need to learn. Sleep Med Rev 2002;6:97-111.

Okajima I, Komada Y, Inoue Y. A meta-analysis on the treatment effectiveness of cognitive behavioral therapy for primary insomnia. Sleep Biol Rhythms 2010, in press (doi:10.1111/j.1479-8425.2010.00481.x)Osman A, Kopper BA, Barrios FX, Osman JR, Wade T. The Beck Anxiety Inventory: reexamination of factor structure and psychometric properties. J Clin Psychol 1997;53(1):7-14.

Perlis ML, Jungquist C, Smith MT, Posner D. Cognitive Behavioral Treatment of Insomnia: A Session-by-Session Guide. Springer: NY, 2005.Perlis ML, Smith MT, Andrews PJ, Orff H, Giles DE. Beta/gamma EEG activity in patients with

primary and secondary insomnia and good sleeper controls. Sleep 2001;24:110-17.

Pervanidou P, Kolaitis G, Charitaki S, Lazaropoulou C, Papassotiriou I, Hindmarsh P, Bakoula C, Tsiantis J, Chrousos GP. The natural history of neuroendocrine changes in pediatric posttraumatic stress disorder (PTSD) after motor vehicle accidents: progressive divergence of noradrenaline and cortisol concentrations over time. Biol Psychiatry. 2007a;62(10):1095-102.

Pervanidou P, Kolaitis G, Charitaki S, Margeli A, Ferentinos S, Bakoula C, Lazaropoulou C, Papassotiriou I, Tsiantis J, Chrousos GP. Elevated morning serum interleukin (IL)-6 or evening salivary cortisol concentrations predict posttraumatic stress disorder in children and adolescents six months after a motor vehicle accident. Psychoneuroendocrinology. 2007b;32(8-10):991-9.

Phillips B, Mannino DM. Do insomnia complaints cause hypertension or cardiovascular disease? J Clin Sleep Med 2007;3:489-494.

Punjabi NM, Sorkin JD, Katzel L, Goldberg A, Schwartz A, Smith PL. Sleep-disordered breathing and insulin resistance in middle aged and overweight men. Am J Respir Crit Care Med 2002;165:677-682.

Quon MJ. Editorial: limitations of the fasting glucose to insulin ratio as an index of insulin sensitivity. J Clin Endocrinol Metab 2001;86:4615-4617.

Rechtschaffen A, Kales A. A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects. NIMH Publication 204; Washington DC: US Government Printing Office. 1968.

Riemann D, Klein T, Rodenbeck A, Feige B, Horney A, Hummel R, Weske G, Al-Shajlawi A, Voderholzer U. Nocturnal cortisol and melatonin secretion in primary insomnia. Psychiatry Res 2002;113:17-27.

Rodenbeck A, Cohrs S, Jordan W, Huether G, Rüther E, Hajak G. The sleep-improving effects of doxepin are paralleled by a normalized plasma cortisol secretion in primary insomnia. Psychopharmacology 2003;170:423-8.

Rodenbeck A, Huether G, Ruether E, Hajak G. Interactions between evening and nocturnal cortisol secretion and sleep parameters in patients with severe chronic primary insomnia. Neurosci Lett 2002;324:163-459.

Roehrs T, Carskadon MA, Dement WC, Roth T. Daytime sleepiness and alertness. In: Kryger M, Roth T, Dement W (Eds). Principles and Practice of Sleep Medicine, 4th Edition. Philadelphia: WB Saunders, 2005;39-50.

Roth T, Heith Durrence H, Jochelson P, Peterson G, Ludington E, Rogowski R, Scharf M, Lankford A. Efficacy and safety of doxepin 6 mg in a model of transient insomnia. Sleep Med 2010;11(9):843-7.

Roth T, Rogowski R, Hull S, Schwartz H, Koshorek G, Corser B, Seiden D, Lankford A. Efficacy and safety of doxepin 1 mg, 3 mg, and 6 mg in adults with primary insomnia. Sleep 2007;30(11):1555-61. 13.Saletu-Zyhlarz G, Abu-Bakr M, Anderer P, et al. Insomnia related to dysthymia: Polysomnographic and psychometric comparison with normal controls and acute therapeutic trials with trazodone. Neuropsychobiology 2001; 44:139–149.

Scharf M, Rogowski R, Hull S, Cohn M, Mayleben D, Feldman N, Ereshefsky L, Lankford A, Roth T. Efficacy and safety of doxepin 1 mg, 3 mg, and 6 mg in

elderly patients with primary insomnia: a randomized, double-blind, placebo-controlled crossover study. J Clin Psychiatry 2008;69(10):1557-64.

Shaver JL, Johnston SK, Lentz MJ, Landis CA . Stress exposure, psychological distress, and physiological stress activation in midlife women with insomnia. Psychosom Med 2002;64:793-802.

Simon GE, Von Korff M. Prevalence, burden, and treatment of insomnia in primary care. Am J Psychiatry 1997;154:1417-1423.

Sivertsen B, Omvik S, Havik OE, Pallesen S, Bjorvatn B, Nielsen GH, Straume S, Nordhus IH. A comparison of actigraphy and polysomnography in older adults treated for chronic primary insomnia. Sleep 2006b;29(10):1353-8.

Sivertsen B, Omvik S, Pallesen S, Bjorvatn B, Havik OE, Kvale G, Nielsen GH, Nordhus IH. Cognitive behavioral therapy vs zopiclone for treatment of chronic primary insomnia in older adults: a randomized controlled trial. JAMA 2006;295:2851-2858.

Smets EM, Garssen B, Bonke B, De Haes JC. The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. J Psychosom Res 1995;39(3):315-25.

Stepanski E, Glinn M, Zorick F, Roehrs T, Roth T. Heart rate changes in chronic insomnia. Stress Med 1994;10:261-66.

Stepanski E, Zorick F, Roehrs T, Young D, Roth T. Daytime alertness in patients with chronic insomnia compared to asymptomatic controls subjects. Sleep 1988;11:54-60.

Suka M, Yoshida K, Sugimori H. Persistent insomnia is a predictor of hypertension in Japanese male workers. J Occup Health 2003;45:344-350.

US Department of Health and Human Services (DHHS). National Center for Health Statistics. Third National Health and Nutrition Examination Survey, 1988-1994. NHANES III laboratory data file. Hyattsville(MD): Centers for Disease Control and Prevention, 1996.

US Department of HEW. Selected symptoms of psychological distress. Rockville(MD): US Department of HEW, 1970.

Varkevisser M, Van Dongen HP, Kerkhof GA. Physiologic indexes in chronic insomnia during a constant routine: evidence for general hyperarousal? Sleep 2005;28:1588-1596.

Vgontzas AN, Bixler EO, Lin HM, Prolo P, Mastorakos G, Vela-Bueno A, Kales A, Chrousos GP. Chronic insomnia is associated with nyctohemeral activation of the hypothalamic-pituitary-adrenal axis: clinical implications. J Clin Endocrinol Metab 2001;86:3787-3794.

Vgontzas AN, Bixler EO, Tan TL, Kantner D, Martin LF, Kales A. Obesity without sleep apnea is associated with daytime sleepiness. Arch Intern Med 1998;158:1333-1337.

Vgontzas AN, Kales A. Sleep and its disorders. Annu Rev Med 1999;50:387-400.

Vgontzas AN, Liao D, Bixler EO, Chrousos GP, Vela-Bueno A. Insomnia with objective short sleep duration is associated with a high risk for hypertension. Sleep 2009;32(4):491-7.

Vgontzas AN, Liao D, Pejovic S, Calhoun S, Karataraki M, Basta M, Fernández-Mendoza J, Bixler EO. Insomnia with short sleep duration and mortality: the Penn State cohort. Sleep 2010;33(9):1159-64.

Vgontzas AN, Liao D, Pejovic S, Calhoun S, Karataraki M, Bixler EO. Insomnia with objective short sleep duration is associated with type 2 diabetes: A population-based study. Diabetes Care 2009;32(11):1980-5.

Vgontzas AN, Mastorakos G, Bixler EO, Kales A, Gold PW, Chrousos GP. Sleep deprivation effects on the activity of the hypothalamic-pituitary-adrenal and growth axes: potential clinical implications. Clin Endocrinol 1999;51:205-215.

Vgontzas AN, Papanicolaou DA, Bixler EO, Kales A, Tyson K, Chrousos GP. Elevation of plasma cytokines in disorders of excessive daytime sleepiness: role of sleep disturbance and obesity. J Clin Endocrinol Metab 1997;82:1313-1316.

Vgontzas AN, Pejovic S, Zoumakis E, Lin HM, Bixler EO, Basta M, Fang J, Sarrigiannidis A, Chrousos GP. Daytime napping after a night on sleep loss decreases sleepiness, improves performance, and causes beneficial changes in cortisol and interleukin-6 secretion. Am J Physiol Endocrin Metab 2007;292:253-261.

Vgontzas AN, Tan TL, Bixler EO, Martin LF, Shubert D, Kales A. Sleep apnea and sleep disruption in obese patients. Arch Intern Med 1994;154:1705-1711.

Vgontzas AN, Tsigos C, Bixler EO, Stratakis CA, Zachman K, Kales A, Vela-Bueno A, Chrousos GP. Chronic insomnia and activity of the stress system: a preliminary study. J Psychosom Res 1998;45:21-31.

Vgontzas AN, Zoumakis E, Bixler EO, Lin HM, Collins B, Basta M, Pejovic S, Chrousos GP. Selective effects of CPAP on sleep apnoea-associated manifestations. Eur J Clin Invest 2008;38:585-595.

Vgontzas AN, Zoumakis E, Bixler EO, Lin HM, Follet H, Kales A, Chrousos GP. Adverse effects of modest sleep restriction on sleepiness, performance, and inflammatory cytokines. J Clin Endocrinol Metab 2004;89:2119-2126.

Vgontzas AN, Zoumakis E, Lin HM, Bixler EO, Trakada G, Chrousos GP. Marked decrease in sleepiness in patients with sleep apnea by etanercept, a tumor necrosis factor-alpha antagonist. J Clin Endocrinol Metab 2004;89:4409-4413.

Walsh JK, Erman M, Erwin CW, et al. Subjective hypnotic efficacy of trazodone and zolpidem in DSMIII-R primary insomnia. Hum Psychopharmacol 1998; 13:191–198.

Ware JC, Pittard JT. Increased deep sleep after trazodone use:Adouble-blind placebo-controlled study in healthy young adults. J Clin Psychiatry 1990; 51:18–22.

Warrington SJ, Ankier SI, Turner P. An evaluation of possible interactions between ethanol and trazodone or amitriptyline. Br J Clin Pharmacol 1984; 18:549–557.

Yamadera H, Nakamura S, Suzuki H, et al. Effects of trazodone hydrochloride and imipramine on polysomnography in healthy subjects. Psychiatry Clin Neurosci 1998; 52:439–443.Zavesicka L, Brunovsky M, Horacek J, Matousek M, Sos P, Krajca V, Höschl C. Trazodone improves the results of cognitive behaviour therapy of primary insomnia in non-depressed patients. Neuro Endocrinol Lett 2008;29(6):895-901.

Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983; 67(6):361-70.