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Treatment of Narcolepsy with Methamphetamine

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Summary: Eight pairs of subjects (each consisting of a narcoleptic and a control matched on the basis of age, sex, educational background and job) were evaluated under the following double-blind, randomized treatment conditions: baseline, placebo, low dose and high dose methamphetamine. Subjects were drug-free for 2 weeks prior to beginning the protocol. Methamphetamine was the only drug taken during the protocol and was given in a single morning dose of 0, 20 or 40–60 mg to narcoleptics and 0, 5 or 10 mg to controls. The protocol was 28 days long, with each of the four treatment conditions lasting 4 days followed by 3 days of washout. Nighttime polysomnography and daytime testing were done during the last 24 hours of each treatment condition. Daytime sleep tendency was assessed with the multiple sleep latency test (MSLT). Daytime performance was assessed with performance tests including a simple, computer-based driving task. Narcoleptics' mean MSLT sleep latency increased from 4.3 minutes on placebo to 9.3 minutes on high dose, compared with an increase from 10.4 to 17.1 minutes for controls. Narcoleptics' error rate on the driving task decreased from 2.53% on placebo to 0.33% on high dose, compared with a decrease from 0.22% to 0.16% for controls. The effects of methamphetamine on nocturnal sleep were generally dose-dependent and affected sleep continuity and rapid eye movement (REM) sleep. Elimination half life was estimated to be between 15.9 and 22.0 hours. Mild side effects emerged in a dose-dependent fashion and most often involved the central nervous system and gastrointestinal tract. We concluded that methamphetamine caused a dose-dependent decrease in daytime sleep tendency and improvement in performance in both narcoleptics and controls. Methamphetamine at doses of 40–60 mg allowed narcoleptics to function at levels comparable to those of unmedicated controls. **Key Words:** Narcolepsy—CNS stimulants—Methamphetamine—MSLT—Polysomnography—Driving task.

Narcolepsy is a neurological disorder affecting some 250,000–350,000 individuals in the United States, a prevalence rate similar to that for multiple sclerosis (1–4). Narcolepsy is thought to stem from genetic or early developmental abnormalities in catecholamine regulation within the brain (5,6). The disorder is characterized by a pentad of symptoms: daytime somnolence, cataplexy, hypnagogic hallucinations, sleep paralysis and disturbed nocturnal sleep (7,8). The etiology of daytime somnolence in narcolepsy is poorly understood, but seems to stem from dysregulation of the sleep/wake cycle, rather than from an excessive need for sleep (9,10). Hypnagogic hallucinations, sleep paralysis and cataplexy are manifestations of an underlying dysfunction in the control and organization of rapid eye movement (REM) sleep (7). Pathological somnolence is by far the most disabling and potentially dangerous symptom of narcolepsy. Pathological somnolence, whether from narcolepsy or from other causes such as sleep loss (11,12), sleep apnea (13) or other sleep disorders (14), produces episodes of unintended sleep, reduced attention and performance errors. Such somnolence has been linked to a variety of transportation and industrial accidents (15). A therapy that eliminates the excessive somnolence of narcolepsy would thus have important implications not only for individual patients but also for public health.

Previous studies have described marked differences between narcoleptics and normal controls with respect to physiological measures of arousal and ability to perform sedentary tasks requiring sustained attention (7,16). Our previous work has shown that treatment of narcolepsy with centrally acting sympathomimetics or other stimulants reduces, but does not eliminate, somnolence or performance deficits (7). Among these compounds, only dextroamphetamine and methylphenidate have narcolepsy listed as an indication. Not surprisingly, these two drugs are the most commonly prescribed pharmacotherapies for narcolepsy (17). However, using objective measures we have found that treatment with dextroamphetamine or methylphenidate, given in divided doses as large as 60 mg per day,

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TABLE 1. *Subject characteristics upon admission into protocol. MSLT results are taken from each patient's diagnostic evaluation*

					MSLT				
	Narcoleptics	Sex	Age	DR and DQ type	Sleep latency	REM periods	Controls	Sex	Age
Pair 1	1N	F	67	DRw15; DQw6	1.4	5	1C	F	71
Pair 2	2N	M	54	DRw15; DQw6	3.3	2	2C	M	53
Pair 3	3N	F	38	DR4; DQw6	1.4	2	3C	F	38
Pair 4	4N	M	20	DRw15; DQw6	1.0	4	4C	M	23
Pair 5	5N	F	52	DRw15; DQw6	2.8	2	5C	F	51
Pair 6	6N	M	21	DRw15; DQw6	2.8	2	6C	M	23
Pair 7	7N	F	34	DRw15; DQw6	1.4	4	7C	F	33
Pair 8	8N	F	50	DRw15; DQw6	1.3	2	8C	F	53

does not normalize sleep tendency or performance (7). Furthermore, surveys indicate that narcoleptics receiving pharmacological treatment report that they function poorly at work and in social situations (17,18). It is likely that efforts to eliminate pathological somnolence with central nervous system (CNS) stimulants are not attempted due to physician concern regarding side effects and physician reluctance to prescribe doses of stimulants in excess of manufacturer's suggested dosage levels (17,19,20).

Methamphetamine is closely related to amphetamine, but with greater central versus peripheral effects than amphetamine, presumably due to its greater lipophilicity (21). In spite of its favorable ratio of central to peripheral effects and clinical reports of its effectiveness (16), methamphetamine does not have narcolepsy listed as an indication (20). At present, methamphetamine is rarely prescribed in the treatment of narcolepsy (17). We undertook this study to test the hypotheses that methamphetamine increases alertness and performance levels in a dose-dependent manner and that methamphetamine is a suitable drug for the treatment of narcolepsy.

METHODS

Subjects

Narcoleptic subjects were recruited from our Sleep Disorders Clinic population of >200 narcoleptic individuals. Once a potential narcoleptic subject was identified, a suitable control subject was recruited by bulletin board notices and/or word-of-mouth. All subjects were informed of the purpose of the study and the anticipated effects of the experimental drug. Subjects gave informed consent by signing a consent form that had previously been approved by the Human Subjects Committee of the Scripps Clinic and Research Foundation. Subjects were paid an honorarium. the final sample consisted of eight narcoleptics (3 males and 5 females; mean age: 42.0 years) and eight healthy controls (mean age: 43.1 years), each of whom was matched to a narcoleptic subject on the bases of age, sex, education and work history. Inclusion criteria for narcoleptics were: 1) clinical history of excessive somnolence; 2) mean sleep latency on a diagnostic four-nap multiple sleep latency test (MSLT) of <5 minutes (22); 3) history of hypnagogic hallucinations and/or cataplexy, but not severe enough to require treatment during the study; 4) absence of other significant sleep pathology, as determined by diagnostic nocturnal polysomnography; 5) two or more transitions to rapid eye movement (REM) sleep on MSLT and 6) willingness to take a stimulant drug during testing protocols. Both narcoleptics and controls underwent diagnostic and polysomnographic evaluation, which included measures of respiration and limb movement, prior to admission into the protocol. Polysomnographic recordings were reviewed to insure that no sleep disorders (other than narcolepsy) were present in the narcoleptic or control groups. Demographic particulars of the eight pairs of subjects are presented in Table 1.

All narcoleptic subjects presented a clear history of cataplexy, but none was judged to be at significant risk by being without anticataplectic medication for the duration of the study. As part of the characterization of our narcoleptic subjects we performed histocompatibility leukocycle antigen (HLA) typing. Seropositivity for HLA DRw15 and DQw6 in Caucasians and Orientals, or seropositivity for HLA DQw6 in African Americans is strongly (but not invariably) associated with narcolepsy (7,23–25). Subject 3N was atypical from the other narcoleptics only in that she carried the DR4 antigen rather than the DRw15 antigen. Caucasian narcoleptics with this antigen and without the DRw15 antigen do exist and have been described by other authors and by our group (24,25). This narcoleptic was typical in all other respects, including a clinical history of cataplexy. None of her testing yielded outlier data points and overall results were not appreciably affected by dropping her data from the analyses. The average sleep latency for our narcoleptic subjects

was 1.93 ± 0.89 minutes. The average number of REM periods was 2.9 ± 1.2.

Design and protocol

The study used a four-condition, double-blind, randomized crossover design. Subjects were studied, two at a time, in narcoleptic and matched control pairs. Narcoleptics were studied under the following treatment conditions: baseline, placebo (0 mg), low dose (20 mg) and high dose (40 or 60 mg) of methamphetamine. Because the stated therapeutic goal of our experimental treatment was to reduce sleep tendency and to improve performance in narcoleptics to levels comparable with those of normal controls, we used controls matched for age, sex, education and occupation. Therefore, in parallel fashion, we studied control subjects under the following treatment conditions: baseline, placebo (0 mg), low dose (5 mg) and high dose (10 mg) of methamphetamine. Although we could have used placebo for all treatment conditions in the control group, we had several rationales for using methamphetamine: 1) we expected control subjects to perform well without methamphetamine, but anticipated some change in performance as a result of the drug; 2) we wanted estimates of metabolism of methamphetamine in non-narcoleptic subjects to compare with narcoleptic subjects; and 3) we had observed differences in performance between narcoleptics and unmedicated controls in our previous work and suspected that those differences were derived, in part, from performance-disrupting effects of the therapeutic agents studied. Medical and ethical considerations precluded giving greater than manufacturer's recommended doses of methamphetamine to normal subjects. Although it is rare for a narcoleptic patient to have severe side effects with stimulants, it is more likely that non-narcoleptic amphetamine abusers will develop side effects such as hypertension and paranoid delusions. Therefore, as a compromise measure, we gave controls a dose range judged to be sufficient to detect changes in performance and still low enough to avoid untoward cardiovascular and psychiatric side effects.

The baseline and drug ingestion periods were each 4 days long. Initially, and between each dose level, there were 3-day periods of no medication (washout periods). The order of the treatment conditions was randomized from subject pair to subject pair using a Latin square. After obtaining informed consent, narcoleptics and controls were admitted into the study and instructed to remain drug-free for 2 weeks prior to their baseline laboratory evaluation. No anticataplectic or other CNS-active medication was taken during the study period. Medication was taken in a single morning dose within 1 hour of awakening. Each dose of experimental drug was prepared by our institutional pharmacy using conventional tablets of Desoxyn® (Abbott Laboratories). Tablets were fractured and placed in unmarked, opaque gelatin capsules, surrounded by powdered sucrose. Placebo capsules contained only powdered sucrose. During the placebo and active drug conditions, each subject swallowed the same number of capsules after awakening in the morning.

Nighttime polysomnography, MSLT and performance testing were done on the last night and day of each drug ingestion period. Urine samples were obtained each morning in the laboratory before initiation of performance testing to rule out the use of drugs other than methamphetamine. On each testing day, at 9:30 a.m. and 3:30 p.m. (approximately 2 and 8 hours, respectively, after dosing), blood samples were drawn to measure serum levels of the experimental drug. Serum levels were assayed using gas chromatography (electron capture), and confirmed by gas chromatography mass spectrometry (Medtox Laboratories, St. Paul, MN).

Nocturnal studies were performed using a standard polysomnographic montage, consisting of central and occipital electroencephalogram (C3–A2 and O1–A2), digastric electromyogram, eye movement activity (electrooculogram), electrocardiogram (V2), and respiratory effort (abdominal and thoracic). A battery of performance tests included a digit-symbol substitution test and a card sorting task (7), the complex cognitive assessment battery (26) and the Steer Clear driving simulator (27). This simulation utilizes a computer program to graphically display a moving automobile, a two-lane highway and intermittent obstacles (cartoon bulls, "steers") on the highway. The subject is instructed to avoid hitting the obstacles by pressing the space bar on a computer keyboard to change lanes. About 650 obstacles were presented during each of two 30-minute-long driving sessions, one given in the morning and one in the afternoon. Sleep tendency was assessed with the research protocol of the MSLT (22). This consisted of four 20-minute nap opportunities offered at 2-hour intervals beginning 2 hours after awakening. With this MSLT protocol, no more than 90 seconds of sleep was allowed in any of the four nap opportunities before subjects were awakened and the test was ended.

Assessment of side effects

In the afternoon, before nocturnal polysomnography, and again the following day, before daytime testing, a physician performed a structured, system-oriented physical examination for drug-related side effects. The physician measured blood pressure and pulse. Respiratory rate was taken from the nocturnal polysomnographic record before sleep onset. Each subject was

TABLE 2 *Order of treatment conditions and dose levels taken by each subject. BL = baseline; PL = placebo*

	Narcoleptics				Controls			
Pair 1	BL	PL	20 mg	40 mg	BL	PL	5 mg	10 mg
Pair 2	BL	20 mg	40 mg	PL	BL	5 mg	10 mg	PL
Pair 3	BL	20 mg	PL	40 mg	BL	5 mg	PL	10 mg
Pair 4	BL	40 mg	20 mg	PL	BL	10 mg	5 mg	PL
Pair 5	BL	PL	40 mg	20 mg	BL	PL	10 mg	5 mg
Pair 6	BL	20 mg	60 mg	PL	BL	5 mg	10 mg	PL
Pair 7	BL	60 mg	20 mg	PL	BL	10 mg	5 mg	PL
Pair 8	BL	PL	20 mg	60 mg	BL	PL	5 mg	10 mg

asked to report any undesired effects experienced during the preceding 7 days. Symptoms were grouped according to physical systems: central nervous; eyes, ears, nose and throat; gastrointestinal; skin; other (impotence, libido changes, irritability). In addition, subjects completed questionnaires that addressed both treatment-related improvements in narcolepsy and potential side effects of treatment. The physician rated all reported symptoms on a 10-point Likert scale (28) from 0–10 (0 = none, 1 = minor, 10 = severe).

Data analysis

As is the case with all repeated measures designs, our protocol did not permit the simultaneous analysis of treatment effect and order of testing effect. Therefore, we assessed the effects of treatment condition and order of testing separately. The narcoleptic and control groups were compared using a two-group repeated measures analysis of variance (ANOVA). Individual cell contrasts were performed with matched pairs *t* tests. When distributions in raw data appeared to deviate from normal, we reanalyzed the data with an appropriate nonparametric test, such as the Mann-Whitney U. We considered as significant a p value of <0.05 after appropriate correction for performing multiple statistical tests. Any p values we report herein resulted from ANOVA or paired *t* tests, but were confirmed with a nonparametric test as well.

As we have already indicated, our narcoleptic subjects did not require separate pharmacotherapy (e.g. imipramine, protriptyline) for ancillary symptoms such as cataplexy. That is, the occurrence of ancillary symptoms in our narcoleptic sample was low. Because of this fact and the fact that the duration of treatment at each dose level was only 4 days, we could not systematically look for treatment-related changes in ancillary symptoms.

Table 2 presents the order of treatment conditions and dose levels taken by each subject. Note that the narcoleptics in pairs 6, 7 and 8 received a 60-mg dose of methamphetamine, rather than 40 mg, during the high dose condition. After pair number 5 completed the protocol, we reviewed side effect data collected on all subjects to that point. As there had been no untoward side effects, we increased the high dose condition to 60 mg. We did this to assess the ability of our narcoleptics to tolerate higher doses of methamphetamine. Inspection of the raw data disclosed that there were too few data points to statistically differentiate between the 40-mg and 60-mg dose conditions. Therefore, for the purpose of statistical analysis, we combined the data from both doses as the high dose condition.

RESULTS

Drug screens and assays

For all subjects, urine screens for drugs other than methamphetamine were negative at all timepoints throughout the protocol Quantitative assays of blood samples disclosed no methamphetamine in the baseline or placebo condition. During the low dose and high dose conditions, methamphetamine was well absorbed and serum levels rose as dose was increased.

Table 3 presents serum levels of methamphetamine for both groups of subjects. Although there was large variability in serum concentrations, methamphetamine was still present at significant levels some 7.5–8 hours after ingestion. Our estimations of half-life, which were based on the linear drop in serum levels between the morning and afternoon measurements, averaged 22.0 hours. We also estimated half-life by fitting the four sets of morning and afternoon serum levels to absorption-elimination curves that peaked 2.5 hours after ingestion, because previously published pharmacokinetic data (29) indicate that methamphetamine reaches peak serum levels 2–3 hours after ingestion. These curve fittings resulted in an average half-life estimate of 15.9 hours, which is in contrast to the 4–5 hour figure cited by the manufacturer (19).

Effects on nighttime sleep

Table 4 presents representative nighttime sleep parameters according to experimental condition. The ef-

TABLE 3. *Means ± standard deviations for serum levels of methamphetamine for narcoleptic and control subjects in the low dose and high dose conditions. The unit of measurement is ng/ml. No methamphetamine was detected in the baseline or placebo condition. The morning (a.m.) blood sample was taken 1.5–2 hours after ingestion of the experimental capsules; the afternoon (p.m.) sample was taken 7.5–8 hours after ingestion*

	Experimental condition			
	Low dose 20 mg		High dose 40–60 mg	
	a.m.	p.m.	a.m.	p.m.
Narcoleptics	50.1 ± 21	45.8 ± 21	116.9 ± 70	92.9 ± 58
	Experimental condition			
	Low dose 5 mg		High dose 10 mg	
	a.m.	p.m.	a.m.	p.m.
Controls	10.5 ± 16	5.9 ± 9	22.9 ± 20	20.3 ± 14

fects of methamphetamine on nocturnal sleep were generally dose-dependent and appeared to be concentrated on parameters reflecting sleep continuity and REM sleep. Nocturnal sleep latency was not systematically affected by experimental condition. Sleep efficiency was significantly reduced in both groups at the high dose. We found no systematic effects for order of laboratory testing in either group.

Effects on daytime measures

Methamphetamine had significant, dose-dependent effects on daytime sleep tendency and daytime performance in both narcoleptics and controls. Space considerations prevent us from discussing all outcome variables in any detail. Overall daytime effects are fairly represented by results of the MSLT and by percent

TABLE 4. *Nighttime polysomnographic parameters for each experimental condition. Means and standard deviations appear in columns 2–5. The significance levels of* F*-ratio for a one-way repeated measures ANOVA appear in last column on the right. All times are in minutes*

	Experimental conditions				p-level of *F*-ratio for conditions
	Baseline	Placebo	Low dose 20 mg	High dose 40–60 mg	
Narcoleptics					
Sleep latency	3.6 ± 1.5	13.9 ± 22.8	4.8 ± 5.4	3.4 ± 2.7	ns
Total sleep time	495.0 ± 28.3	473.5 ± 37.1	486.4 ± 35.5	435.9 ± 55.2	ns
Sleep efficiency	91.6 ± 4.0	87.0 ± 7.2	91.0 ± 6.6	80.9 ± 10.4	$p < 0.03$
Stage 1 NREM	69.8 ± 19.0	69.8 ± 17.7	68.1 ± 27.1	67.6 ± 24.7	ns
Stage 2 NREM	258.1 ± 40.5	264.3 ± 44.2	289.3 ± 62.1	263.7 ± 43.4	ns
REM latency	53.2 ± 35.0	37.0 ± 41.6	84.7 ± 53.8	185.8 ± 175.0	$p < 0.03$
REM time	99.7 ± 19.9	65.3 ± 14.5	71.2 ± 14.9	42.9 ± 29.8	$p < 0.0001$
SWS time	67.4 ± 42.7	61.7 ± 30.1	59.6 ± 34.6	61.9 ± 37.4	ns
Number of awakenings	25.3 ± 10.6	25.6 ± 13.6	26.6 ± 18.0	29.5 ± 15.4	ns
	Experimental conditions				p-level of *F*-ratio for conditons
	Baseline	Placebo	Low dose 5 mg	High dose 10 mg	
Controls					
Sleep latency	9.9 ± 4.2	9.4 ± 7.3	6.7 ± 3.2	10.2 ± 5.4	ns
Total sleep time	481.8 ± 34.4	480.5 ± 31.4	499.7 ± 30.7	468.2 ± 40.3	$p < 0.01$
Sleep efficiency	90.3 ± 4.5	91.8 ± 4.1	92.5 ± 4.6	88.7 ± 6.3	$p < 0.03$
Stage 1 NREM	34.6 ± 8.0	38.7 ± 8.9	45.3 ± 10.3	46.2 ± 9.3	$p < 0.03$
Stage 2 NREM	302.6 ± 33.2	314.3 ± 32.0	319.5 ± 43.1	297.7 ± 39.0	ns
REM latency	95.2 ± 26.6	82.0 ± 40.6	125.9 ± 61.8	130.5 ± 52.6	ns
REM time	81.5 ± 16.2	76.1 ± 13.5	82.6 ± 21.6	68.8 ± 14.6	ns
SWS time	63.1 ± 40.5	51.5 ± 32.2	52.3 ± 35.0	55.4 ± 40.0	ns
Number of awakenings	14.4 ± 4.9	15.3 ± 4.5	15.1 ± 5.6	20.6 ± 6.0	ns

Sleep latency: the time between lights out and three continuous 30-second epochs of stage 1 NREM sleep or the first epoch of any other sleep state or stage. Sleep efficiency: the ratio of total sleep time to total time in bed expressed as a percent. REM latency: the time between sleep onset and the first 30-second epoch of REM sleep. REM time: number of minutes spent in REM sleep. SWS: Slow wave sleep, time spent in stages 3 and 4 NREM sleep. Significance levels were set at .05 or lower; ns: not significant.

TABLE 5. *Mean ± SD sleep latencies (in minutes) on the MSLT and percent of objects hit averaged over morning and afternoon sessions of the Steer Clear driving simulator as a function of experimental group and experimental condition. The baseline MSLT sleep latency values for the narcoleptics were not significantly different than the diagnostic MSLT values presented in Table 1*

	Experimental condition			
	Baseline	Placebo	Low dose 20 mg	High dose 40–60 mg
Narcoleptics				
MSLT	4.53 ± 3.41	4.29 ± 3.12	7.75 ± 4.82	9.27 ± 4.65
% Objects hit	2.96 ± 2.23	2.53 ± 2.29	0.47 ± 0.30	0.32 ± 0.29
	Experimental condition			
	Baseline	Placebo	Low dose 5 mg	High dose 10 mg
Controls				
MSLT	12.25 ± 4.22	10.35 ± 5.26	14.64 ± 3.99	17.11 ± 3.79
% Objects hit	0.83 ± 1.02	0.22 ± 0.26	0.14 ± 0.19	0.16 ± 0.19

of objects hit during each of the two presentations of the Steer Clear driving task (27). We saw parallel improvements in the digit-symbol substitution test, the card sorting task and the complex cognitive assessment battery. Table 5 presents mean MSLT sleep latencies and percent of objects hit averaged over morning and afternoon sessions of the Steer Clear driving simulator. Results are presented as a function of experimental group and experimental condition.

Note that both narcoleptics and controls typically fell asleep during each of the four 20-minute long nap opportunities of the MSLT. The baseline mean MSLT sleep latency of 4.53 ± 3.41 minutes for our narcoleptic subjects is in good agreement with reported values (7,30). Although the baseline mean appears somewhat higher than that usually reported for samples of narcoleptic patients, the mean MSLT values observed during the diagnostic polysomnography of these same narcoleptic subjects were quite typical of narcoleptics (7) and not significantly different from the baseline (1.93 ± 0.89 vs. 4.53 ± 3.41; ns). The baseline mean MSLT sleep latency of 12.25 ± 4.22 minutes for our control subjects is also in good agreement with the range reported by other authors (31,32). Overall, and within each treatment condition, narcoleptics fell asleep more quickly than controls (all p values <0.03). For both narcoleptics and controls, methamphetamine increased MSLT sleep latencies in a dose-dependent fashion (both p values <0.0005).

The mean MSLT value for narcoleptics who received high dose methamphetamine (9.27 ± 4.65) did not significantly differ from that of controls during either the baseline or placebo conditions (12.25 ± 4.22 and 10.35 ± 5.26, respectively). A power analysis on the difference scores between the narcoleptics in the high dose condition and the controls in the baseline condition disclosed that we would need sample sizes of 41, 51 and 69 pairs of subjects to detect a 3-minute between-groups difference at the 0.80, 0.90 and 0.95 levels of confidence, respectively. We would need sample sizes of 89, 122 and 152 pairs of subjects to detect a 2-minute between-groups difference at the 0.80, 0.90 and 0.95 levels of confidence, respectively. We performed parallel analyses to assess differences among the first, second, third and fourth laboratory testing sessions regardless of the experimental condition. This analysis disclosed no significant effect for order of testing in either group.

The percentages of objects hit by our narcoleptic and control subjects are consistent with published values for pathologically sleepy and normal populations, respectively. Findley et al. reported that patients with severe sleep apnea hit a mean of 5.5% of objects presented, whereas controls hit 1.1% (27). In the baseline and placebo conditions narcoleptics hit more objects than controls (all p values <0.04). For narcoleptics and controls, methamphetamine decreased the number of objects hit, apparently in a dose-dependent fashion (both p values <0.02). The narcoleptics who received high dose methamphetamine did not hit more objects than controls who received placebo (ns). We found no significant effect for order of testing in the narcoleptic group. There was an order of testing effect in controls, who hit more objects during the first time in the laboratory than during any other condition ($p < 0.02$), but controls were already performing at near optimal levels. We interpret the pattern of results for experimental condition and order of testing to reflect a practice effect that is overshadowed by treatment effect only in the narcoleptics.

Figure 1 summarizes the effect of dose level on MSLT sleep latencies in terms of mean and distribution of individual data points for both narcoleptic and control subjects. Note that the distributions of sleep latencies

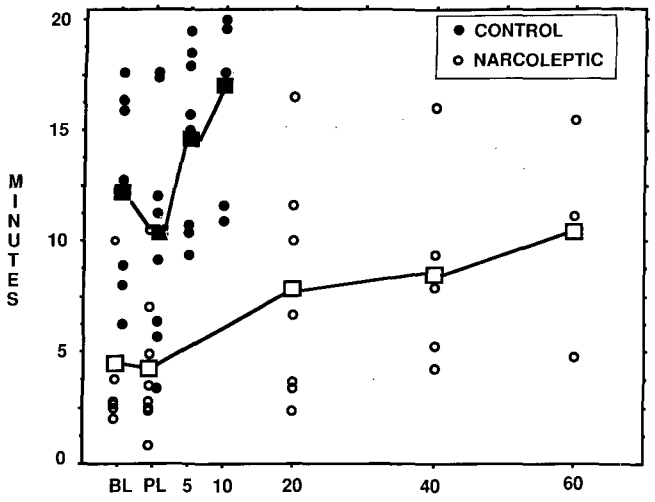

FIG. 1. Mean MSLT sleep latencies, in minutes, as a function of experimental condition. The horizontal axis represents the experimental condition: baseline, placebo and 5–60 mg of methamphetamine. The vertical axis represents mean MSLT sleep latency. A point is plotted for each narcoleptic and control subject. The squares connected by lines represent the average for each experimental condition.

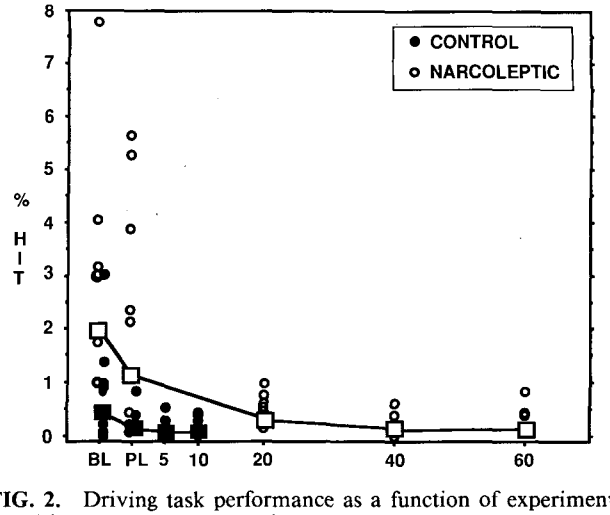

FIG. 2. Driving task performance as a function of experimental condition. The horizontal axis represents the experimental conditions: baseline, placebo and 5–60 mg of methamphetamine. The vertical axis represents mean percent of objects hit on the Steer Clear driving task. A point is plotted for each narcoleptic and control subject. The squares connected by lines represent the average for each experimental condition.

within each dose level do not appear to be skewed or truncated, with the possible exception of the controls at the 10-mg dose. MSLT sleep latency increased in every narcoleptic subject treated with methamphetamine. However, despite the improvement with methamphetamine, the mean sleep latencies of two narcoleptics remained at a grossly pathological level (<5 minutes) during the high dose condition (see lower right quadrant of Fig. 1).

Figure 2 illustrates the effects of 0, 20, 40 and 60 mg of methamphetamine on performance during the Steer Clear driving simulator task in narcoleptics and the analogous effects of 0, 5 and 10 mg of methamphetamine in controls. Note that the distributions appear to be skewed with the greatest concentration at low values. We retested the data with the Mann-Whitney U test, which confirmed the statistical significance that we had determined using parametric tests. Note that at both the 40- and 60-mg doses, narcoleptics hit objects at rates that were not statistically distinguishable from those of unmedicated controls.

Serum methamphetamine levels vs. sleep parameters and performance

There was a positive relationship between serum methamphetamine and daytime function and serum methamphetamine and nighttime sleep. These relationships are exemplified by the scatterplot in Fig. 3, relating mean MSLT sleep latency (vertical axis) to mean serum levels of methamphetamine (horizontal axis). Note that for both narcoleptics and controls, there was a positive relationship between the average serum level of methamphetamine and average MSLT sleep latency. The slope of the linear regression line relating average serum level to average MSLT sleep latency was 0.272 (90% confidence interval: 0.077–0.467) for controls versus 0.045 for narcoleptics (90% confidence interval: 0.03–0.06). Thus, the slope for controls is significantly steeper than that for the narcoleptics, suggesting that controls are more sensitive to the alerting effects of methamphetamine than are narcoleptics. In the narcoleptic group, at an average methamphetamine serum level of about 160 ng/ml, the average MSLT sleep latency was comparable to the MSLT sleep latency for the control group in the baseline and placebo conditions. On a subject-by-subject basis, however, there was no simple relationship between the serum levels and any outcome parameter. For example, in narcoleptics, the correlation between individual serum blood levels and individual MSLT sleep latencies was only 0.28.

Side effects

Clinical findings

Table 6 presents afternoon measures of blood pressure and pulse, as well as respiratory rate at the beginning of nocturnal polysomnography. Within either group, there was no significant effect of experimental condition. There was also no significant difference between narcoleptics and controls on any measure.

TABLE 6. *Measures of blood pressure, pulse rate and respiratory rate listed according to group and measure (vertically) and experimental condition (horizontally). ns: not significant*

	Experimental conditions				p-level of *F*-ratio for conditions
	Baseline	Placebo	Low dose 20 mg	High dose 40–60 mg	
Narcoleptics					
Systolic BP	122.8 ± 21.8	117.3 ± 19.3	115.8 ± 20.1	118.4 ± 19.4	ns
Diastolic BP	68.9 ± 15.7	66.1 ± 10.5	66.4 ± 10.4	70.9 ± 10.7	ns
Pulse rate	67.9 ± 3.6	70.8 ± 5.7	67.5 ± 7.0	71.8 ± 6.5	ns
Respiration rate	18.5 ± 3.3	18.3 ± 3.7	17.1 ± 3.5	17.8 ± 3.9	ns
	Experimental conditions				p-level of *F*-ratio for conditions
	Baseline	Placebo	Low dose 5 mg	High dose 10 mg	
Controls					
Systolic BP	124.6 ± 30.1	115.0 ± 6.7	115.4 ± 12.2	116.8 ± 8.5	ns
Diastolic BP	66.9 ± 6.3	64.6 ± 6.1	66.8 ± 10.5	67.1 ± 7.0	ns
Pulse rate	63.0 ± 7.9	63.0 ± 8.8	60.3 ± 75.8	63.3 ± 9.6	ns
Respiration rate	16.0 ± 3.6	17.0 ± 4.5	16.4 ± 2.6	17.9 ± 3.2	ns

Subjective reports

Table 7 presents symptomatic complaints reported over the course of the study and possibly related to use of the experimental drug. Each entry represents the number of subjects reporting the listed symptom, regardless of severity. Data are presented for the narcoleptic and control groups according to organ system and experimental condition.

In general, reported symptoms were dose dependent. They primarily reflected central nervous system (nervousness, insomnia, akathisia and headache) and gastrointestinal (nausea, abdominal pain and loss of appetite) effects. No complaints were judged severe enough to necessitate medical intervention, termination of drug treatment or exclusion from the study. Likert scale intensity data revealed that the side effects were generally mild to moderate (Likert rating <7) and did not interfere with normal daily activity. No clinically significant psychiatric or cardiovascular effects related to methamphetamine treatment in either control or narcoleptic subjects were observed. No trends were evident with respect to symptom type or severity. For example, some narcoleptic patients complained of moderate to severe headache (Likert rating >7) during the low-dose condition, but had no headache complaint during the high dose condition. The behavioral changes noted most often by both narcoleptics and controls were increased talkativeness in social situations and increased willingness to begin new projects at home and at work.

DISCUSSION

To our knowledge, this is the first double-blind, placebo-controlled study of the effects of methamphetamine in narcoleptics and matched controls. In this short-term study of eight narcoleptic subjects, methamphetamine reduced sleepiness and deficits in performance to levels that were not statistically distinguishable from eight matched controls. Although this does not mean that the treated narcoleptics and controls produce identical scores, the differences between narcoleptics and controls were markedly reduced. At the level of difference observed when the narcoleptics were medicated, at least five times the number of subjects would have to be studied to statistically detect a difference between groups. This study is noteworthy

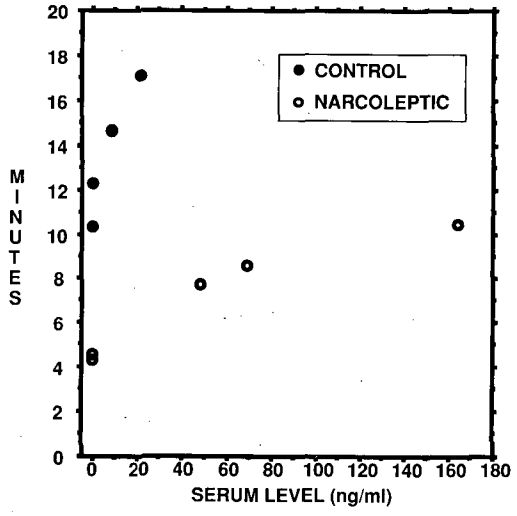

FIG. 3. Average of the morning and afternoon serum levels of methamphetamine (horizontal axis) vs. the average MSLT sleep latency (vertical axis) measured during the baseline, placebo, low dose and high dose treatment conditions for narcoleptic and control subjects. Two open circles were generated for narcoleptics in the high dose condition (rightmost circles), one for the five narcoleptics who received 40 mg and one for the three narcoleptics who received 60 mg.

TABLE 7. *Number of narcoleptic and control subjects who reported possible treatment-associated side effects. Data are presented according to organ system (vertically) and experimental condition (horizontally)*

	Narcoleptics (n = 8)				Controls (n = 8)			
			LD	HD			LD	HD
Symptoms by system	BL	PL	20 mg	40–60 mg	BL	PL	5 mg	10 mg
Nervous								
Nervousness	0	0	2	2	0	0	1	2
Insomnia	0	0	2	5	0	0	0	3
Dizziness	0	0	1	0	0	0	0	1
Headache	1	0	3	4	0	0	1	2
Akathisia	0	0	2	3	0	0	0	1
Dyskinesia	0	0	0	0	0	0	0	1
Chest discomfort	0	0	1	1	0	0	0	1
Gastrointestinal								
Nausea	0	1	0	0	0	0	0	1
Abdominal pain	0	0	1	1	0	0	0	1
Loss of appetite	0	0	4	3	0	0	1	2
Weight loss	0	0	1	1	0	0	0	0
Eyes, ears, nose and throat								
Dry eyes	0	0	1	1	0	0	0	0
Dry mouth	0	0	0	3	0	0	1	4
Blurred vision	0	0	0	0	0	0	0	1
Difficulty in accommodation	0	0	0	0	0	0	0	0
Skin								
Pain	0	0	0	0	0	0	0	0
Itching	0	0	1	0	0	0	0	1
Peeling	0	0	0	0	0	0	0	0
Discoloration	0	0	0	0	0	0	0	0
Other								
Impotence (n = 3 males)	0	0	0	0	0	0	0	0
Libido change	0	0	0	0	0	0	0	0
Irritability	0	0	0	0	0	0	0	0

because methamphetamine is not marketed for the indication of narcolepsy and because the narcoleptics received 35–40 mg more than the maximum dose recommended by the manufacturer for treatment of obesity. Structured, system-oriented physical examinations and a side effect questionnaire disclosed some side effects in over half of our subjects (5 of 8 narcoleptics and 4 of 8 controls). In about one-third of our subjects, the clinical significance of side effects was judged to be moderate. No side effects were judged to be severe.

There were at least two subjects, the narcoleptics from pairs 4 and 8, who did not show great improvement on the MSLT and whose test results could be interpreted as reflecting a lack of response to treatment (see the two open circles in the lower right of Fig. 1 representing MSLT means <5 minutes). The individual MSLT means for the narcoleptic of pair 4 were: baseline—2.6; placebo—7.0; 20 mg—3.6 and 40 mg—4.3. The MSLT means for the narcoleptic of pair 8 were: baseline—2.0; placebo—3.5; 20 mg—3.4 and 60 mg—4.8. These subjects were certainly among the sleepiest of our narcoleptic group, but they appeared to show dose-dependent improvement over their baseline MSLT values. Both subjects reported marked clinical improvement in their symptoms during active treatment conditions. Review of their nocturnal sleep disclosed no pattern that might explain the absence of an MSLT response. The narcoleptic from pair 4 reported better symptom control with methamphetamine than with his usual medication, methylphenidate. Prior to participating in our study, the narcoleptic from pair 8 had abandoned all drug therapy because of perceived lack of efficacy. After completion of the protocol, she asked to continue her treatment with methamphetamine and continues to report excellent symptom control.

The design of our study did not permit a detailed examination of methamphetamine pharmacokinetics. For each subject, however, we did estimate the rate of methamphetamine elimination from the two serum levels measured at 1.5 and 7.5 hours after ingestion. Although crude and highly variable, these estimates of methamphetamine half life in our sample were substantially longer than the 4–5-hour figure cited by the manufacturer (19). Other investigators have also reported amphetamine half lives of >4–5 hours, with values as long as 16–34 hours observed in patients with

urine pHs above 6.7 (33,34). Although we did not measure urine pH in our subjects, we considered the possibility that methamphetamine caused our subjects to hyperventilate, leading to an alkaline urine. However, when we compared respiratory rates at the beginning of nocturnal polysomnography among each of the four experimental conditions, we detected no drug-related increase (Table 6). Regardless of the pharmacologic half life of methamphetamine, patients reported that drug effects were "wearing off" by late afternoon. Inspection of mean MSLT sleep latencies during methamphetamine treatment revealed that, for both narcoleptics and controls, the shortest sleep latency occurred during the last nap of the day. These observations suggest a decline in therapeutic efficacy beginning about 6 hours after ingestion. We believe that our half life estimates and clinical impressions are consistent with the observations of Daly and Yoss (16), who reported that the duration of methamphetamine's therapeutic activity was 5–16 hours.

There also appeared to be a linear relationship between the average serum level of methamphetamine and the therapeutic effect, associated with levels of sleep tendency and performance that were not distinguishable from the control group occurring at a methamphetamine serum level of about 160 ng/ml. Although our study did not explore the mechanism of action of methamphetamine, the amphetamines in general are thought to act by releasing dopamine and, to some extent, norepinephrine from CNS neurons (21). We and others have speculated that the relative efficacy of drugs in the treatment of narcolepsy is related to the degree to which the drugs act on CNS dopamine systems (20,35,36). Within this group of drugs, our favorable results with methamphetamine may stem from methamphetamine's higher ratio of central to peripheral effects (21).

Although methamphetamine has been widely used to treat obesity and attention deficit disorder for decades, an American Narcolepsy Association survey found that only 4% of narcoleptic patients were treated with methamphetamine (17). This survey also found that many narcoleptics discontinue use of all stimulant drugs because of perceived ineffectiveness and/or factors relating to drug availability. Our current findings may have profound implications for the management of disabled narcoleptics, who have never had an adequate trial of a stimulant at a dose that controls daytime somnolence and performance deficits to a point that permits essentially normal function throughout the day.

Before we advocate widespread use of methamphetamine to treat narcolepsy, further assessment of long term safety and efficacy must be performed. There were several limitations of the present study:

1) Because we and others have found that the elimination half life of methamphetamine is in the range of 5–16 hours in some subjects, our washout periods may have been too short to completely clear methamphetamine from the systems of those subjects with slower elimination rates.

2) The 4-day drug ingestion period may have been too short to achieve steady-state levels of methamphetamine, thus our assessments of undesirable drug side effects may have missed problems that might have emerged with long-term, daily drug ingestion.

3) Full evaluations of long-term safety and side effect issues in a chronic syndrome such as narcolepsy, including the issues of drug tolerance and dose escalation, require the study of larger patient samples over longer treatment periods.

4) The issue of optimal dosing can be evaluated with studies comparing various treatment regimens. For example, would it be more efficacious to use divided doses of methamphetamine throughout the day, or to use a single dose of the sustained release formulation in the morning? Weighting against any advantage in dividing the dose, of course, is the increased chance of disturbing nocturnal sleep, particularly in subjects who metabolize methamphetamine slowly. Although all our narcoleptic subjects showed objective and clinical improvement, sleep tendency of some individual narcoleptic subjects was not brought into a normal range. This observation generates additional questions. Would subjects who still had increased sleep tendency during the high-dose condition have responded to even higher doses of methamphetamine? Would other drugs commonly used in the treatment of narcolepsy also reduce sleep tendency and performance (as did methamphetamine) if they were given at doses greater than those recommended by the manufacturer? For example, we have reported that methylphenidate (60 mg given in divided doses) brought sleep tendency and performance of narcoleptics to about 80% of normal, leaving patients partially untreated (7). The present data, combined with our clinical experience, suggest that methylphenidate might show greater efficacy at daily doses of 80–240 mg.

5) None of our narcoleptic subjects required concomitant medication for cataplexy. Would the dose-response and side effect picture for methamphetamine have changed using the present protocol if a daily anticataplectic agent had been given?

Finally, there are several societal and ethical issues that deserve mention. We acknowledge that amphetamines, including methamphetamine, are prescription drugs that are popular as substances of abuse throughout the world (37,38). Our opinion is that this abuse potential adversely affects the care of narcoleptics because physicians are reluctant to prescribe and patients

reluctant to take such drugs. However, stimulant abuse or diversion are not reported to occur in narcoleptic patients with a frequency that would lead to clinical concern (7,17,39). Another prominent factor that probably contributes to the reluctance of physicians to prescribe doses of psychostimulants aimed at elimination, rather than reduction, of somnolence and performance deficits is concern regarding risks of undesirable or perhaps dangerous side effects. However, a disabled narcoleptic patient might justifiably request the opportunity to experience maximum pharmacologically mediated reduction in sleepiness, and, equipped with the experience of optimum therapeutic control, to then participate in a process of decision-making that balances side effect "costs" against reduced disability "benefits". Other factors that may influence a physician against use of these compounds include drug availability, Drug Enforcement Agency surveillance and inconclusive diagnostic work-up.

In summary, doses of methamphetamine higher than those recommended in the treatment of obesity normalized sleep tendency and performance without unacceptable side effects in eight well-characterized narcoleptic patients. In clinical practice, methamphetamine may be underutilized in the treatment of narcolepsy due to factors unrelated to its medical utility, such as currently approved clinical indications and concerns about abuse. Our data indicate that methamphetamine may be a useful treatment in narcolepsy and that further studies on long-term safety and efficacy should be performed.

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Note: This article was planned for the April issue, which included articles on the controversy over amphetamines in narcolepsy. However, due to scheduling problems, publication of this article was delayed for one issue.