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Disturbed sleep predicts hypnotic self-administration

Timothy Roehrs*, Alicia Bonahoom, Bonita Pedrosi, Leon Rosenthal, Thomas Roth

Henry Ford Hospital, Sleep Disorders and Research Center, 2799 West Grand Boulevard, Detroit, MI 48202, USA

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Abstract

Objectives: To evaluative whether polysomnographically determined sleep variables in a large group of subjects reflecting a wide range of sleep disturbance would be predictive of the self-administration of capsules before sleep.

Methods: Sixty-four healthy men and women with and without insomnia (aged 21–55 years) were given an opportunity to self-administer placebo or triazolam (0.25 mg) capsules (single-choice method — available capsule or no capsule) before sleep in three separate studies. All qualified using the identical criteria based on a standard nocturnal polysomnogram. Screening sleep measures then were used to predict subsequent placebo and triazolam self-administration.

Results: The percent of placebo and triazolam choices did not differ between or within the three studies. Persons with persistent psychophysiologic insomnia self-administered more capsules than persons with sleep state misperception or normals, with the subject groups not differing in placebo vs. active drug preference. Screening polysomnographic measures predicted percent of capsule choices. The single best predictor was the ratio of minutes of stage 3–4 sleep to minutes of wake plus stage 1 sleep with $R = 0.44$. The addition of % stage 3–4 sleep, wake before sleep and total sleep time increased R to 0.49. On morning mood ratings less ability to concentrate and greater fatigue (Profile of Mood States) predicted percent of capsule choices with $R = 0.36$.

Conclusions: These results show that the extent of sleep disturbance predicts the likelihood of self-administering a capsule before sleep regardless of whether it is placebo or active drug.

Keywords: Triazolam and placebo preference; Hypnotic self-administration; Insomnia patients; Stage 3–4 sleep; Stage 1 sleep

1. Introduction

The benzodiazepine hypnotic self-administration pattern of patients with insomnia differs from that seen in daytime studies of benzodiazepine self-administration in normals and patients with anxiety [1,2]. Insomniacs self-administer capsules at bedtime in a high and persistent rate compared to that in the daytime studies [3–5]. Insomniacs do not differentially self-administer placebo vs. active drug in a single-choice methodology (i.e. take available capsule or no capsule), although if given a choice they do select active drug [5]. Given insomniacs' high and persistent rate of hypnotic self-administration, the oft expressed concern regarding the abuse liability of hypnotics seems to be supported by these studies [6,7].

Yet, high self-administration rates do not necessarily reflect abuse. Insomniacs do not escalate the nightly dose in the short-term and the majority of insomniacs do not self-administer the drug during the daytime when given the opportunity [4,8]. Thus, the high nightly rate of self-administration may reflect an insomniac's persistent attempt to improve their sleep. That is, the 'hypnotic' self-administration of insomniacs is therapy-seeking behavior and not drug-seeking behavior, at least initially. If the former is true, the degree of sleep disturbance should be predictive of 'hypnotic' self-administration rates. These analyses were done to evaluate whether or not polysomnographically determined sleep variables in a large group of subjects reflecting a wide range of sleep disturbance with and without the presence of insomnia complaints would be predictive of 'hypnotic' self-administration.

2. Methods

2.1. Subjects

Sixty-four men and women, 21–55 years of age, with and without insomnia served in three different experiments, all with the same entry criteria. All subjects were in good physical and psychiatric health, except for the insomnia complaint in the insomnia groups, as determined by the screening procedures described below. The studies were

* Corresponding author. Tel.: +1-313-916-5177; fax: +1-313-916-5167.
E-mail address: taroehrs@aol.com (T. Roehrs).

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reviewed and approved by the Human Rights Board of the institution. All subjects signed a written, informed consent and received payment for their participation.

2.2. Procedure

Subjects underwent a medical history, drug-taking history, physical examination, and laboratory blood and urine tests prior to a screening nocturnal polysomnogram. Subjects were excluded if they had acute or chronic medical conditions that required treatment or were currently taking CNS acting drugs. The urine tests were also used to screen subjects for the current use of illicit drugs. Subjects with a current or past history of psychiatric disorders, drug addiction, and alcoholism were excluded based on a brief psychiatric screen, the Minnesota Multiphasic Personality Inventory (MMPI) and a urine drug screen. No subjects had participated in a previous self-administration experiment and none had taken other psychiatric medications. No subjects had previously used hypnotics for sleep.

Each subject underwent a sleep disorders evaluation including a sleep history and a nocturnal polysomnogram. Table 1 outlines the characteristics of the normals and insomnia groups in each experiment. To qualify as having insomnia, subjects had a complaint of insomnia for at least 1 year, an estimated nightly sleep time of less than 6.5 h, and a sleep efficiency of 85% or less on the screening polysomnogram. These subjects qualified for a diagnosis of psychophysiological insomnia (PPI) (ICSD 307.42-0) [10]. To qualify as having insomnia with sleep state misperception (SSM) subjects had a complaint of insomnia for at least 1 year, estimated their nightly sleep time as less than 6.5 h, and had a sleep efficiency of 85% or greater on the screening polysomnogram, while estimating their sleep time on the screening night as less than 6.5 h. These subjects qualified for a diagnosis of SSM (ICSD 307.49-1) [10]. To qualify as a normal, subjects reported that they slept normally and had a sleep efficiency of greater than 85% on the screening polysomnogram.

For the screening polysomnogram subjects arrived at the sleep laboratory 1.5 h before their usual bedtime. They were prepared for a standard polysomnographic assessment [9]. A standard 8 h all-night polysomnogram was obtained and it included assessments of respiration (a nasal/oral thermistor recording airflow) and leg movements (a tibialis EMG). No subject had evidence of apneas or periodic leg movements on the nocturnal polysomnogram. All insomnia subjects qualified for either a diagnosis of PPI or SSM, based on the International Classification of Sleep Disorders [10].

Experiment 1 included normals (NOR), insomniacs with disturbed sleep (PPI), and insomniacs with normal sleep (SSM). Experiment 2 included both PPI and SSM subjects and Experiment 3 included only PPI subjects. In each experiment subjects who qualified entered the experimental phase of the study within 1 week of having qualified. They received 4–6 consecutive sampling nights on which color-coded placebo or triazolam 0.25 mg capsules were administered. Immediately following the sampling nights, on the 4–7 choice nights that followed subjects could choose to self-administer either the same color-coded capsule (to avoid color preferences, colors associated with active drug and placebo were counterbalanced) received on the sampling nights, or take no capsule. Each experiment was conducted in a repeated measures design and thus each subject had the opportunity to self-administer placebo and triazolam (0.25 mg). The order of the placebo and active drug phases was counterbalanced among subjects and phases were separated by 1–2 weeks. Thus, each subject served for 8–13 consecutive nights on each of two occasions separated by a recovery period (1–2 weeks).

To standardize and control the choice self-administration procedures, on each choice night the subjects completed a form on which they indicated their choice for, or refusal of, a capsule. They also indicated why they made the choice and then signed the form. The chosen capsules were then dispensed by the technician 30 min prior to bedtime and the technician observed its consumption. On all sampling nights capsules were administered by the technician and the form given to the subject instructed them to make note of the capsule color as they would subsequently have the opportunity to choose capsules based on the color-coding.

Every study night subjects slept at the Sleep Disorders Center, going to bed at their usual bedtime and arising 8 h later. On all nights, prior to taking or choosing capsules, before bedtime, subjects completed a pre-sleep questionnaire that inquired about caffeine, daytime napping, drug and alcohol intake, daytime sleepiness, and any unusual events the previous day. In the morning after arising

Table 1
Characteristics of subjects in each group and experiment

	Subject groups[a]			Experiments		
	PPI	SSM	NOR	1	2	3
n	41	16	7	22	18	24
Age (years)[b]	35.1 (5.3)	35.1 (7.2)	36.0 (6.1)	35.9 (5.7)	34.4 (7.0)	35.2 (5.0)
Sex (M/F)	26/15	10/6	3/4	11/11	6/12	8/16

[a] PPI, persistent psychophysiological insomnia; SSM, sleep state misperception; NOR, normal.
[b] Mean (SD).

Table 2
Polysomnographic measures in each group[a]

	PPI	SSM	NOR	$F=$	$P<$
TST (min)	369.1 (55.0)^{A}	449.2 (24.2)^{B}	452.0 (18.6)^{B}	22.34	0.0001
WBS (min)	41.3 (29.1)^{A}	11.8 (6.73)^{B}	11.4 (7.98)^{B}	11.24	0.0001
LTPS (min)	47.3 (31.4)^{A}	14.3 (8.23)^{B}	12.4 (8.57)^{B}	12.45	0.0001
WDS (min)	52.7 (42.9)^{A}	18.5 (23.4)^{B}	15.6 (12.5)^{B}	6.68	0.002
ENTW (#)	18.8 (9.35)^{A}	12.5 (6.75)^{B}	8.4 (8.59)^{B}	6.07	0.004
ENT1 (#)	12.7 (10.2)^{A}	21.2 (9.35)^{B}	26.6 (7.26)^{B}	8.81	0.0001
WDS + S1 (min)	69.9 (48.2)^{A}	29.7 (22.9)^{B}	26.9 (13.4)^{B}	7.43	0.001
R34/WK1	0.13 (0.21)^{A}	0.42 (0.24)^{B}	0.77 (0.63)^{B}	17.57	0.0001
% St 1	17.2 (16.8)	11.2 (3.28)	11.3 (1.54)	1.39	NS
% St 2	59.6 (13.9)	59.9 (6.52)	51.9 (4.29)	1.37	NS
% St 3–4	5.72 (5.98)^{A}	10.3 (4.53)^{B}	14.7 (6.18)^{B}	9.58	0.0001
% St REM	17.5 (6.49)	18.6 (3.31)	22.1 (5.29)	1.96	NS

[a] TST, total sleep time; WBS, wake before sleep; LTPS, latency to persistent sleep; WDS, wake during sleep; ENTW, entries to wake; ENT1, entries to stage 1; WDS + S1, minutes of wake + stage 1; R34/WK1, ratio of minutes of stage 3–4 to minutes of wake + stage 1. ^{A,B}Means with different letters differ by Tukey post-hoc comparisons.

subjects completed post-sleep questionnaires that queried regarding the quantity and quality of their previous night's sleep. Subjects also completed the Profile of Mood States (POMS) before bedtime and upon arising in the morning. The POMS is an adjective checklist assessing mood states which yields six scales: vigor, fatigue, concentration, anger, tension, and depression.

The following study restrictions were agreed to by all subjects: (1) no alcoholic or caffeinated beverages after 16:00 h on study nights; (2) no napping during the study; (3) no changes in bed or wake times during the study; (4) 8 h in bed each night during the nights at home; and (5) no other medications without the approval of the investigator.

2.3. Analyses

The primary outcome variable for this study was the percent of capsule choices for placebo and active drug (i.e. the number of nights a capsule was chosen per the number of possible nights a capsule could be chosen). Percent capsule choices was used because the number of choice nights differed among the three experiments (4–7 nights). Percent capsule choices were compared with mixed design MANOVAs (General Linear Models, SAS Institute, Cary, NC) with group as a between-subject factor and drug vs. placebo as a within-subject factor. For the within-subject factor conservative degrees of freedom corrected by the Greenhouse–Geiser method were used.

The screening polysomnograms were scored by individuals unaware of the subject's sleep/insomnia diagnoses. In addition to the standard sleep efficiency measures and sleep stage measures (see Table 2), a derived measure of sleep disturbance, the ratio of minutes of stage 3–4 to minutes of wake + stage 1, was used [11]. This measure has been used in previous research to assess the second half of the night sleep disturbance produced by ethanol consumption [11]. The screening polysomnographic measures were compared with one-factor (diagnostic groups) ANOVAs followed by Tukey post-hoc comparisons. The multiple regression analyses were conducted using the MAXR procedure (SAS Institute, Cary. NC), in which the best one-variable model, the best two-variable model, and the best n-variable model are fitted to maximize the R^2. Thus, variables from the total pool of predictors are switched in and out of any given model to maximize the R^2.

3. Results

The screening polysomnographic measures for each diagnostic group are presented in Table 2. While the only polysomnography criterion on which subjects qualified for a diagnostic group was sleep efficiency (e.g. total sleep time given an 8 h time-in-bed), the groups also differed on both sleep latency measures, wake during sleep, entries to wake, entries to stage 1, minutes of wake + stage 1, ratio of minutes of stage 3–4 to minutes of wake + stage 1, and percent of stage 3–4. In all cases the post-hoc comparisons showed that the PPI group differed from both the NOR and SSM groups, while those two groups did not differ.

The percent of drug and placebo choices for each patient group is presented in Table 3. The patient groups differed significantly ($F_{2,37} = 8.73$, $P < 0.001$) in the percent of total drug and placebo choices with the PPI group choosing a capsule (either drug or placebo) on a greater percentage of opportunities than the NOR and SSM groups ($P < 0.05$). The SSM and NOR groups did not differ in the total percentage of capsules chosen. The percent of drug vs. placebo

Table 3
Percent of capsules (mean (SD)) self-administered in each subject group

	PPI	SSM	NOR
Placebo	83.2 (28.5)	48.4 (37.9)	31.0 (39.0)
Triazolam	78.8 (24.5)	47.4 (35.6)	21.4 (36.9)
Total	81.1 (22.5)	48.9 (36.4)	26.2 (34.8)

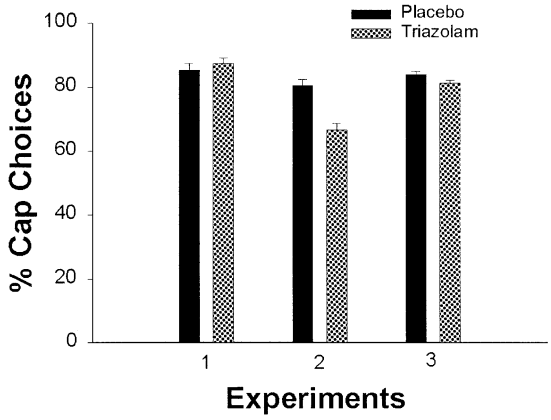

Fig. 1. The mean (±SEM) percent of placebo and triazolam (0.25 mg) capsules self-administered by PPI insomniacs in each of the three experiments.

choices was not different overall and the diagnostic groups did not differ in choosing drug vs. placebo. To assess the consistency of capsule choices among the three experiments the PPI insomniacs from each experiment were compared. In Fig. 1 the percent of drug and placebo choices for PPI insomniacs in each experiment is presented. No differences among experiments in the percentage of placebo or drug choices were found.

Given that percent of placebo and drug choices did not differ, the percent of total capsule choices (both placebo and drug) was used as the dependent variable in four sets of regression analyses. The nine clinical MMPI scales, excluding scale 5 (the masculine–feminine scale), were used as predictor variables. These variables were submitted to the multiple regression analysis. No single or group of MMPI scales were predictive of mean percent of capsule choices.

The screening polysomnographic variables were submitted to a similar analysis. The sleep variables (all 11 variables in Table 2) used included all sleep stage percentages, total sleep time, wake before sleep, latency to persistent sleep (10 min of continuous sleep), wake during sleep (wake time after persistent sleep and before final awakening), entries to wake (a shift from any sleep stage to wake), entries to stage 1 (a shift from any other sleep stage to stage 1) and two derived measures of sleep disturbance, wake

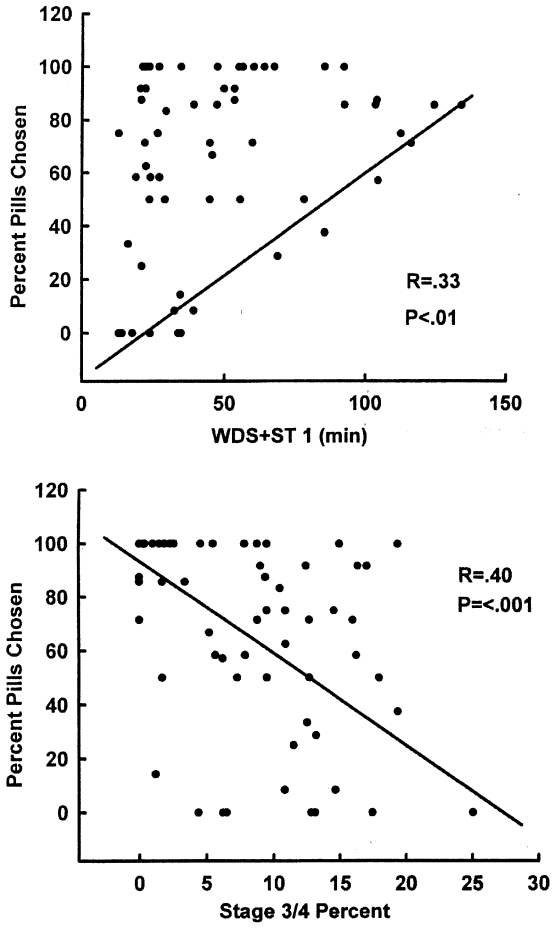

Fig. 2. The percent of capsule choices (both placebo and active drug) plotted as a function of the minutes of wake + stage 1 sleep (top) and % of stage 3–4 sleep (bottom).

during sleep + minutes of stage 1 sleep and the ratio of minutes of stage 3–4 to minutes of wake + stage 1.

Table 4 presents the regression models developed to predict percent of capsule choices. The single best predictor was the derived measure of sleep disturbance, the ratio of minutes of stage 3–4 to minutes of wake + stage 1. The more disturbed sleep was (i.e. the less stage 3–4 and the more wake + stage 1), the greater the percent of capsule choices on the subsequent capsule choice nights. Fig. 2 presents the

Table 4
Sleep predictors of percent of capsule choices

Regression models	Predictor variables[a]	$R=$	$F=$	$P<$
Single best	R34/WD1	0.44	14.85	0.0003
Best 2 variables	R34/WD1, TST	0.46	8.33	0.0006
Best 3 variables	R34/WD1, WBS, TST	0.48	6.01	0.001
Best 4 variables	R34/WD1, WBS, TST, % St 3–4	0.49	4.72	0.002
Best 10 variables	All variables except LPS	0.54	2.13	0.03
All 11 variables	All variables including LPS	0.54	1.90	0.06

[a] R34/WD1, ratio of minutes of stage 3–4 to minutes of wake + stage 1; TST, total sleep time (min); WBS, wake before sleep (min); % St 3–4, percent stage 3–4; LPS, latency to persistent sleep (min).

Table 5
Morning POMS predictors of percent of capsule choices

Regression models	Predictor variables[a]	$R=$	$F=$	$P<$
Single best	Con	0.19	2.34	0.13
Best 2 variables	Con, Fat	0.36	4.29	0.02
Best 3 variables	Con, Fat, Vig	0.37	3.07	0.03
Best 4 variables	Con, Fat, Vig, Ten	0.38	2.48	0.05
Best 5 variables	All variables except Ang	0.39	2.00	0.09
All 6 variables	All variables	0.40	1.71	0.14

[a] Con, ability to concentrate; Fat, fatigue; Vig, vigor; Ten, tension; Ang, anger.

simple correlations of minutes of stage 3–4 sleep and minutes of wake + stage 1 to percent of capsule choices. The total amount of sleep and the speed of falling asleep were variables entered in the two- and three-variable models. The four-variable model added percent stage 3–4 sleep. Given that stage 3–4 is age-dependent, age was entered into the regression as a variable. It had no effect with the overall correlation (all 11 variables) going from $R = 0.54$ to 0.55.

The pre-sleep and morning POMS scores on the six scales were submitted to similar analyses. No single or group of pre-sleep POMS scales were predictive of mean percent of capsule choices. The morning POMS scores yielded significant predictive models. Table 5 presents the regression models developed for the morning POMS scale scores. The single predictor model did not achieve significance. The best two-, three-, and four-variable models all achieved significance. For the two-variable model less ability to concentrate and greater fatigue predicted a greater percent of capsule choices on the subsequent capsule choice nights, with $R = 0.36$ for this model. The three- and four-variable models added vigor and tension, respectively, but these two additional predictors only increased R to 0.38.

4. Discussion

The results of this study show that the extent of sleep disturbance predicts the likelihood of capsule self-administration before sleep, regardless of whether the capsule is placebo or active drug. This finding suggests that insomniacs' short-term high and persistent self-administration of capsules before sleep is insomnia relief-seeking behavior and not drug-seeking, at least for the short-term duration (i.e. 1 week) of this study. This is not to say that with chronic use, what initially may be therapy-seeking behavior does not shift to drug-seeking behavior in the long term.

The most significant finding that emerged from these data is the fact that a ratio of minutes of stage 3–4 sleep to minutes of wake plus stage 1 sleep was the single best predictor of the likelihood of self-administering capsules before sleep. As Fig. 2 depicts, each of these measures by themselves were strong correlates of 'hypnotic' self-administration. But, the derived measure, a ratio of these two parameters, was the strongest single predictor. This ratio probably reflects the 'depth' or the ease of arousability from sleep.

It should be noted that in this study the entry criteria for PPI insomniacs did not include any 'depth' or fragmentation index. PPI insomniacs entered based on a sleep efficiency of $<85\%$ over the 8 h bedtime. No stage 1 or 3–4 criteria were present. The SSM insomniacs and normals had to have sleep efficiencies of $>85\%$. Thus, the predictive significance of stage 3–4 sleep and stage 1 sleep is not an artifact of the selection criteria of these studies. Also this relationship is more than a simple group difference as the groups differed on almost all of the variables. Furthermore, while they differed on stage 3–4, they did not differ on stage 1.

The predictive significance of stage 3–4 sleep and stage 1 sleep is important for several reasons. Generally, hypnotic efficacy studies that have used polysomnographic measures have selected insomniacs based on latency to sleep onset and/or shortened total sleep times and these same parameters are used as the primary outcome measures. Indices of 'depth', or conversely, the fragmentation of sleep, have not been consistently used as selection or outcome measures and possibly should be.

Sleep fragmentation, which can be indexed by heightened percentages of stage 1 sleep and lessened percentages of stage 3–4 sleep, is emerging as an important polysomnographic characteristic of the sleep of insomniacs. A recent study that assessed over 6 weeks the consistency of the sleep of PPI and SSM insomniacs, defined in the same manner as in these studies, found that the SSM insomniacs had elevated percentages of stage 1 sleep, similar to that of the PPI insomniacs [12]. Stage 3–4 sleep percentage was reduced relative to normals in the PPI insomniacs and similar to normals for the SSM insomniacs. The study concluded that SSM may be a prodromic or transitional state of sleep disruption between normal sleep and objectively disturbed sleep. Another study that assessed the self-administration of low dose ethanol before sleep by PPI insomniacs found that the self-administered dose of ethanol (0.45 g/kg) increased the percentage stage 3–4 sleep to the level of the age-matched normals [13].

Secondly, this finding is important in that a large body of literature suggests stage 3–4 sleep, or computer-scored slow wave sleep, is restorative sleep. Stage 3–4 sleep, by itself or as part of the ratio, was an important predictor of capsule self-administration in this study. Consistent with this result was the finding that morning self-ratings of mood showed that level of fatigue and ease of concentration were also self-administration predictors. That is, less stage 3–4 sleep and greater morning fatigue predicted capsule choices. However, the mood rating correlation coefficients were not as robust as those for the sleep measures.

It also is important to note the various measures that did not emerge as predictors. None of the MMPI scales were predictive. However, subjects were screened with the MMPI and no subjects with scores beyond the normal range were included in these studies. Thus, the screening criteria may

have restricted the range of MMPI scores and limited the possibility of finding significant predictors. That was not the case with the POMS where predictors were found. However, notable are the POMS scales that did not have predictive significance. Depression and anger scores failed to predict capsule self-administration and tension was a weak predictor. Thus, personality and mood variables, excepting fatigue and ability to concentrate, were not strongly predictive of self-administration.

The trait-like nature of these findings must be underscored. The screening sleep and next-morning POMS variables were predictive of subsequent self-administration of the subjects during the next 4–7 nights. A previous study showed that among PPI insomniacs the night-to-night variability in their sleep predicted their capsule choices on the subsequent night [5]. Thus, both trait-like and state-like sleep variables are predictive of capsule choice, in the first case between subjects with different levels of sleep disturbance and in the second case within subjects on a night-to-night basis.

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