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ARE OVER-THE-COUNTER SLEEP MEDICATIONS EFFECTIVE? ALL-NIGHT EEG STUDIES

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The use of hypnotic drugs is the most frequent method for treating insomnia. Over the past several years, we have systematically evaluated the effects of hypnotic drugs on all night electrophysiologic sleep parameters.[1,2] The sleep laboratory, in addition to providing an excellent technical environment for studying the effects of various drugs on sleep stages, also provides the most objective and rigorous means of evaluating the degree, length, and type of effectiveness of hypnotic drugs. For example, in previous studies,[3] we found that chloral hydrate (Noctec®) 1000 mg. and glutethimide (Doriden®) 500 mg. initially produced significant decreases in sleep latency (sleep induction), but after several days of drug administration the effectiveness of these drugs was greatly diminished. Flurazepam (Dalmane®) 30 mg., on the other hand, was found to both significantly induce and maintain sleep over the entire two-week drug administration period.

Table I — *Ingredients of Non-Prescription Sleep Medications**

Name of Drug	Methapyrilene HCl	Scopolamine HBr
Sominex	25 mg.	.25 mg.
Sleep-Eze	25 mg.	.125 mg.
Quiet World	16.67 mg.	.083 mg.
Nytol	25 mg.	—
Dormin	25 mg.	—
Compoz	15.mg.	.15 mg.

*A number of these drugs also contain salicylamide.

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The widespread availability of over-the-counter medications can be justified if, indeed, they are effective in relieving the symptoms of insomnia. However, as with many prescription drugs, claims of effectively inducing and/or maintaining sleep have not been verified in the sleep laboratory. It was, therefore, decided to evaluate a representative (Table I) and commonly used, non-prescription sleep medication (Sominex®) in the sleep laboratory and objectively determine by means of all-night electrophysiologic tracings its effectiveness in inducing and maintaining sleep and its effects in altering basic sleep patterns.

METHODS

Five male subjects, ages 24 to 35 years, with a history of moderate to severe insomnia were used as investigational subjects. The primary sleep difficulty for four of the five subjects was in falling asleep (a history of 45 minutes or more to fall asleep at least four times weekly); three of these subjects also reported some difficulty in staying asleep. The remaining subject had a primary complaint of difficulty in staying asleep. None of the subjects was taking, or gave a history of taking, any drugs within the last three months. Other than the insomnia, all were in good physical health. During the experiment, the subjects were instructed not to nap. Since exercise can significantly affect sleep patterns,[4,5] they were also told to maintain similar levels of physical activity from day to day throughout the study.

Each subject slept in the laboratory for eight consecutive nights in sound-attenuated and temperature-controlled rooms. Following application of the various electrodes, subjects were ready for sleep at approximately 11:00 P.M. They then received either the active drug, (two capsules containing the ingredients of two Sominex tablets — a total of 50 mg. of methapyrilene HCl and 0.5 mg. of scopolamine HBr), or two placebos. Both placebos and active drug were given in identically-matched capsules and following their administration, the lights were turned out and the subjects were allowed eight hours until awakened in the morning. Administration of drug and placebo was on a double-blind basis.

The laboratory schedule was as follows (P=Placebo and D=Drug):

1	2	3	4	5	6	7	8
P	P	P	D	D	D	P	P

The first two placebo nights were allowed for adaptation to the laboratory. Records from the third placebo night were used to determine each subject's baseline sleep pattern. The fourth laboratory (first drug) night revealed initial drug effects while the next two drug nights (nights 5 and 6) allowed for measuring the short-term cumulative drug effects. Administering a placebo on the last two experimental nights (nights 7 and 8) allowed for the measuring of immediate withdrawal effects.

Each subject was continuously monitored with electroencephalographic (EEG), electromyographic (EMG) and electrooculographic (EOG) recordings. For each subject, there were three recording channels for monitoring eye movements, two for EMG and three for EEG. The scoring of these all-night records was carried out independently of any knowledge of the experimental condition according to the criteria of Dement and Kleitman[6] as recently modified by a representative group of international sleep researchers.*[7]

* Rapid eye movement (REM) sleep which is characterized by intermittent bursts of rapid eye movements and (NREM) non-rapid eye movement sleep comprise the two major classes of sleep, with NREM sleep further divided into sleep stages 1, 2, 3 and 4. REM and NREM sleep alternate periodically throughout the night with the recurrence of REM sleep approximately every 90 minutes. REM sleep occupies 20% of a night's sleep, stage 1, 5%; stage 2, 50-55%; stage 3, 10%; and stage 4, 10%. For further description of sleep stages and cycles the following references are suggested.[8,9]

The all-night tracings allowed a determination of the effectiveness of the drugs in inducing and maintaining sleep, as well as effects of the drug on the absolute amount and percent of each sleep stage, REM-NREM cycling and on other sleep stage-related parameters. Time from lights out until sleep onset (sleep latency) was the measure used for evaluating sleep induction. Sleep onset was defined as the first minute of stage 2 sleep or first two minutes of stage 1 sleep. The measures used for evaluating sleep maintenance were wake time following initial sleep onset and number of awakenings for each night. Total wake time consisted of sleep latency plus wake time after sleep onset and served as a measure of sleep throughout the night — that is, sleep induction and maintenance combined.

RESULTS

A. Effects on Sleep Induction and Maintenance (Table II)

The mean values for sleep latency, wake time after sleep onset, total wake time, and total number of wakes from condition to condition (that is, baseline versus drug versus withdrawal) are compared in Table II. There was very little change in sleep latency on the first two drug nights and an increase in this parameter on the third (last) drug night. The increased value for sleep latency on the last drug night was primarily due to the extremely poor night of sleep of one subject. On the first placebo-withdrawal night, sleep latency was moderately elevated over baseline value (not significant) but by the second placebo-withdrawal night the value of this parameter approximated that of baseline.

Table II — *Effects of Sominex on Sleep Induction and Maintenance Mean Values, N=5*

Night	Condition	Sleep Latency *	Wake Time After Sleep Onset	Total Wake Time	Total No. of Wakes
1	Placebo	54.8	12.0	66.8	6.2
2	Placebo	32.4	12.2	44.6	7.8
3	Placebo	42.4	20.8	63.2	6.6
4	Drug**	42.4	13.2	55.6	7.0
5	Drug	55.8	22.6	78.4	9.0
6	Drug	84.4	13.2	97.6	6.6
7	Placebo	65.4	29.4	94.8	8.2
8	Placebo	43.4	26.6	70.0	9.4

* Sleep latency, wake time after sleep onset and total wake time are expressed in minutes.

** 2 Sominex tablets (total dose, methapyrilene HCl 50 mg., scopolamine HBr .5 mg.)

Wake time after sleep onset was somewhat decreased on the first and third drug nights (not significant) while it was similar to the baseline value on the second drug night and the two placebo-withdrawal nights. The

total wake time and total number of wakes were fairly consistent from night to night and condition to condition.

In Table III, the values for sleep latency are listed for each subject from condition to condition. With drug administration, there was little change in sleep latency for any of the subjects.

Table III — *Effects of Sominex on Sleep Latency* Individual Values*

Night	Condition	Subjects** 1	2	3	3	5
1	Placebo	85	33	35	105	16
2	Placebo	42	25	37/	45	13
3	Placebo	113	45	21	18	15
4	Drug+	68	61	28	29	26
5	Drug	103	53	22	15	86
6	Drug	247	62	42	56	15
7	Placebo	82	57	6	49	133
8	Placebo	99	66	25	20	7

* Sleep latency expressed in minutes

** Subjects 1-4 gave a history of primary difficulty in falling asleep, while subject 5 a history of primary difficulty in staying asleep.

\+ 2 Sominex tablets (total dose, methapyrilene HCl 50 mg., scopolamine HBr .5 mg.)

B. Effects on Sleep Stages and Other Parameters (Table IVA and B)

On night 4, the first drug night, there was a slight to moderate decrease in both the absolute minutes and percent of REM sleep as compared to baseline (Table IVA). There was also a marked lengthening of the interval from sleep onset to the first REM period and a slight decrease in the total number of REM periods for the night. Analysis of REM sleep by thirds of the night showed that REM sleep was markedly suppressed in the first two-thirds of the night (31.2 vs 50.4) and increased slightly over baseline in the last third (59.6 vs 54.4) (Table IVB). None of the mean values for night 4 showed a statistically significant change compared to night 3. In each case, four of the five subjects showed a clear-cut decrease in the total amount of REM sleep, the amount of REM sleep in the first two-thirds, and an increase in the interval from sleep onset to the first REM period.

On night 5, the absolute minutes of REM sleep were slightly decreased while the percent of REM sleep was similar to baseline. REM sleep was still suppressed in the first two-thirds with an increase in the last third compared to baseline but these changes were less than those on night four.

Table IV A — *Effects of Sominex on Sleep Stage**

Night, Condition	Percent Sleep Stages					Sleep Onset to 1st REM	No. of REM Periods
	REM	1	2	3	4		
3. Placebo	23.3(104.8)**	6.6	56.4	11.1	2.6	92.6	3.8
4. Drug***	20.4(91.8)	6.5	64.5	4.1	4.5	172.0	3.4
5. Drug	23.1(98.6)	7.0	58.8	7.7	3.4	96.6	3.4
6. Drug	22.8(95.8)	7.4	57.4	10.1	2.3	95.8	3.8
7. Placebo	24.3(100.6)	8.1	55.0	9.8	2.8	107.8	3.6
8. Placebo	24.0(106.2)	8.0	56.0	7.6	4.4	77.6	4.2

* Mean Values (N=5)

** Absolute minutes of REM sleep are in parenthesis

*** 2 Sominex tablets (total dose, methapyrilene HCl 50 mg., scopolamine HBr .5 mg.)

Table IV B - *Effects of Sominex on mean REM Minutes by Thirds of Night*

	Baseline		Drug		Withdrawal	
	N3	4	5	6	7	8
First 1/3	14.6	9.8	10.6	8.2	13.0	13.6
Second 1/3	35.8	22.4	30.0	37.6	37.4	35.0
Last 1/3	54.4	59.6	58.0	50.0	50.2	57.6
TOTAL	104.8	91.8	98.6	95.8	100.6	106.2

On night 6, both the absolute and percent of REM sleep were slightly decreased due to a slight suppression in the first two-thirds of the night. The interval from sleep onset to the first REM was not delayed and the other REM parameters were similar to baseline.

On withdrawal nights (7-8) all of the REM parameters were similar to baseline except for a moderate decrease in the interval to the first REM period on night 8. The decreases in REM sleep on the drug nights were associated with a reciprocal increase in stage 2 sleep. The other NREM sleep stages showed little change from baseline to drug to withdrawal conditions.

DISCUSSION

Four of the five subjects in this study gave a clinical history of moderate to marked difficulty in falling asleep. In the laboratory the mean sleep

latency (42.4 minutes) for all five subjects was slightly over twice that of normal young adults previously studied in our laboratory. The results show that two Sominex tablets had no favorable effect on sleep induction when administered to these insomniac subjects who had primarily moderate to severe difficulty in falling asleep. Since difficulty staying asleep was not the primary complaint of these insomniac subjects, it was difficult in this study to accurately assess the effects of this over-the-counter sleep medication on sleep maintenance. However, it should be noted that no definite, favorable trends were noted in terms of enhancing sleep maintenance especially with the total number of wakes per night which remained quite consistent from placebo to drug to placebo conditions.

The consequences of sustained insomnia are apparent in reduced work effectiveness, emotional instability and often constant tiredness. With time, this pervading problem can take a tremendous physical and emotional toll. To solve their sleeping problems, many individuals depend upon hypnotics prescribed by their physicians. Yet, recent studies in our sleep laboratory have demonstrated that many of these medications not only may alter sleep patterns, but also may lose their effectiveness with prolonged use leading to increased dosages.[10] Both of these effects have been strongly implicated in the development of drug dependence.

Over-the-counter sleep medications offer an alternate solution. It is probable that many people, fearing the possible addiction to prescription hypnotics, turn to these non-prescription medications in the belief that they are safer. However, clinical disturbances have been reported with varying dosages of these drugs.[11-14] As has been noted by the manufacturers themselves, the recommended doses for these drugs may precipitate acute glaucoma, especially in elderly patients who have a narrow, corneal-iris angle. In addition, two to three times the recommended dosage may result in transient disorientation and hallucinations[12] especially in emotionally unstable individuals. For example, two psychiatric patients treated by one of us (A.K.) reported transient hallucinations and disorientation after taking only "several" Sominex tablets. These changes were terrifying to these patients as they did not understand their origin and interpreted their occurrence as indicating basic psychological changes. With a marked overdose of these drugs (15 to 30 tablets) a stuporous state, confusion, extreme psychiatric disturbance, coma, and even death have been reported.[11,12,14]

The results of our sleep laboratory study of Sominex indicate that such sleep medications at the recommended dosage are ineffective in relieving moderate to severe insomnia. This being the case, it is quite possible that people with this kind of insomnia may increase the dosage in an attempt to find an effective level. While patients under a physician's care can report a drug's ineffectiveness and receive further treatment and counseling, this is not usually available for the user of non-prescription sleep

medications. Yet, as the reports presented above suggest, even increasing the dose of these drugs two to three fold may lead to adverse side effects.

In addition to these possible clinical difficulties, the results of our study show that Sominex is a mild suppressor of REM sleep. This suggests that increasing the dose beyond that used in this study would result in a significant suppression of REM sleep. This, in fact, was shown to be the case in another electrophysiological study which evaluated the effects of scopolamine HBr (0.006 mg./kg.) administered intramuscularly on single nights to normal subjects.[15] Results showed that REM sleep was very markedly suppressed, especially in the first part of the sleep period as shown by a marked delay in the first REM period. REM density was also decreased. No other sleep stages were affected except for stage 2 which increased. Although the dosage level in terms of mg./kg. was similar to that used in our study, the increased amount of drug absorbed, as well as the increased speed of absorption when a drug is administered intramuscularly, could easily account for the more marked suppression of REM sleep in their study. Their results strongly suggest that, if increased doses of over-the-counter sleep medications are taken by mouth, marked REM suppression would occur.

We do not know the specific significance of the presence or absence of a given sleep stage. While it was previously thought that REM deprivation led to gross psychological changes, this is now known not to be the case. With our current state of knowledge, we cannot say that suppressing REM sleep, stage 4 sleep, or any sleep stage is either "good" or "bad." The only important clinical correlate of sleep stage alterations that has been noted to date relates to the adverse clinical changes associated with increases in REM sleep following the withdrawal of REM-suppressant drugs.[1] These changes include an increase in both the frequency and intensity of dreaming often in the form of unpleasant dreams and nightmares especially in patients with significant preexisting psychopathology. Oswald and his associates[16,17] as well as our group[2] both support the concept that the changes occurring following withdrawal of REM suppressant drugs are important factors in the development of drug dependence.

The major value of non-prescription sleep medications may be in relieving mild forms of insomnia. Results from a previous clinical study[18] relying on subjective evaluations (patients' reports and nurses' observations) showed that both methapyrilene and phenobarbital alone exhibited greater hypnotic action than placebo. There were several shortcomings in this study. For example, nurses observations were only once every hour, and the design of the study was such that different drugs were given on successive nights. We now know that the sleep of one night is in part dependent on the sleep of a preceding night and, therefore, do not interchange drugs in any of our drug studies unless a prolonged wash-out period is allowed.[1] In spite of these limitations, the study[18] still

suggests the possibility that non-prescription sleep medications may be effective in cases of mild insomnia. This remains an important area for future investigations in the sleep laboratory. If over-the-counter sleep medications are shown to be effective in mild insomnia, then the benefits probably outweigh the disadvantages previously described. If clear-cut effectiveness is not demonstrated for these drugs, their use should be discouraged.

SUMMARY

A commonly used, non-prescription sleep medication (Sominex®) was evaluated in the sleep laboratory, using subjects with moderate to severe insomnia who primarily had difficulty in falling asleep. Subjects were monitored with electroencephalogran (EEG), electromyelogram (EMG), and electrooculogram (EOG) for eight consecutive nights: three placebo nights, three drug nights, and two placebo nights. Results showed that Sominex in its recommended dose did not produce any favorable effects in terms of inducing sleep. The principal sleep alteration produced by the drug was a slight decrease in REM sleep on the first drug night.

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