RISKS FOR TRANSITION FROM THERAPEUTIC HYPNOTIC USE TO ABUSE

Grant No: R01DA038177

Principal Investigator: Timothy Roehrs, PhD

Clinical Trials Registration
NCT02456532

Note: The enclosed protocol was in use unaltered from the first subject entered into this NIDA sponsored mechanistic study regarding the risks associated with chronic hypnotic use until the last subject was completed 6-2022. The protocol is active during the analysis period which started 6-2022.

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(Rev. 1 8/3/2015)

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PROJECT SUMMARY/ABSTRACT

The acknowledged drugs of choice for the pharmacological treatment of insomnia are the benzodiazepine receptor ligand hypnotics (BzRL). Our nighttime studies show that with therapeutic doses used either short-term or chronically, the abuse liability of BzRLs in insomnia is not seen universally and is relatively low. The data from our last grant, a first-ever study, showed the abuse liability of chronic zolpidem use in insomniacs was low. Yet case reports and retrospective studies continue to report BzRL dependence and for the majority of these cases the abuse developed through initial therapeutic use. In our study some subjects showed an increase in dose across time. **Understanding the transition from therapeutic use to abuse and identifying risk factors, such as specific patient and drug characteristics, is both mechanistically and clinically important.**

Our preliminary data have shown that a subset of insomniacs, those insomniacs that have signs of hyperarousal as reflected by elevated Multiple Sleep Latency Test (MSLT) scores, increased their nightly zolpidem dose across time. BzRLs have differential receptor binding affinities and associated anxiolytic or antidepressant properties. Zolpidem has selective alpha 1 BzRL affinity and little mood activity and thus may show less risk for **transition from therapeutic use to abuse** than another currently frequently prescribed BzRL with less alpha subtype selectivity such as eszopiclone. **We propose to study the abuse liability of a selective (zolpidem) vs nonselective (eszopiclone) hypnotic during chronic use (six months) in an at-risk sub-population (insomniacs with hyperarousal shown by elevated MSLTs).** The proposal is highly innovative as it reflects a paradigm shift in understanding the abuse liability of hypnotics.

In the end, this proposal will generate a unique set of data addressing a number of previously clinically important unanswered questions regarding hypnotic abuse by insomniacs (i.e., its likelihood as a function of arousal state and specific hypnotic pharmacology, of dose escalation over time and change in mood/drug effect ratings over time). It will provide clinicians with behavioral indicators of abuse risk.

1. INTRODUCTION

We thank the reviewers for their careful review of our proposed research project and for the recognition of the innovative and clinically significant aspects of this project. We address various identified weaknesses in our research plan and indicate in the text by a change in font.

Two reviewers asked why hyperaroused insomnia is a risk for transition from therapeutic BzRL use to abuse and what the underlying mechanism for the transition might be. Many theories of addiction hypothesize that stress increases vulnerability to drug abuse (1). Animal literature and human neuroimaging studies have identified brain circuits involved in stress that include release of CRF from the paraventicular nucleus and NE activation initiated in locus coeruleus. This CRF/NE activation also activates dopaminergic brain motivational pathways known to be engaged by drugs of abuse including ventral tegmental area and nucleus accumbens. So stress co-activates brain stress and reward circuits simultaneously. Thus, at a behavioral level stress enhances the positive rewarding properties of drugs with abuse liability.

Among common physiological stressors is insomnia. In a subset of persons with insomnia in our preliminary data we found indications of stress and enhanced abuse liability. Those with hyperaroused insomnia as defined by MSLT showed elevated daytime urinary NE and they were also those that dose escalated. Previously, we showed such at-risk persons also self-administered a hypnotic outside of the therapeutic context (i.e. during the day). We also have hypothesized that a hypnotic that differentially reduces stress (eszopiclone) associated with insomnia will have a higher abuse liability.

A reviewer questioned the role of anxiety. We addressed anxiety and mood assessment in section D6.7 and its analysis in section D8. As to differential pre-existing anxiety, it will be used as a covariate in analyses. As to tolerance, it has been shown tolerance does not develop to eszopiclone effects over a year (2).

The rationale for measurement of HPA markers and choice of specific markers was also questioned. We will limit assays to urinary NE and salivary cortisol. The rationale for these markers is discussed above. Our preliminary data showed NE elevations in our hypothesized at-risk subset of people with insomnia. The stress and abuse vulnerability literature also suggests cortisol elevation. While our preliminary data did not show statistically significant cortisol elevation, the more selective inclusion criteria and frequent sampling in this proposal should reduce the variability in this measure and enhance our ability to show the predicted differences.

The study design and subject characteristics were questioned. This is a between group design comparing <u>two</u> levels of arousal (MSLT-defined) randomized to <u>three</u> treatments, yielding a total of six groups with n=20 per group. We anticipate, based on our previous grant, 50% of persons with insomnia will qualify for the ≥ 13 min and 40% for the ≤ 11 to > 5 min MSLT groups. We have decreased the upper age entry criteria to ≤ 64 yrs to avoid the need to use lower doses in those > 65 yrs. Age will not be considered as a variable as our previous grant showed no age differences in efficacy or safety. We also will expand the alcohol or substance abuse history exclusion from two years to lifetime. We will exclude all Axis I and Axis II psychiatric disorders. We will caution regarding eating prior to capsule ingestions as part of our standard medication and sleep hygiene instructions.

1) Sinha R. Chronic stress, drug use, and vulnerability to addiction. Ann NY Acad Sci. 2008,1141:105130.

2) Roth T. Walsh JK, Krystal A, Wessel T, Roehrs TA. An evaluation of the efficacy and safety of eszopiclone over 12 months in patients with chronic primary insomnia. Sleep Med. 2005;6:487-495.

2. AIMS

The acknowledged drugs of choice for the pharmacological treatment of insomnia are the benzodiazepine receptor ligand hypnotics (BzRL). Our nighttime studies show that with therapeutic doses used either short-term or chronically, the abuse liability of BzRLs in primary insomnia is not seen universally and is relatively low (1-9). The data from our last grant, a first ever study, showed the abuse liability of chronic zolpidem use in insomniacs was low. Yet case reports and retrospective studies continue to report BzRL dependence and for the majority of these cases the abuse developed through initial therapeutic use (10-12). In our last study some subjects showed an increase in dose across time (see Section C). **Understanding the transition from therapeutic use to abuse and identifying risk factors, such as specific patient and drug characteristics, is both mechanistically and clinically important.**

Our preliminary data have shown that a subset of insomniacs, those insomniacs that had signs of hyperarousal as reflected by elevated Multiple Sleep Latency Test (MSLT) scores, increased their nightly zolpidem dose across time. BzRLs have differential receptor binding affinities and associated anxiolytic or antidepressant properties. Zolpidem has selective alpha 1 BzRL affinity and little mood activity and thus may show less risk for **transition from therapeutic use to abuse** than another currently frequently prescribed BzRL with less alpha subtype selectivity such as eszopiclone. **We propose to study the abuse liability of a selective (zolpidem) vs a nonselective (eszopiclone) hypnotic during chronic use (i.e. six months) in an at-risk population (i.e. insomniacs with hyperarousal shown by elevated MSLTs).** This proposal is designed with these aims and will test the following hypotheses:

2.1. To evaluate hypnotic self-administration by primary insomniacs as a function of their daytime MSLT-defined arousal status and the available BzRL hypnotic.

a. Insomniacs with hyperarousal vs those without will self-administer a hypnotic at greater rates.

b. Insomniacs will more likely self-administer a drug with mood effects (i.e., anxiolytic properties, eszopiclone), versus a hypnotic without these mood effects, zolpidem.

2.2. To evaluate changes in the rate of hypnotic self-administration and subjective effects of insomniacs with hyperarousal vs those without during chronic nightly use.

a. Hyperaroused insomniacs, after six months of nightly use of eszopiclone, will show increased rates of self-administration and greater "drug liking” and "euphoria” ratings than those using zolpidem nightly.

2.3. To evaluate the ability to stop using hypnotics when instructed to discontinue use after six months of chronic nightly hypnotic use.

a. Hyperaroused insomniacs will self-administer a greater number of hypnotics during discontinuation than non-hyperaroused insomniacs

b. A greater number of eszopiclone vs zolpidem capsules will be self-administered during the discontinuation.

2.4. To evaluate indices of HPA augmentation as predictors of hypnotic self-administration.

a. Levels of urinary catecholamines, specifically norepinephrine, will predict the likelihood of self-administration of hypnotics.

3. RESEARCH STRATEGY

A. Significance

The acknowledged drugs of choice for the pharmacological treatment of insomnia are the benzodiazepine receptor ligand hypnotics (BzRL). However, case reports and cross-sectional studies continue to report BzRL dependence and for the majority of cases the dependence developed through initial therapeutic use (10-12). We have argued that an important distinction in assessing the abuse liability of prescription drugs is differentiating therapy seeking from drug seeking behavior (9). This distinction becomes difficult in situations where therapy seeking evolves into drug seeking. This path to BzRL dependence, from therapeutic use to drug abuse, has been described as "chronic quasi-therapeutic abuse" or "iatrogenic dependence" (13). In a previous grant we hypothesized a path to abuse of hypnotics by insomniacs in which chronic nighttime BzRL use leads to tolerance development, dose is increased, and rebound insomnia occurs making it difficult to discontinue drug use. While demonstrating dependence risk in a subset of individuals, the results of that grant did not completely support our hypothesis. We showed over twelve months of nightly zolpidem use tolerance for most does not develop (14), for most insomniacs dose is not escalated (15), and for most rebound insomnia does not occur on discontinuation (16). Importantly in some insomniacs dose was escalated.

Primary insomnia and probably also co-morbid insomnia, is hypothesized to reflect a 24-hr state of hyperarousal. This hyperarousal is evident in primary insomniacs' prolonged sleep latencies (i.e., about one standard deviation above normals) on the MSLT during the day, despite disrupted and shortened nocturnal sleep the previous night (17-19). Evidence also suggests that this physiologic hyperarousal is associated with activation of the sympathetic nervous system (SNS) and hypothalamic-pituitary-adrenal (HPA) axis. Insomniacs show elevated levels of circulating catecholamines (20), increased metabolic rates (19), increased body temperature (21), and altered heart rate variability (22), and pupillometry patterns (23). HPA augmentation in insomnia is indicated by elevated levels of nighttime urinary free cortisol proportional to the amount of wakefulness during the night (19). An activated SNS and HPA axis suggests a central mechanism possibly involving corticotropin releasing factor (CRF) neurons. Neuroimaging findings in insomniacs support a hyperarousal hypothesis. Primary insomniacs, relative to healthy controls, showed greater cerebral glucose metabolism during sleep, while awake, and at the transition from wake to sleep and particularly in brain arousal centers (24). Importantly, these studies all compared insomniacs to non-insomniacs rather than assessing individual differences among insomniacs in level of hyperarousal.

We confirmed the presence of hyperarousal in some primary insomniacs (about half) as defined by the MSLT (25). Further, no previous study had assessed the stability of elevated MSLT scores within an individual across time and we found that MSLT elevation in insomnia is a stable "trait-like" finding (25). Finally, we found that elevated MSLTs are associated with elevated levels of daytime urinary norepinephrine relative to non-elevated MSLTs (see Section C). This is a first validation of the construct of hyperarousal in insomnia using two concurrent “independent" measures. While the majority of insomniacs in our previous grant did not escalate their hypnotic dose, a subset, those among the top third with MSLT elevation did escalate hypnotic dose (see Section C). **These hyperaroused insomniacs may represent an at-risk population for a transition from therapeutic hypnotic use to abuse.**

The pharmacology of specific BzRLs may also be important. Our short-term studies used triazolam, while our last grant used zolpidem. The present proposal will evaluate an extended release formulation of zolpidem and eszopiclone. This change occurs due to a shift in clinical

practice and our desire to study drugs with differing receptor binding properties, but comparable hypnotic efficacy. These two BzRLs have important differential receptor affinities and anxiolytic properties. Zolpidem is $GABA_A$ receptor selective acting primarily at the alpha 1 receptor, while eszopiclone is non-selective acting at both alpha 1 and alpha 3 receptors (26). In ranking BzRLs as to abuse liability, the non-receptor selective (i.e., diazepam, triazolam, eszopiclone, alprazolam) drugs were ranked higher than those that are more selective (i.e., zolpidem, zaleplon) (13). Accompanying the differential receptor selectivity are differences in mood effects. Triazolam and alprazolam have anxiolytic and antidepressant properties, as does the alpha 1 and 3 BzRL non-benzodiazepine drug, eszopiclone (27). In contrast, zolpidem does not have anxiolytic or antidepressant properties, as shown in animal studies and at least one clinical study (26, 28). **This raises the critical question as to whether zolpidem, being alpha 1 specific and without anxiolytic properties, has less risk for abuse by insomniacs than a non-selective BzRL with anxiolytic properties such as eszopiclone.**

That is not to say that zolpidem is without risk, there are reports of zolpidem abuse (12). Daytime studies in healthy normals and drug abusers have shown comparable abuse risk between zolpidem and other BzRLs (13, 29–31). Importantly, none of these studies have assessed insomniacs or nighttime use. Rather, these studies were carried out in sedative abusers and there is no question that both drugs possess sedative effects, but importantly not comparable anxiolytic mood effects. We hypothesize hyperaroused insomniacs are an at-risk population and in addition that a differential risk between eszopiclone and zolpidem will be shown in insomnia populations with nighttime use. To show a differential risk of specific BzRLs in hyperaroused insomniacs will further be supportive of our hypothesis that the modulation of mood is another therapeutic effect sought by hyperaroused insomniacs. Then a transition to abuse occurs over time. **This shift to potential abuse will be reflected in dose escalation and increased ratings of “drug-liking” and “euphoria” over time.** Analyses of case reports regarding abuse of BzRLs consistently show dose escalation (10-12). And assessment of subjective effects associated with drug administration is a standard approach to assessing the abuse liability of a given drug (32).

Finally, discontinuation of chronic hypnotic use remains an important clinical problem limiting the usefulness of hypnotics and also reflects what is termed "iatrogenic dependence” (13). While in our last grant we found little evidence of rebound insomnia on discontinuation of 12 months of nightly zolpidem use (16), clinicians report a return of sleep disturbance on discontinuation that leads to a resumption of hypnotic use (33). Importantly, triazolam, a nonspecific BzRL was the first drug for which rebound insomnia was described and we were able to show dose dependent rebound (1, 2). While rebound is a potential mechanism for difficulty stopping medication, it is not a necessary condition for difficulty stopping medication use. Difficulty discontinuing medication must be measured directly. Understanding risks for discontinuation difficulties as a distinct form of abuse, in addition to likelihood of dose escalation and increased ratings of “drug-liking” and "euphoria", is clinically important. **The question arises as to whether hyperaroused insomniacs and those using a non-selective BzRL would encounter greater inability to stop hypnotic use defined by continued use despite the instruction to discontinue.**

B. Innovation

This proposal reflects a paradigm shift in understanding the abuse liability of hypnotics. Previous studies have focused on the nighttime characteristics of the sleep of the insomniac, or the effectiveness of the hypnotic for a given person, or its discontinuation effects as risk factors for abuse. Here we suggest that abuse risk is an attribute of insomnia per se which is seen to a greater degree in a subset of insomniacs. We are suggesting that level of 24-hr hyperarousal is what places these individuals at greater risk for hypnotic abuse.

This proposal also focuses on differential mechanisms of action of hypnotics and their relation to individual differences in level of arousal as factors contributing to the risk for the often reported shift from therapeutic hypnotic use to abuse. For some medications, including BzRLs, epidemiological data suggest in many persons with drug abuse problems, the abuse began as legitimate therapeutic use.

This proposal studies a unique population, drug naïve patients likely to be prescribed these drugs for their insomnia. Laboratory studies of hypnotic abuse liability have been traditionally conducted in healthy normals or individuals with a sedative drug abuse history.

This proposal uniquely combines several well established methodologies, human drug abuse liability assessment using different measures (i.e., dose escalation, enhanced "drug liking euphoria", and inability to stop taking medication) with electrophysiological assessment of nocturnal sleep and daytime sleepiness/alertness to better characterize insomnia, nightly actigraphic assessment of sleep during chronic use, and concurrent hormone assays.

In the end, this proposal will generate a unique set of data addressing a number of previously clinically important unanswered questions regarding hypnotic abuse by insomniacs (i.e., likelihood as a function of arousal state, of dose escalation over time, and of change in mood/drug ratings over time). It will provide clinicians with indicators of abuse risk and begin to identify ways for clinicians to recognize the extent of the risk.

After study completion and identification of subjects demonstrating risks for abuse we propose to assess various indicators that clinicians might use to predict the likelihood of transition from therapeutic use to abuse. In this proposal we intend to administer a number of questionnaires at baseline and during the six month assessment that may predict likelihood of transition (see Section D).

In summary we are 1) comparing insomnia subgroups, 2) comparing hypnotics with different binding affinities, 3) using two different paradigms to identify risk, and 4) studying hypnotic naïve insomniacs, a population likely to receive a hypnotic prescription and potentially at risk.

C. Published and Preliminary Data

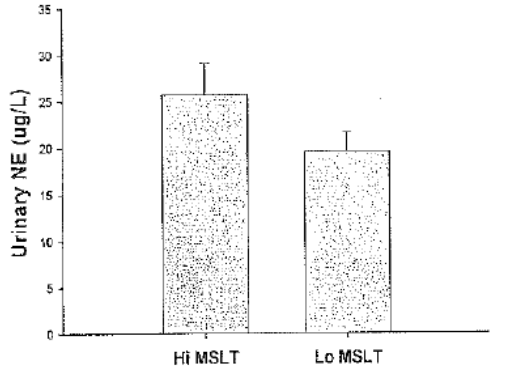

Figure 1. Daytime (800-1500 hr) urinary NE for Hi (n=42) and Lo (n=25) MSLT insomniacs (p<0.03)

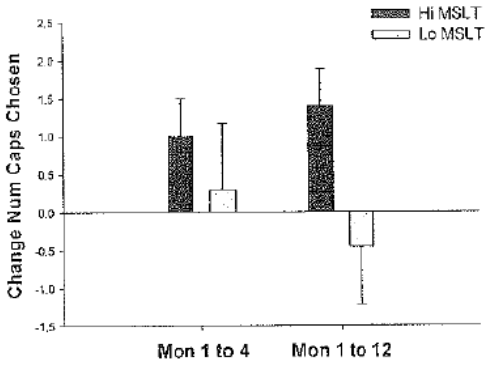

Figure 2. Change in number of capsules chosen (placebo + zolpidem) on months 1 to 4 and 1 to 12 for Hi (n=27) and Lo (n=11) MSLT insomniacs (p<0.08)

Our previous grant evaluated the efficacy and abuse liability of 12 months nightly use of the hypnotic, zolpidem, by primary insomniacs. Our results showed that 1) zolpidem is preferred to placebo by insomniacs, but its overall rate of self-administration does not increase over 12

months of nightly use (8), while the nightly use of a subset is associated with "dose" escalation. 2) 12 months of nightly zolpidem use does not produce rebound insomnia or withdrawal signs and symptoms after chronic use, although 40% of participants showed rebound insomnia on at least one of the discontinuation nights (15); 3) relative to placebo zolpidem increases total sleep time and this hypnotic efficacy does not diminish over 8 months of nightly use (13); 4) some primary insomniacs express hyperarousal, as reflected in elevated MSLT scores relative to a control sample from the general population, which is a stable finding suggesting a trait characteristic (24), and the most severe insomniacs (i.e., lowest total sleep time) have the highest MSLTs, a relation that differs from that in healthy normal sleepers (24) and finally; 5) the hyperarousal defined by MSLT in this subset of insomniacs is associated with elevated daytime urinary norepinephrine and escalating capsule (both placebo and active drug) self-administration over time (see Figs 1 and 2 above).

The implications of these results is extensive in that we have shown with first-ever findings 1) chronic zolpidem use leading to abuse is not a general characteristic of the drug producing no overall nighttime dose escalation or rebound insomnia, 2) zolpidem remains effective for 8 months of nightly use, 3) about half of primary insomniacs are hyperaroused as defined by MSLT, and the hyperarousal is a reliable and trait like finding, and 5) elevated MSLTs (e.g., hyperarousal) are associated with higher concurrent daytime urinary norepinepherine levels and increasing drug self-administration. This increase was not differential between zolpidem and placebo groups. Thus, the increase was associated with arousal status and not zolpidem (alpha 1 specific). **Consequently, we are proposing a paradigm shift for understanding hypnotic abuse, focusing in this proposal on self-administration and subjective effects in an at risk sub-population of insomniacs and on drugs with a hypothesized differential increased abuse liability, including drug discontinuation difficulty.**

D. Approach

D.1 Overview

We propose to study clinical doses of zolpidem CR (6.25 & 12.50 mg) and eszopiclone (2 & 3 mg) using self-administration methods to further assess hypnotic abuse liability in an at-risk population (i.e., insomniacs with the highest MSLTs). This is a sub-population of insomniacs that appears to have an enhanced abuse liability risk, defined as escalating dose, subjectively by increased “drug liking" and "euphoria", and discontinuation difficulty.

We have chosen to compare zolpidem CR and eszopicione, two BzRLs that can be matched for duration of activity by using the CR preparation of zolpidem. Both of these medications have indications for both sleep onset and sleep maintenance difficulties. Eszopiclone binds at alpha 1 and 3 subunits with alpha 3 subunits known to have anxiolytic effects in insomniacs (27). In contrast, zolpidem binds only at alpha 1 and while sedative effects have been shown, it does not possess anxiolytic effects (27). Our plan is to study a total of 120 insomniacs (six groups of n=20 per group: placebo, zolpidem CR, eszopiclone and two MSLT levels per drug group) over the five years (30 per year anticipating about a 30% drop-out rate).

D.2. Subjects

The inclusion-exclusion criteria of our last grant will be maintained for this proposal with one exception. The major exception will be that primary insomniacs with hyperarousal, defined as a MSLT score of ≥ 13 min, which represents the top 50% of insomniacs (25), and those without, defined as a MSLT score of ≤ 11 (normal MSLT) and ≥ 5 min on the screening assessment will be entered into the study. The ≥ 5 min exclusion is to avoid pathologically sleepy participants. A total of 120 insomniacs will be randomized to a placebo, zolpidem CR, or eszopiclone nightly treatment for 6 months (n=40 per drug group which includes 20 MSLT ≥ 13 min and 20 with

MSLTs ≤ 11 min and ≥ 5 min) within each group.

D.2.1 Subject Recruitment and Retention

Subjects, as previously, will be recruited primarily from two sources, the family practice clinics of the Henry Ford Health System, including the system's health maintenance organization, the Health Alliance Plan, which is an approximately 500,000 member plan, and public advertisements. We have been able with two research assistants to recruit and enter 30 subjects per year. Our subject retention in a previous grant was higher than expected. Only 32% of subject/patients were unable to complete the entire one year study, typically for the study's interference with social, family, or job responsibilities. With a 6 month rather than 12 month study, conducted at-home rather than in the laboratory, we anticipate we will be able to even better retain participants. Compliance in the last grant with the monthly and quarterly clinic and sleep laboratory visits was extremely high, 93%, which we attribute to the weekly interactive telephone interviewing (IVR) we used. We intend to use a weekly web based questionnaire in this grant. Previously, we did not experience any serious adverse events that led to subject loss. As was the case in the last study, this study conduct will be monitored by an independent DSMB.

D.2.2. Inclusion Criteria

1) total n=120, age 21-64 yrs

2) non-pregnant females who agree to standard birth control for 6 months and males

3) ≥ 1 insomnia complaints: >30 min sleep latency, < 6 hrs sleep, or non restorative sleep.

4) meet DSM-V criteria for insomnia disorder (780.52) alone or comorbid with stable medical diseases, but psychiatric diseases within the past year will be excluded.

5) routinely spend > 6 and ≤ 9 hrs time in bed.

6) **have a screening MSLT ≥ 13 min or ≤ 11 min and ≥ 5 min).**

D.2.3. Exclusion Criteria

1) a body mass index >38

2) acute or unstable illness: conditions making it unsafe for subject to participate, conditions with a potential to disturb sleep (i.e. acute pain, respiratory infection), and conditions which could interact with the pharmacokinetics or pharmacodynamics of either drug.

3) chronic illnesses; renal failure, liver disease, seizures, and dementing illnesses.

4) current or past year psychiatric disease: depression and schizophrenia.

5) a 2-yr history of alcohol or substance abuse, prestudy positive urine drug screen

6) previous discontinuation of chronic hypnotic use

7) consuming >14 standard (1oz) alcoholic drinks/week or caffeine consumption >300 mg/day

8) smoking during the night (11pm-7am).

9) medications including anxiolytics, hypnotics. both prescription and OTC, antidepressants, anticonvulsants, sedating H1 antihistamines (non-sedating second generation H4 antihistamines are allowed), systemic steroids, respiratory stimulants and decongestants,

prescription and OTC stimulants, prescription and OTC diet aids, herbal preparations, and narcotic analgesics. All medications and doses will be documented.

10) sleep disordered breathing (SDB) and periodic leg movements (PLMs) defined as ≥ 10 apnea-hypopneas or PLM events associated with EEG arousal per hour of sleep time, or any other primary sleep (e.g., restless legs syndrome) or circadian disorder.

11) sleep efficiency >85%

D.3. Study Groups

Qualifying insomniacs, MSLT ≥13 min and MSLT ≤11 min and ≥ 5 min will be randomly assigned to one of three groups: placebo, zolpidem CR or eszopiclone. All in the six study groups will take their assigned medication at bedtime for six months. For the two-week self-administration assessments of month 1 and 3 choices will be 0, 1, 2, or 3 of their assigned nightly study medication. For the placebo group the choice will be up to three placebos. For the two-week discontinuation assessment the choice will be 0, 1, 2, or 3 of their assigned medication and dose (see Section D.6.7).

D.4. Study Drugs

The drugs will be zolpidem CR 12.50 mg and eszopiclone 3 mg with one exception are the indicated clinical doses for both drugs. We are aware of the recent May 2013 FDA advisory regarding zolpidem dosing for women, but are concerned that use of a reduced dose of zolpidem for women will be associated with reduced hypnotic efficacy and bias our comparative data, importantly, the FDA advisory regarding reduced dose was based on a pharmacokinetic increase in the AUC for women. To our knowledge no studies have reported a pharmacodynamic difference between men and women (34,35). Our own one year zolpidem study did not find gender differences on any efficacy or safety measure. Thus, rather than study non-equipotent doses, we will use a higher dose than the newly recommended dose for women. This will be clearly explained in the informed consent. We will be monitoring via a weekly web based questionnaire for morning residual effects. We will designate daytime sedation/somnolence as an AE of special interest in reporting to the DSMB. An important side effect occurring with eszopiclone (20%) is metallic taste, in secondary sensitivity analyses we will account for zolpidem residual effects and eszopiclone metallic taste effects.

Medications will be prepared by the HFHS research pharmacy, as white capsules regardless of drug group. The consent form and the choice forms (see section D.6.7) will explain that medication choices may be their nighttime medication or placebo. In the active drug groups the first two available capsules will be the low dose of the assigned drug (6.25 mg for zolpidem CR and 2 and 1 mg eszopiclone) and the third capsule placebo. This is done to assure that no subject will self-administer greater than the clinically indicated dose during the choice phase of months 1 and 3.

D.5. Treatment and Laboratory Assessment Schedule

D.5.1 General Schedule

Subjects qualifying on the pre-study screening will be scheduled for sleep laboratory assessment. During this night a clinical polysomnogram (CPSG) will be conducted that includes screening for sleep efficiency, sleep disordered breathing (SDB) and periodic leg movements (PLMs). This CPSG is followed the next day by a standard clinical Multiple Sleep Latency Test (MSLT), conducted according to standard guidelines. Based on the screening MSLT, insomniacs with hyperarousal (MSLT ≥ 13 min) and those without (MSLT ≤ 11 and ≥ 5 min) will be entered.

Subjects passing the CPSG screening for sleep efficiency, SDB and PLMs and meeting the

daytime MSLT criteria will be randomized to begin taking their assigned study medication nightly at home after one week of medication free actigraphy monitoring. Subjects will wear actigraphs nightly during the six months. Prior to each choice assessment at a clinic visit subjects will be instructed regarding the choice or discontinuation procedures. Actigraphic total sleep time will be used to assess treatment efficacy (wks 1-2) for zolpidem CR and eszopiclone in comparison to placebo. Similarly, in month 3 and 6 differential hypnotic tolerance development can be evaluated. Change from the two baseline nights in actigraphic total sleep time in the active drug groups relative to placebo will be used as a covariate to correct for possible differential hypnotic effects.

Table 2. Schedule Post Randomization

Month 1 Assessments		Month 3 Assessments		Month 6 Assessments	
Efficacy	Choice	Efficacy	Choice	Efficacy	Discontin
Wks 1-2	Wks 3-4	Wks 1-2	Wks 3-4	Wks 1-2	Wks 3-4

D.6 Assessment Procedures

D.6.1 Sleep and Hypnotic Use Logs

Prior to the clinical interview and entry into the sleep laboratory each prospective subject is required to keep a one-week sleep and drug use log. Daily bedtime, latency to sleep, total sleep time, number of awakenings, time of arising, hypnotic use, and other drug (both prescription and non-prescription) and alcohol use is reported on the log and used in the clinical interview.

D.6.2 Clinical Interview and Diagnosis

The clinical screening conducted by a board-certified sleep specialist, includes a medical history and brief physical examination and sleep history to rule out acute and chronic sleep and circadian disorders and medical illnesses requiring exclusion. In addition standard laboratory blood and urine analyses are done to confirm good physical health. The Structures Clinical Interview for DSM-V (SCID-5-RV) will be used to screen for current major psychiatric disease and a history of alcohol or substance abuse. During the screening period the following will be documented: illicit drug, alcohol, caffeine, nicotine, OTC, and prescribed drug use. Urine samples are used to confirm self-reported drug use. Based on all the screening procedures and the results of the screening CPSG/MSLT, where the absence of SDB and PLMs is established, subjects qualify for our modified DSM V diagnosis of insomnia. The modification is that a screening CPSG sleep efficiency (sleep time/time in bed) of ≤ 85% is required.

D.6.3 Nocturnal Polysomnography and MSLT

All CPSGs and MSLTs will be conducted as described in our previously published studies (9). Bedtimes for screening and experimental nights will be established as described previously (9).

D.6.4 Post Sleep Questionnaires

Specified weeks (3,4,7,11,12,18,23,24) throughout the study subjects will complete a morning questionnaire. Time to fall asleep, number and duration of awakening, total sleep time, and sleep quality are assessed. These results will be used to assess self-rated hypnotic efficacy for eszopiclone and zolpidem CR. In addition subjects will be asked to rate their current state of

alertness and ability to concentrate to assess daytime residual sedation. They will also complete drug effects questionnaires during the assessment periods (see section D.6.7).

D.6.5 HPA Hyperactivity Assessments

Urine for catecholamines and salivary cortisol measurements will be collected on the first 2 days of each of the choice assessments in months 3 and 6. Urine collections done at home will be gathered in four 8-hr aliquots while subjects are receiving their appropriate treatment. The collection begins with the first void after lights-out on night 1 and continues through night and day 2 (i.e., 32 hours total). The subjects will return the four collection vessels to the sleep laboratory. After measuring total volume, four 20 ml samples of each aliquot will be frozen at -70 F until assayed. Assays for epinephrine, norepinephrine, dopamine, dihydroxyphenylalanine (DOPA), dihydroxyphenylacetic acid (DOPAC) and dihydroxyphylglycol (DHPG) will be performed at Warde Laboratories (Ann Arbor, MI) using HPLC. Saliva samples will be taken at 10am, 12pm, 2pm, and 4pm and assayed for salivary cortisol using RIA (Warde Laboratories, Ann Arbor, MI). The third aliquot will be assayed at HFH for urine creatinine to index completeness of urine collection. The fourth aliquot will be kept as reserve. The primary dependent measure of analysis for HPA hyperactivity will be urinary norepinephrine over the whole 32 hrs and each 8 hr collection aliquot, which allows us to assess both sleep-related and daytime effects. In our preliminary data norepinephrine levels were elevated in the MSLT-defined hyperaroused insomniacs and predicted dose escalation (see section C). The secondary measures will be the other catecholamines and metabolites listed above.

D.6.6 Self-administration Assessments

The two week self-administration assessments will be conducted in a very similar manner to the previously published self-administration assessment with two changes (15). We will use a free choice rather than a forced choice and we will do a 14 night rather than a 4 night choice assessment. A free choice procedure is used because it models the clinical situation and the number of choice nights is increased to enhance the power to detect predicted differences. On each night (at bedtime) of the two week assessment the subjects will be asked to choose whether or not they want their medication and will be given the option of taking 0, 1, 2, or 3 capsules of their medication. For the zolpidem CR group the first two capsules will be 6.25 mg zolpidem and a third placebo for a total possible dose of 12.50 mg each night and for the eszopiclone group 2mg, 1 mg and placebo for a total possible dose of 3 mg.

To standardize choice procedures subjects will receive forms on which they are instructed about the medication they are receiving and the need to assess effective dosage for them. On the form they specify whether or not they want their medication and the number of capsules they desire on a given night. As noted above, the consent form and these choice forms will specify that the available medications may include their nightly medication or placebo. On discontinuation assessments they will be instructed <u>to try to stop</u> using their medication or reduce the numbers of nights they use it over the next two weeks. The choice will be 0, 1, 2, or 3 capsules on each of their 14 nights. The available capsules will be their previously experienced clinical dose (12.5 mg zolpidem CR or 3 mg eszopiclone). After each two week assessment (both choice and the discontinuation weeks) subjects will return their choice forms and the opened vs. unopened packages to justify choice forms and capsule usage. Two dependent measures for the *choice assessments* will be the number of medication choices made for the 14 nights and the average nightly dose (i.e. number of capsules) when capsule is chosen. For *discontinuation* the measures will be number of nights a capsule is chosen and the number of capsules chosen.

D.6.7 Drug Effects/Mood Assessments

In lab office visit will include Profile of Mood States (POMS), Beck Depression Inventory II (BDI II), Beck Anxiety Inventory Scale(BAI), Epworth Sleepiness Scale (ESS) and the Insomnia Severity Indes (ISI). Weekly web based questionnaires will include the Visual Analog Scale (VAS) assessments of “drug liking” and “euphorogenic” effect. These will be completed on day 1 of each tri-monthly assessment. Drug/mood effects assessments will also be done on the mornings after the choice and discontinuation assessments but based on our previous grant experience over 4-7 day assessments there may be a reduced “n” as some subjects will display no capsule choices.

D.6.8 Weekly Web Based Monitoring and Monthly Clinic Visits

Subjects will be monitored on a weekly basis by a web based questionnaire regarding their sleep and drug use. In addition to providing weekly self-report efficacy data, this has ensured that patients are following the study protocol and it maintains clinical contact. Subjects not completing their questionnaire within 24 hrs are then contacted by phone by study staff. At the monthly clinic visits the appropriate medication supply is refilled and medication packages returned to assess compliance. The sleep logs maintained every night will be checked to assess compliance to the sleep schedule. Efficacy and side effects will also be assessed by questionnaire at the monthly clinic visit. Additionally, at each monthly visit the BDI II and BAI are conducted to monitor any changes in, or emergence of new, physical and psychological signs and symptoms, which serves for safety monitoring particularly in the untreated placebo group.

D.7. Outcomes, Comparisons and interpretations

D.7.1. Chronic Hypnotic Efficacy

The hypnotic efficacy of zolpidem CR and eszopiclone will be evaluated in comparison to the placebo group on the two week actigraphy recordings of months 1, 3, and 6. A difference of each drug from placebo on the primary efficacy measure, total sleep time, will confirm the expected hypnotic efficacy of each drug. The absence of a difference between drugs will suggest they have comparable hypnotic efficacy, secondary analyses will be performed on other hypnotic measures like latency to sleep, wake after sleep onset, and number of awakenings. These comparisons of efficacy measures on months 1, 3 and 6 are predicted to show no loss of efficacy with chronic treatment. It is hypothesized that both drugs will differ from placebo at all time points, but not each other. The change from baseline in total sleep time for a given subject can be used as a covariate when analyzing self-administration data if efficacy differences between hypnotics are found. If loss of efficacy is found we will assess whether it is specific to one of the drugs. Further, we will determine whether or not loss of efficacy is predictive of dose escalation or discontinuation difficulty.

D.7.2. Abuse Liability Discontinuation Risks

The aims of this proposal (aims 1, 2, and 3) are to address the three specific questions.

What is the abuse liability of hypnotics in hyperaroused vs non-hyperaroused insomniacs as operationalized by likelihood of increasing self-administration and increased subjective effects assessments?

Is there differential liability between a hypnotic with alpha 1 receptor selectivity and no anxiolytic/mood properties and one with no selectivity (i.e., also binds to alpha 3) and known anxiolytic/mood properties?

What is the discontinuation difficulty as seen in self-administration rates and mood effects differentially as a function of the insomniacs' arousal status and the pharmacology of the two hypnotics?

The primary behavioral risk of abuse measures will be the total number of nights a capsule is chosen on the 14 choice nights and the number of capsules chosen on those nights a capsule choice is made. An increase in number of active drug choices versus placebo group choices over the 14 choice nights from month 1 to 3 will indicate risk of abuse which we hypothesize will occur in the hyperaroused insomniacs only (aim 1). A comparison of eszopiclone to zolpidem CR in active drug choices will indicate the importance of the pharmacological profile of a given drug to its abuse liability with eszopiclone hypothesized to show greater self-administration (aim 1). Differential effects of the two drugs and the two insomnia groups in the subjective effect assessments will be investigated as mediators of these differential abuse liabilities. It can be argued that the self-administration of eszopiclone by the hyperaroused insomniacs represents therapy seeking for anxiety. However, it is important to remember that all these participants will have been screened for anxiety disorders. Also, while self treatment may explain acute effects, it would not explain dose escalation across time. The hypothesized change in mood/drug effects and self-administration rates across time are the key comparisons in this proposal that will reflect increased abuse risk.

We have hypothesized an interaction of these two main effects (aim 2). An increase in the number of nightly active drug choices from month 1 to month 3 will suggest either tolerance development, reinforcement of anxiolytic/mood effects, or the learning of new drug effects with its use. To differentiate between these possibilities we will look at drug versus placebo effects on actigraphy in weeks 1-2 of each month. The absence of a loss of sedative/hypnotic effects over the 6 months for each drug will suggest reinforcement of mood effects, or learning of new drug effects (i.e., "drug-liking", "euphoric" effects). The various mood and drug-effect questionnaire (POMS, VAS, and BAI) measures will reveal subjective effects associated with the self-administration of the subjects. Changes in these effects over the 6 months will confirm possible reinforcement of mood effects or learning of new drug effects with greater exposure to active drugs. Assessment of changes in self-reported drug effects will reveal if new drug effects are being learned. Nightly self-administered doses (i.e., number of capsules chosen) over the 2 choice weeks is the second abuse liability outcome measure and similar interpretations for this measure apply.

Discontinuation difficulty will be reflected in the number of nights over the 14 discontinuation nights a capsule is chosen and number of capsules chosen (aim 3). We have hypothesized greater difficulty (i.e., more drug choices) as a function of arousal status ("hyperaroused" vs not) and pharmacology of the hypnotic (eszopiclone vs zolpidem CR).

D.7.3 Hormone Levels and Specific Aim 4

Total 24-hr and 8-hr urinary norepinepherine levels are the dependent measures to address specific aim 4. A reduction in norepinepherine levels (24 hr or any 8 hr aliquot), in the zolpidem and eszopiclone groups relative to the placebo group will indicate a unique therapeutic effect of the hypnotics, correction of the hyperarousal seen in insomnia. However, in our last grant we did not find significant drug vs placebo changes in norepinephrine levels, either 24 hr or daytime levels. Levels remained high in month 1 and 8 of the last grant for the hyperaroused insomniacs vs the non-hyperaroused insomniacs, with no drug vs placebo differences (see section C). This proposal will present an opportunity for replicating in an enriched sample of insomniacs with elevated MSLTs, this important finding and thereby identify a possible risk marker of abuse liability. Importantly, we previously only tested the alpha 1 specific drug zolpidem, while in the present proposal we expect to find these effects with eszopiclone differentially from zolpidem.

We did not find urinary cortisol differences between hyperaroused vs non-hyperaroused insomniacs or between drug vs placebo. We did find significant time of day differences in 3 hr urinary cortisol aliquots (800-1500 hrs vs 1500-2300 hrs), with the morning aliquot being higher than the evening aliquot, a known characteristic of 24-hr cortisol rhythms thereby validating our study sample.

D.8 Data Analyses

D.8.1 Analyses

Hypnotic efficacy will be analyzed as a randomized clinical trial. Since the outcome variables are measured on multiple occasions during months 1, 3, and 6, the appropriate method for analysis is that of generalized estimating equations (GEE). For example, if the outcome is total sleep time a specific model would be written containing terms

$$Y_{ijk} = \mu + \alpha_i + \beta_j + \gamma_{ij} + \epsilon_{ijk}$$

representing the overall mean (μ), treatment effects (α), occasion effects (β), interactions (γ) and error variance (Є). Observations within a subject on multiple occasions are correlated, and this correlation structure is accounted for when estimating treatment effects. In addition this framework enables us to test for trends in the data over measurement intervals, to incorporate changes over months into the model, and to explore interactions between treatment and time. Additional covariates, such as age, gender and sleep time, can easily be incorporated into this overall framework. The active drug versus placebo group data on weeks 1-2 of month 1, 3, and 6 will be the data analyzed. The primary efficacy measure will be total steep time. The three treatment groups will be a between subject factor and nights and months will be within subject factors. Self-reported measures of sleep collected on the post sleep questionnaires and other sleep measures will also be analyzed in this manner. We do not anticipate differential hyperaroused vs non-hyperaroused effects as our last grant data did not show differential hypnotic efficacy as a function of level of arousal.

For the *abuse liability* assessment the absolute number of active drug choices (14 total choices possible in month 1 and 3) and the total number of nightly capsules chosen (42 total possible per subject each month) will be determined. A change score from month 1 to month 3 in these two measures will be the outcome measures used to assess abuse liability. The analysis will be a two factor between groups design testing drug group and arousal status. We are predicting main effects of drug and arousal groups and as well *an interaction of these*: greater abuse liability in hyperaroused insomniacs and with eszopiclone. Hypnotic efficacy can be used as a covariate if necessary. Also a set of secondary sensitivity analyses will be done to account for possible zolpidem residual effects in women and eszopiclone metallic taste effects.

The difficulty discontinuing hypnotic use assessment will compare the number of capsule choices on the 14 nights, using a two factor between groups design testing drug group and arousal status. As in the abuse liability analyses, we are predicting main effects of drug and arousal groups and *an interaction of these*: greater discontinuation difficulty in hyperaroused insomniacs and with eszopiclone.

The morning *subjective drug/mood effects* collected on the two week efficacy assessments (weeks 1-2) for month 1, 3, and 6 will be used to assess drugs/mood effects and their changes over time. As noted, while we are assessing these effects during the choice weeks, complete

data for each subject on choice nights may not be available. Based on our previous experience exclusive non self administration may occur and based on our hypothesis the zolpidem group should make fewer active drug choices than the eszopiclone group, thereby possibly diminishing the available “n” for analyses in the zolpidem group. In the week 1-2 assessments, where there should be complete data, we are predicting greater mood effects and drug liking effects in hyperaroused insomniacs and with eszopiclone which increases over months reflected in change scores from month 1 to 3 and month 1 to 6.

D.9. Sample Size Justification

The standard formulas, which are conservative for this situation because of the multiple measurement protocol described previously, show that effect sizes of 0.68 or greater are detectable for the outcomes in this study including efficacy and subjective measures with three subject groups each having a sample size on n=20 and correcting for multiple comparisons.

Effect sizes considerably greater than this were found in our short-term daytime self administration studies (1-7). An effect size of 2.0 differentiated number of active drug choices of insomniacs with high MSLTs versus those with low MSLTs (7). The power with n=15 vs 7 per group was 0.98. The last grant was designed to detect effect sizes of 0.60 and greater with a 0.80 power based on our short-term studies. As such, we were prepared to detect a 0.50 capsule increase in average nightly dose with n=15-20 per group. Such a 0.5 capsule increase was found in the placebo group from month 1 to months 4 and 12 in our last grant (8). Here we are predicting a differential between group (eszopiclone vs zolpidem CR) increase in our outcome variables and we anticipate greater between group variability. Conservatively, to detect efficacy, mood and subjective drug effect changes, and importantly self-administration changes, we have chosen the upper range of n (n=20) for this project.

D.10 Future Studies

Given use of the MSLT to identify at-risk insomniacs is burdensome for patients and clinicians, we will assess the various self-report measures of this proposal to develop tools that a clinician could use to identify at-risk individuals. For example, if the Epworth Sleepiness Scale (ESS) functions in hyperaroused insomniacs as the MSLT, unusually low ESS scores may identify at risk hyperaroused insomniacs, or unusually short diary sleep times, given short sleep times are associated with high MSLTs, or short actigraphic determined sleep times. Elevated BAI scores or consistently elevated POMS Arousal subscale scores may similarly identify hyperaroused insomniacs at risk to escalate dose and report increased “drug liking" and “euphoria" over time.

D.11. Potential Problems/Limitations

While this is the first study to systematically address individual and drug differences to define the risk of clinical hypnotic use evolving into abuse, there are some limitations of this proposal.

1) We are studying insomniacs without psychiatric co-morbidity limiting the generalizability of our results. While many patients in clinical practice have co-morbid psychiatric conditions, limiting the study sample avoids the confounding of these co-morbidities in assessing the abuse risk of “hyperaroused" insomnia itself.

2) There are other measures of hyperarousal (e.g., cortisol, FDG, PET, etc) reported in the literature and the question is whether our results will generalize to hyperarousal defined with such other measures. The literature regarding cortisol is equivocal and in our own data we have failed to find cortisol elevations. Use of various neuroimaging methods for this large of a study is not feasible. We have chosen elevated MSLT as it is one of the more reliable measures of hyperarousal in insomnia and we found it to be stable and to relate to elevated urinary norepinephrine levels.

3) This research will evaluate two FDA approved BzRLs. Other drugs are used “off-label" to treat insomnia and will likely have their specific risks. But, we believe it inappropriate to study non-approved medications. Thus, this grant will assess abuse risk of "best practice".

4) We recognize the limitation that we have chosen to study the 12.5 mg zolpidem dose in women which may lead to an increased rate of daytime residual effects given the recent FDA warning. This may lead to a necessity to reduce dose in some women. But we are concerned that use of a reduced dose of zolpidem for women will be associated with reduced hypnotic efficacy and thereby bias our comparative assessments.

4. Human Subjects

4.1. Ethics of the Proposed Trial

Questions may be raised about the ethics of placing patients with chronic insomnia on placebo or on active drug for the long-term, 6 months in this proposal. In terms of long-term active drug use, it should be noted that in the general population a growing percentage of people are using hypnotics on a nightly basis long-term and our last grant data suggest the risks associated with chronic use (12 months) are low. Next insomnia is a chronic disorder lasting typically for two years and it may in fact represent a lifelong predisposition. This same class of drugs, the BzRLs, is indicated for the long-term treatment of anxiety disorders. There are no data to indicate that this class of drugs is associated with increased rates of side effects in long-term use. Throughout the study all patients will be followed medically and their side effects assessed carefully. Additionally, at each monthly visit the BDI II will be conducted to assess any changes in, or emergence of new physical and psychological signs and symptoms, particularly in the untreated placebo group. In our last grant participants were in the study receiving placebo or zolpidem for 12 months and no serious adverse events were experienced. This study will be shorter and thus with less potential risk.

A possible risk is addiction, which most of the epidemiological and laboratory data suggest is minimal. To minimize this possibility, patients will be screened for a previous history of drug abuse or alcoholism, which are the best predictors of a potential addiction to BzRLs. At the end of the study every subject will be discontinued from drug and will be drug free. All will be returned to their primary care physician to resume their treatment of choice if their insomnia continues. In exit interviews they will be given feedback as to the nature of their insomnia, sleep hygiene and behavioral treatment instructions, and guidelines regarding their liability of dependence to BzRLs, particularly in those that escalate dose and reflect "drug-liking" and euphoria in subjective assessments.

As to placing patients with chronic insomnia on placebo long-term, the majority of patients with chronic insomnia (75-90%) receive no treatment. The patients in the placebo group of this project will be followed closely medically and assessed for "side effects". If their insomnia of the "side effects" require they be discontinued from the study, the double-blind will be broken and those on placebo will be sent to their primary care physician to be placed on active drug. Our data from the last grant did not show a differential loss of participants from the placebo versus active drug group. As with the active drug groups, all will be given feedback as to the nature of their insomnia, sleep hygiene and behavioral treatment instructions, and guidelines regarding the liability of dependence to BzRLs during exit interviews.

There may be concerns regarding women in the zolpidem CR group receiving the 12.50 mg dose, given the FDA June 2013 advisory. Subjects will be informed on the consent form that women, if assigned to the zolpidem group, will receive a zolpidem dose that the FDA recently suggested should be lower. Subjects will be monitored weekly via the web based questionnaire and face-to-face in monthly clinical visits. They will be asked to report any experienced side

effects and in women reporting daytime residual effects the nightly dose will be lowered to 6.25 mg.

Similarly with regard to the recent FDA guidance regarding eszopiclone and dose titration from a starting dose of 1 mg to 3 mg (the upper clinical dose), a fixed dose of 3 mg is being used in this study. The dose as a starting dose may produce residual sedation in some patients. AEs of residual sedation associated with either zolpidem of eszopiclone will be designated an AE of interest and reported to the DSMB.

4.2. Consent Process and Human Participant Protections

4.2.1. A total of 120 men and women, aged 21-64 yrs, with primary insomnia, but otherwise healthy, will serve as subjects in the experiment. They will be recruited through the outpatient clinics of the Henry Ford Health System and newspaper advertisements. Our inclusion experience in previous grants reflects the richly diverse participant population we are able to recruit. Good physical health will be determined based on a physical examination by one of the staff physicians, standard laboratory analyses of blood and urine samples and the Cornell Medical index. Each participant will also receive a standardized psychiatric evaluation.

4.2.2. The data collected from each participant will include standard physiological and actigraphic recordings of sleep, self reports of sleep and daytime sleepiness, measures of psychological function, records of drug use and alcohol use, and responses to questionnaires regarding mood and sleep.

4.2.3. Subjects will be recruited from the hospital primary care clinics and the community. Each subject will sign an informed written consent as approved by the hospital's Institutional Review Board. After presenting the subject the written informed consent letter, the subject will have the study presented to him/her orally by the investigators or their research assistant. The participant then will be asked if he/she has any questions about any part of the protocol. If there are questions, further explanations will be offered. Finally, the participants will be asked to explain to the interviewer the major experimental manipulations outlined in the study. If it is clear the subject still does not understand, she/he will be disqualified from participation.

4.2.4. Each subject will be instructed regarding the risks associated with zolpidem and eszopiclone. They will be cautioned not to eat within 2 hrs prior to consumption of their medication and to avoid the use of alcohol within 4 hrs of medication. They will be instructed not to drive or operate machinery in the morning if they still feel sleepy and to report such to the study coordinator. They will be instructed to maintain a regular sleep schedule and to remain in bed for 7-9hrs.

4.2.5. The equipment and procedures for polysomnographic recording are in standard sleep laboratory use and present no potential dangers to the subject. On the first night of the recording, some subjects experience slight discomfort due to the attachment of the electrodes and the change in sleep environment. However, this is a transient problem which quickly disappears with adaptation to the hospital conditions. The at-home actigraphy involves wearing a wrist-watch type device and presents no discomfort. The side effects associated with the standard hypnotics, zolpidem and eszopiclone, being administered nightly at home involve clinical doses and they include most commonly sleepiness, dizziness, lightheadedness, metallic taste, difficulty with coordination and uncommonly difficulty concentrating, memory problems, and confusion, and rarely hallucinations and loss of personal identity. The risk of privacy violations will be managed by housing the consent documents and a code which links the participant's name with their unique study identification number in a cabinet in the PIs office. All clinical, PSG and MSLT, actigraphic outputs, and questionnaire data collected in the study will use the participants study identification number.

4.2.6. The overall potential risk to the participants is small. All participants will be under continuous 24 hour monitoring while in the sleep center. The center where the study will be conducted is an outpatient medical clinic of a hospital where 24 hour medical coverage is available in the event of adverse effects. When at home, the participants will be monitored weekly for any side effects by a web based questionnaire and monthly by clinic visits. To ensure confidentiality, subject code numbers will be used to maintain the privacy of all information obtained from and about subjects in the study. At no time will a subject's full name or any identifying information be made available to anyone not directly involved in the study.

4.2.7. The risks, as outlined above, to the participants in this study are small. There may be direct benefits to the participants in that their insomnia will be improved. The benefits to society gained from the information generated by this study will be enormous and far outweigh any subject risks. The information to be obtained from this study will provide for a better understanding of the efficacy and safety of hypnotics used chronically. The results have a potential to change the practice of insomnia treatment. The benefits of this study outweigh the study risks.

4.3. Data Safety Monitoring Plan

All participants complete a web based questionnaire weekly and they are questioned as to unusual events the past week. Monthly participants have a face-to-face clinical visit at which time the BDI II will be conducted to assess any changes in, or emergence of new physical and psychological signs and symptoms. Again participants are asked about the experience of any adverse events. Adverse events reported are monitored by the PI and it is determined as to any event's seriousness and relatedness to the study drug or study procedures. Serious adverse events are immediately reported to the local IRB, to the Data Safety Monitoring Board (DSMB), and to the NIH funding institute.

An independent Data Safety Monitoring Board (DSMB) will be established to ensure the integrity of the data being collected in this project and to ensure the safety of patient-subjects in this study. The DSMB will consist of two Henry Ford Hospital Senior Staff persons and a Wayne State University (WSU) School of Medicine person selected for expertise in clinical psychopharmacology and human subjects protection. The board will consist of a psychiatrist (WSU) with a human subjects protection sub-specialty (WSU, RB chair), a psychiatrist (HFHS) with extensive experience in clinical psychopharmacology, and a statistician (HFHS). Quarterly reports are submitted to the DSMB members outlining the number of subjects screened, number of subjects entered, number of subjects dropping out with their reasons for discontinuing, and the number of adverse events and serious adverse events. The DSMB will also meet in person on an annual basis to review the study conduct. As with all research projects at this institution, all serious adverse events are reported immediately (within 48 hrs) to the Human Rights Committee.

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MEMO

To the IRB

In reviewing this project and consent please consider several choices that were made:

1.) This project is designed to place some subjects on placebo for six months. The rationale for and ethics of doing such is discussed in the Human Subjects section of the grant application (pg 17 ff). On the grant review critique, the reviewers recognized this design choice and considered it scientifically and ethically justified.

2.) For both drugs a fixed high clinical dose with no gender dose adjustment is being done. This choice is also discussed in the Human Subjects section of the grand application (pg 17 ff). On the grant review critique, the reviewers recognized this design choice and considered it scientifically and ethically justified.

3.) On the consent form the side effects for zolpidem CR and eszopiclone are not listed separately. The various side effects for the most part overlap. But, one side effect is unique to eszopiclone, metallic taste. To list that separately with eszopiclone could potentially break the double blind.