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Hyperarousal in Insomnia and Hypnotic Dose Escalation

T.A. Roehrs[1,2] and **T. Roth**[1,2]

[1]Sleep Disorders and Research Center, Henry Ford Hospital, Detroit, MI

[2]Psychiatry and Behavioral Neurosciences, Wayne State University, Detroit, MI

Abstract

Background—Given concern regarding the abuse liability of hypnotics this study assessed hyperarousal in people with insomnia and its relation to hypnotic self-administration over 12 months of nightly hypnotic use.

Methods—Ninety-five subjects with insomnia, 32–64 yrs old, received a screening nocturnal polysomnogram (NPSG) and Multiple Sleep Latency Test (MSLT) the following day and were randomized to take zolpidem 10 mg or placebo nightly for 12 months. During months 1 and 8, while taking their prescribed medications, NPSGs and MSLTs were conducted and urine was collected (0700–1500 hr) and analyzed for norepinephrine (NE) levels. A subset (n=54) underwent hypnotic self-administration assessments in months 1, 4, and 12.

Results—Mean daily sleep latency on the screening MSLT was distributed across the full range of MSLT latencies (2–20 min). Those with the highest screening MSLT latencies had the higher NE levels compared to those with the lowest MSLT latencies. In the subset undergoing the self-administration assessment those with the highest MSLT latencies chose more capsules (placebo and zolpidem) and increased the number of capsules chosen in months 4 and 12 relative to month 1 compared to those with the lowest MSLT latencies.

Conclusions—These data show that some insomniacs are hyperaroused with high MSLT/NE levels and compared to low MSLT/NE insomniacs, they increase the number of capsules (zolpidem and placebo) self-administered on months 4 and 12 relative to month 1.

Keywords

insomnia; MSLT; NE; hypnotic self-administration

Corresponding Author: Timothy Roehrs PhD, Sleep Disorders & Research Center, Henry Ford Hospital, 2799 W. Grand Blvd., Detroit, Michigan 48202, troehrs1@hfhs.org.

Conflicts:

T. Roehrs: consultant – Lundbeck, Pfizer; speaker – Pernix; grantee – Merck

T. Roth: consultant – Actelion, Addrenex, Cephalon, Eisai, Intec, Merck, Pfizer, Sanofi, Sepracor, Shire, Somaxon, TransOral; speaker – Cephalon, Sanofi; grantee – Merck

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INTRODUCTION

Insomnia is generally considered a disorder of hyperarousal.[1] One of the reported signs of hyperarousal is an elevated Multiple Sleep Latency Test (MSLT) average daily sleep latency. In a large sample (N=95) of people with insomnia average daily sleep latency on the MSLT was significantly elevated compared to an age- and sex-matched general population-based representative control sample and these MSLT findings in insomnia were stable over eight months.[2] Yet, some smaller sample studies have failed to show MSLT elevations in people with insomnia.[3–5] In part, the discrepancy may be due to the fact not all insomniacs show MSLT elevation, which was revealed in the larger sample study.[2] Among the 95 people with insomnia in the previously cited study, the MSLT latencies ranged from 2–20 min with approximately 30% having latencies of 10 min or less.[2]

Hyperarousal in insomnia has been shown on a number of other physiological measures, including elevated levels of circulating catecholamines[6], increased basal metabolic rate[7], increased body temperature[8], altered heart rate[9,10], elevated beta EEG frequency[11,12], and cortical activation on functional neuroimaging.[13] However, to date only a single study has shown “hyperarousal” on concurrent physiological measures, that being increased metabolic rate in conjunction with elevated MSLTs relative to age-match controls.[7] But no study has shown differences on concurrent physiological measures among insomniacs, that is between insomniacs with and without MSLT-defined hyperarousal. Thus, we sought in this study to determine whether or not daytime urinary norepinephrine (NE) levels would differ among insomniacs as a function of their MSLT average daily sleep latency. We hypothesized that insomniacs with MSLT-defined hyperarousal would also show concurrent elevated daytime NE levels compared to those without MSLTdefined hyperarousal.

Hyperarousal in insomnia potentially reflects an activated stress system. Many theories of addiction hypothesize that stress increases vulnerability to drug abuse.[14] 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.[14] This CRF/NE activation also activates dopaminergic brain motivational pathways known to be engaged by drugs of abuse including the ventral tegmental area and nucleus accumbens. Thus stress co-activates brain stress and motivational circuits simultaneously.[14]

The acknowledged drugs of choice for the pharmacological treatment of insomnia are the benzodiazepine receptor ligand hypnotics (BzRL). Studies have shown that with therapeutic doses used either short-term or chronically, the abuse liability of BzRLs in insomnia is relatively low.[15] 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.[16] In this study we sought to determine whether elevated MSLT average daily sleep latency (i.e. hyperarousal) and elevated NE levels in insomniacs would be predictive of increasing rates of self-administration during 12 months of nightly use of zolpidem 10 mg or placebo. We hypothesized that insomniacs with elevated MSLT latencies and NE levels would show increasing rates of hypnotic self-administration.

METHODS

Participants

Persons 21–65 yrs old with difficulty falling asleep and/or staying asleep were recruited. Ninety-five participants (42 men and 53 women), aged 32–65 yrs, meeting Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM IV-TR) criteria for primary insomnia entered a trial of the efficacy and abuse liability of chronic hypnotic use (see Table 1 for sample demographics). All were in good physical and psychiatric health based on an extensive screening as previously described.[17]

The Institutional Review Board of the Henry Ford Health System approved the study protocol. All participants provided informed consent and were paid for participation. The study was posted on clinicaltrials.gov.

Study Design

The trial was a mixed design, double-blind, placebo-controlled, study with a between group comparison of insomniacs randomly assigned to use zolpidem 10 mg or placebo nightly for 12 months. After the screening NPSG and MSLT, subjects received a single NPSG and next-day MSLT on week one of month 1 and again after 8 months of nightly use of their assigned medication. The NPSG-defined hypnotic efficacy data for month 1 and 8 were previously published.[17] Concurrent with the MSLT done on month 1 and 8, urine was collected (0700–1500 hrs) for NE analyses, which along with the MSLT data, are one focus of this report.

Procedures

The general health, psychiatric and sleep disorders screening of the participants has been described previously[17] The standard Rechtschaffen and Kales methods for recording of sleep were used[18] and the MSLT was performed according to the standard protocol[20, 21]. The screening MSLT was used to define insomnia associated with “hyperarousal”. A previous report from this clinical trial showed that MSLT results are highly repeatable over 8 months[2].

Table 2 presents the timing of assessments over the 12 month study. During week 4 of month 1 and week 1 of month 8 subjects entered the laboratory for a NPSG and MSLT while taking their assigned nightly hypnotic treatment (zolpidem 10 mg or placebo). Urine was collected in an 8 hr aliquot (0700–1500 hrs) over the time period of the MSLT assessments. Assays were performed for NE by Warde Laboratories (Ann Arbor, MI) using HPLC.

A randomly selected subsample of the subjects (n=54) underwent a hypnotic self-administration assessment in months 1, 4, and 12. The other half of the subjects underwent a rebound insomnia assessment, the results of which have been previously reported[22]. The hypnotic self-administration assessment involved a 7 night protocol in which the first two nights were sampling nights and the next five nights were choice nights. For the zolpidem group the color assigned to placebo and zolpidem capsules differed and on sampling nights one of each color-coded capsule was administered each night, so that both zolpidem and placebo were sampled. For the placebo group both capsules were placebo, but the colors

administered differed each sampling night. Subjects were instructed on sampling nights to attend to the capsule color because on choice nights they would select which medication they wanted for a given night based on the capsule color of the sampling nights. On the following 5 choice nights, based on their sampling experience, the subjects were instructed to choose a capsule color and then were given the option on that night of taking up to three capsules of their chosen color. For the zolpidem group capsules were 5 mg each for a total possible nightly dose of 15 mg. For the placebo group the capsules were placebo, up to three nightly, regardless of color choice. All capsules were taken 30 min before lights out.

Statistical Analyses

To produce separation for the NE and hypnotic dose escalation comparisons and maintain sufficient "n" in the subgroups, the MSLT distribution (2–20 min) of the current study was divided at approximately one standard deviation on either side of the mean for MSLT latencies shown in a representative population sample drawn from southeastern Michigan where the mean was approximately 11.2 min with a deviation of 3 min[21]. Those showing elevated MSLT latencies (i.e., ≥ 15 min) (n= 42: Hi MSLT group) were compared to those showing lower MSLT latencies (i.e., ≤ 10 min) (n= 27: Lo MSLT group). Subjects with MSLT latencies of 11–14 min (n= 26) were not included. In the subset undergoing the self-administration assessment (N=54), 27 had Hi MSLT latencies and 13 had Lo MSLT latencies. The remaining 14 were intermediate and were not included in these analyses. Table 2 outlines the Ns for the MSLT groups.

Daytime NE levels in months 1 and 8 and total number of capsules chosen (both placebo and zolpidem) in the placebo and zolpidem groups on months 1, 4 and 12 were compared between the two MSLT groups. To assess possible dose escalation change scores were calculated to compare the change in number of capsules chosen from month 1 to month 4 and to month 12.

Mixed design MANOVAs were used to compare the two MSLT groups on NE levels in month 1 and 8 and on number of capsules self-administered in months 1, 4, and 12 and on the change from month 1 to months 4 and 12. Similarly, the zolpidem vs placebo comparison on NE levels in months 1 and 8 was done using mixed design MANOVAs.

RESULTS

The average daily MSLT in the Hi MSLT group was 17.6±1.7 min and in the Lo MSLT group it was 7.1±2.8 min. Those with Hi MSLT latencies compared to those with Lo MSLT latencies had significantly higher daytime urinary NE levels in month 1 (23.2±2.9 vs 21.6±1.9 ug/L) and in month 8 (28.2±4.0 vs 17.6±2.29 ug/L) ($F=4.67$, $p<0.03$; main effect of MSLT groups). There also was a months by MSLT group interaction ($F=6.93$, $p<.01$). In the Hi MSLT group, NE levels increased from month 1 to 8, while in the Lo MSLT group they declined slightly. Table 3 presents NE levels in the two MSLT groups at month 1 and 8. Daytime NE levels did not differ as a function of nightly hypnotic use (placebo vs zolpidem) over the 8 months ($F=0.69$, NS) (see Table 3). Figure 1 presents the average of month 1 and 8 NE levels in the Hi versus Lo MSLT groups.

The NE levels in the subset of subjects undergoing the dose escalation assessment were higher in the Hi MSLT group in month 1 (27.3±4.5 vs 18.9±2.6 ug/L) and month 8 (30.5±6.2 vs 17.6±4.1 ug/L) ($F=4.78$, $p<.03$) than those in the Lo MSLT group (see Table 3); unlike the full data set, the MSLT group by month interaction was not significant.

As to capsule choice, a total of 15 possible capsules could be chosen each month over the five choice nights. The placebo group increased the average number of placebo capsules taken over months (M1: 8.2, M4: 9.9, M12: 9.7) ($F=4.38$, $p<.004$), while the zolpidem group did not (M1: 8.7, M4: 8.9, M12: 9.0) (NS). The average number of capsule choices in the zolpidem group includes both placebo and zolpidem capsules. Of note, the zolpidem group did chose zolpidem on more of the nights than placebo (80%), but did not differentially chose a greater number of placebo capsules on nights placebo was chosen compared to zolpidem capsules on nights zolpidem was chosen.

Across both treatment groups those with Hi MSLT latencies (≥15 min) took a greater number of capsules (placebo or zolpidem) in months 1, 4, and 12 than those with Lo MSLT latencies [(M1: 9.4 vs 8.4, M4: 10.4 vs 8.7, M12: 10.7 vs 8.0; ($F= 4.19$, $p<.05$)]. Within the placebo group alone, those with Hi MSLT latencies choose more capsules than those with Lo MSLT latencies [(M1: 9.9 vs 5.5, M4: 11.1 vs 7.5, M12: 10.7 vs 7.0; ($F=3.88$, $p<. 06$)]. Finally, there was a trend showing those with Hi MSLT latencies were more likely to increase (as reflected in a positive change score) the number of capsules taken from month 1 to that in months 4 (1.0 vs 0.3) and 12 (1.4 vs −0.5) compared to those with Lo MSLT latencies ($p<.08$). Figure 2 presents the escalation of number of capsules chosen from month 1 to month 4 and 12.

DISCUSSION

These are the first data in individuals with insomnia that differentiates those with hyperarousal from those without using two concurrent physiological measures, daytime urinary NE and MSLT. All subjects met DSM-IV-TR criteria for insomnia with the additional criteria of having a sleep efficiency of ≤ 85% on a screening NPSG. MSLT criteria were not imposed and the MSLT average daily sleep latencies ranged from 2–20 min. Approximately 30% had MSLT latencies of 10 min or less, while 50% had latencies of 15 min or more.

Of significance is the absence of a placebo vs zolpidem drug effect on NE or MSLT. In month 1 after three weeks of nightly use of their assigned hypnotic and further after 7 months of nightly use, MSLT and NE levels remained elevated in the hyperaroused vs non-hyperaroused insomniacs. As previously reported, PSG measures of sleep were improved in the zolpidem compared to placebo groups; sleep time was increased by about 45 min[22]. The absence of a reduction in MSLT/NE levels, despite improved nightly sleep over seven months, suggests the hyperarousal of insomnia is a trait characteristic in these individuals.

The dose escalation in the aroused insomniacs with Hi MSLT/NE levels compared to the non–aroused insomniacs suggests a heightened risk for hypnotic abuse. The fact that it was primarily the placebo group that escalated the number of capsules chosen is further

informative. Sleep was not improved in the placebo group over months; there was no placebo effect. The insomnia in this group remained severe. In other words, given an ineffective “hypnotic” the hyperaroused insomniac is at risk for dose escalation. But, the dose escalation only occurred in the hyperaroused insomniacs. An alternative explanation is that the hyperaroused insomniacs require higher doses of active drug. We intend to analyze PSGs collected during month 1 and 8 of the study to determine whether basal PSG measures are predictive of dose escalation in the hyperaroused insomniacs. Furthermore, we will assess whether or not there is a differential zolpidem versus placebo effect in the hyperaroused versus non-hyperaroused insomnia or whether there is a reduction of drug effects from month 1 to month 8.

A study limitation is the relatively small “n” within the four-way subgroups (Hi vs Lo MSLT and placebo vs zolpidem) among those subjects undergoing the dose escalation assessment. Within the placebo group the “n” for Hi MSLT was 14 and for Lo MSLT it was 4. In the zolpidem group it was Hi MSLT = 13 and Lo MSLT = 9. Consequently, total number of capsules chosen and change in number of capsules chosen from month 1 to month 4 or 12 within a particular subgroup comparison (e. g., within the placebo group a comparison of Hi vs Lo MSLT choices) did not differ significantly. Only trends were observed for these interactions. This large study was originally designed with the expectation that all insomniacs would show hyperarousal and the primary comparison would only involve a placebo vs zolpidem comparison across months. But not all insomniacs were hyperaroused.

CONCLUSION

In conclusion, this study has shown that 1) not all people with insomnia are hyperaroused as shown by MSLT, 2) hyperarousal in insomnia as defined by MSLT is also seen in elevation of daytime NE, 3) Hi daytime MSLT/NE is associated with enhanced risk of hypnotic dose escalation, and 4) the dose escalation is expressed primarily in insomniacs receiving placebo.

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Highlights

- not all people with insomnia are hyperaroused as shown by MSLT.
- hyperarousal in insomnia as defined by MSLT is also seen in elevation of daytime NE. 3) Hi daytime MSLT/NE is associated with enhanced risk of hypnotic dose escalation.
- the dose escalation is expressed primarily in insomniacs receiving placebo.

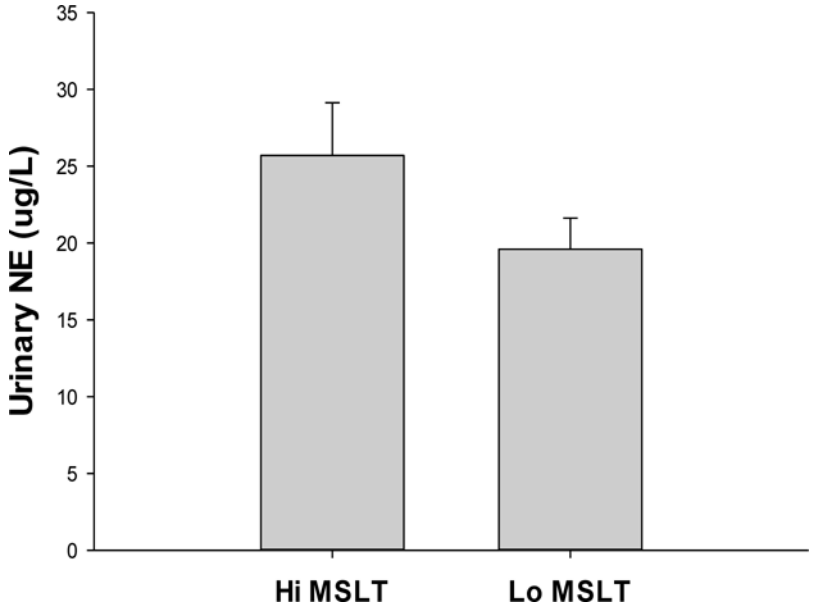

Figure 1.

Daytime (0700–1500 hrs) urinary norepinephrine (NE) in people with insomnia and Hi MSLT (≥15 min) latencies vs Lo MSLT (≤ 10 min) latencies ($p < .03$)

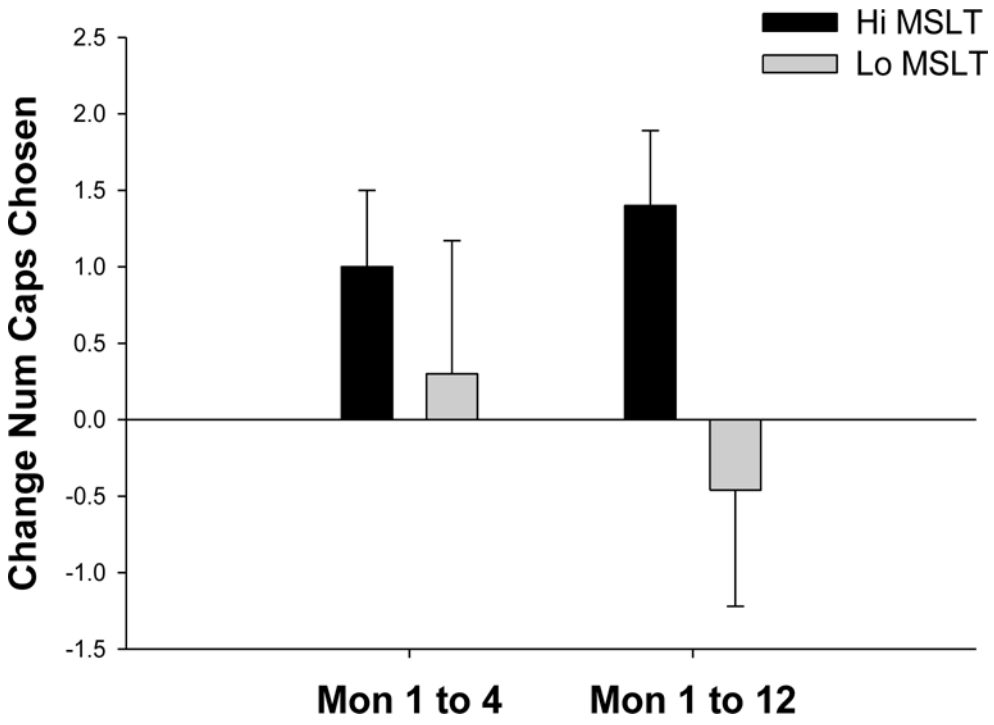

Figure 2.

Change in number of capsules chosen (placebo and zolpidem) from month 1 to month 4 and month 12 in Hi and Lo MSLT groups ($p<.08$).

Table 1

History of Insomnia Groups

	PLACEBO	ZOLPIDEM
N	45	50
Average Age (range)	49.44 (30–70)	49.58 (23–68)
Gender	Males: 16	Males: 26
	Females: 29	Females: 24
INSOMNIA MEASURES		
Reported Sleep Time (hrs) ± SD; median	5.58 ± 1.04 5.50	5.17 ± 1.22 5.25
NPSG Sleep Time (hrs) mean ± SD; median	5.90 ± 0.74 6.02	6.02 ± 0.78 6.12
SL NPSG (min) ± SD median; range	44.26 ± 38.35	35.46 ± 29.32
	33; 2–169	26; 5–141
WASO NPSG (min) ± SD median; range	98.44 ± 40.67	95.15 ± 42.26
	91.5; 22–185.5	92.0; 24.5–218.5
Age of insomnia onset median; range	38.60 40; 10.5–65	36.46 38.5; 7–58
Duration of insomnia median; range	10.93 7; 1–31	12.92 8; 1–54
SELF REPORTED ALCOHOL AND DRUG CONSUMPTION		
Alcohol (drinks/week: N)	0–1: 31	0–1: 31
	2–6: 6	2–6: 16
	7–14: 7	7–14: 3
	16: 1	16: 0
Caffeinated Beverages (drinks/week: N)	0–1: 9	0–1: 13
	2–6: 7	2–6: 16
	7–14: 16	7–14: 12
	16 or more: 13	16 or more: 9
Previous Illicit Drug History	No drug history: 31	No drug history: 41
	Marijuana use ≥ 2 yrs ago: 3	Marijuana use ≥ 2yrs ago: 5
	Marijuana use >10 yrs ago: 10	Marijuana use >10 yrs ago: 4
	Cocaine use 20 yrs ago: 1	Cocaine use: 0
Current Nicotine Usage (Cigarettes smoked per day)	Non smokers: 37	Non smokers: 41
	1–2: 3	1–2: 3
	4–5: 2	3–5: 4
	>6: 3	>6: 2

Table 2

Timing of Assessments and Study Group Ns

Assessment by Month				
Screen	**Month 1**	**Month 4**	**Month 8**	**Month 12**
NPSG	NPSG	Self Admin	NPSG	Self Admin
MSLT	MSLT		MSLT	
	Urinary NE		Urinary NE	
	Self Admin			
Study Ns				
	Whole Grp		Self Admin Grp	
Hi MSLT	42		27	
Lo MSLT	27		13	
Inter MSLT[1]	26		14	
TOTAL	95		54	

[1] Inter MSLT not used in the study comparisons

NPSG = nocturnal polysomonography; MSLT = Multiple Sleep Latency Test; Urinary NE = urinary collection (07–1500 hr) for norepinephrine levels; Self Admin = one week hypnotic self administration assessment

Table 3

Daytime (0700–1500 hrs) Urinary Norepinephrine Levels as a Function of MSLT and Nightly Drug

	Lo MSLT	**Hi MSLT**
Whole Sample		
Number Subjects	27	42
Month 1	21.6 (1.9)	23.2 (2.9)
Month 8	17.6 (2.2)	28.2 (4.0)
Self-Administration Sub Sample		
Number Subjects	13	27
Month 1	18.8 (2.6)	17.6 (4.0)
Month 8	27.3 (4.5)	30.5 (6.2)
Drug Effects		
	Placebo	**Zolpidem**
Number Subjects	45	50
Month 1	24.5 (2.7)	19.8 (1.6)
Month 8	23.2 (2.7)	23.1 (3.1)

Data are Means (SEM) ug/L

Lo MSLT vs Hi MSLT: $p<.03$ and .04 in both samples

Zolpidem vs Placebo: NS