

FIGURE 1. Discriminative Stimulus Effects In Cocaine-Trained Rats.

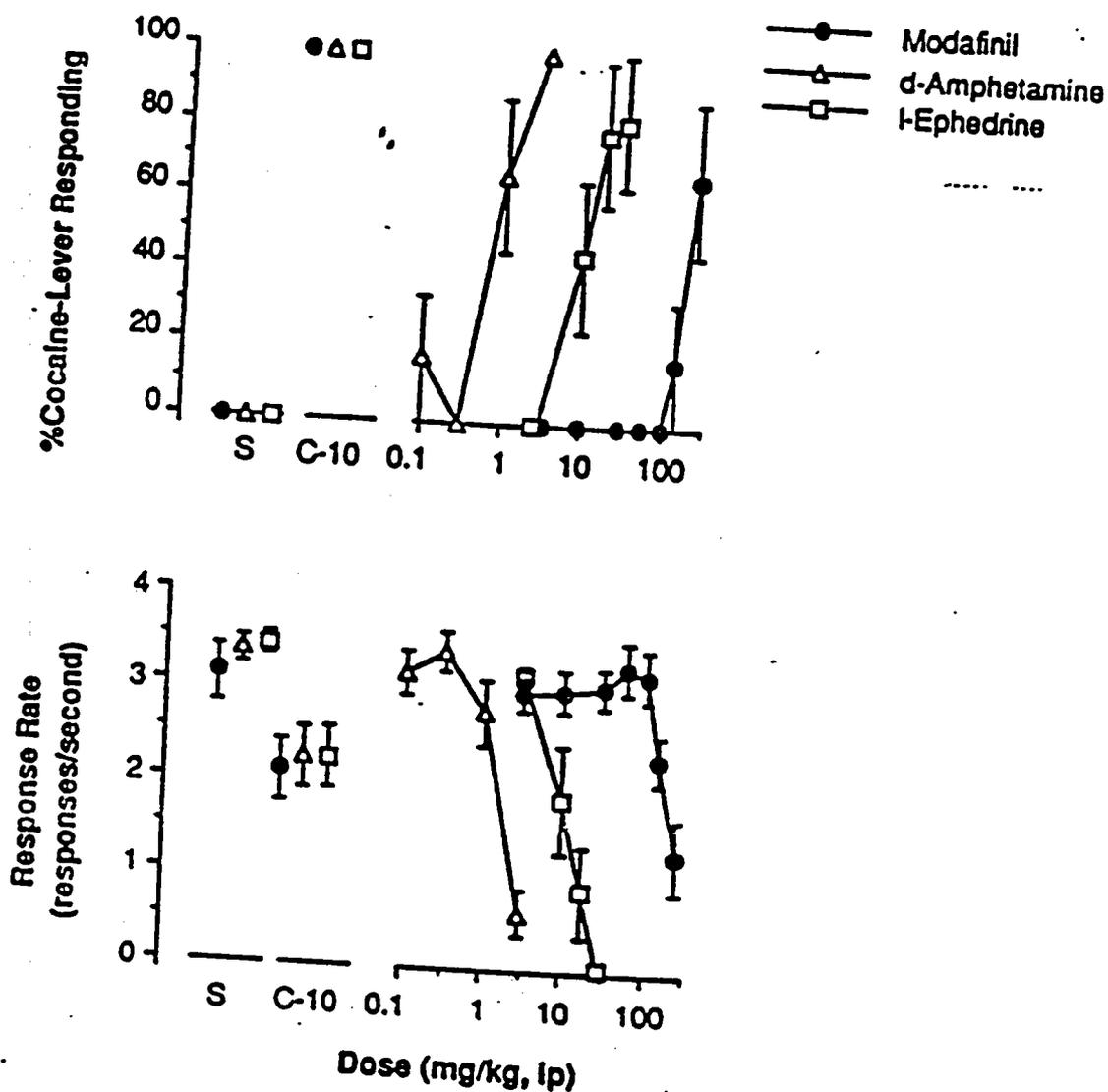


Figure 1. Mean (\pm SEM) percentage of cocaine-lever responding (upper panel) and response rates (lower panel) following various doses of modafinil, d-amphetamine or l-ephedrine in rats trained to discriminate 10 mg/kg cocaine from saline. Points above S and C-10 represent corresponding vehicle and cocaine (10 mg/kg) control tests conducted before each dose-effect curve determination.

FIGURE 2. Antagonism Test with 0.3 mg/kg Prazosin.

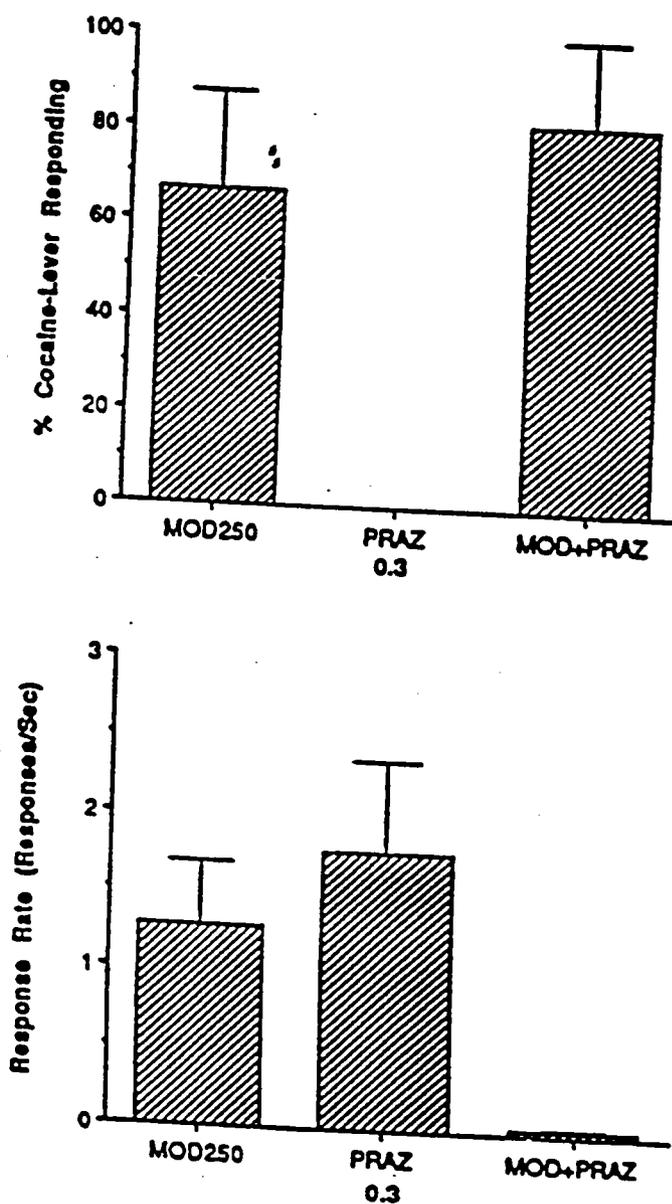


Figure 2. Mean (\pm SEM) percentage of cocaine-lever responding (upper panel) and response rates (lower panel) following administration of 250 mg/kg modafinil, 0.3 mg/kg prazosin and these doses of modafinil and prazosin in combination.

REINFORCING EFFECTS. Four rhesus monkeys were trained to self-administer cocaine (0.02 mg/kg/infusion in 1 monkey; 0.05 mg/kg/infusion in 3 monkeys) under a fixed-ratio 10 schedule of drug delivery. Using the standard substitution procedure, vehicle (ethanol-emulphor), saline, modafinil (0.03, 0.1, and 0.3 mg/kg/injection), d- amphetamine (0.01 or 0.03 mg/kg/injection), and l-ephedrine (0.1 mg/kg/infusions) were substituted for cocaine once stable responding (defined as: when 3 consecutive sessions were obtained in which the number of cocaine infusions did not vary more than 20% among sessions) were obtained. The test drugs were substituted for four consecutive days. In between substitution tests, the monkeys were returned to cocaine baseline conditions for at least 3 sessions.

Under baseline conditions, cocaine (0.02, 0.05 mg/kg/infusion) maintained rates of responding that was higher than that of saline vehicle in every animal (Figure 3, as copied from the sponsor's submission). The within session time course of cocaine infusions under baseline conditions are presented in Figure 4 (as copied from the sponsor's submission). In 3 of the 4 subjects, the greatest number of infusions occurred during the first quarter of the session; the fourth monkey, responding for cocaine was maintained at a similar rate throughout the entire session.

The results in Figure 3 clearly show that modafinil did function as a positive reinforcer; in all monkeys, at least one dose of modafinil maintained number of infusions above the range of infusions obtained for saline and vehicle. Modafinil at a dose of 0.3 mg/kg/injection was self-administered by all 4 monkeys; and 0.1 mg/kg/infusion modafinil was self-administered by two monkeys. These doses of modafinil were self-administered at rates equal to or greater than the rates of base-line cocaine infusions. Generally, as the dose of modafinil was increased, the number of infusions obtained first increased than decreased for the monkeys self-administering modafinil, resulting in an inverted U-shaped function relating infusion number to dose (figure 3). As the dose per infusion was increased, intake (mg/kg/1-hr session) of modafinil was generally increased; the mean intake of modafinil for all 4 monkeys ranged from 0.4 mg/kg to 34.7 mg/kg at the 0.03 mg/kg/infusion and 0.3 mg/kg/infusion, respectively (Figure 5; as copied from the sponsor's submission).

The pattern of responding maintained by modafinil is presented in figure 4. In some monkeys, modafinil (0.1 and 0.3 mg/kg/infusion) self-administration was the greatest in the first 2 quarters of the session; whereas in some monkeys it was distributed fairly evenly throughout the entire one hour session.

As a positive test, d-amphetamine and l-ephedrine were substituted for cocaine in 3 monkeys. Results presented in figure 6 (as copied from the sponsor's submission) clearly show that both d-amphetamine and l-ephedrine maintained rates of responding higher than that of saline; that is, they are positive reinforcers. In all 3 monkeys, the mean number of d-amphetamine and l-ephedrine infusions were comparable to the cocaine baseline.

To assess the role of the adrenergic system in the reinforcing effects of modafinil, antagonism test with prazosin was conducted. Prazosin (0.1 mg/kg) was administrated intravenously 15 minutes prior to the self-administration substitution session with modafinil (0.05 and 0.3 mg/kg/injection) or vehicle (1:1 ethanol:emulphor). Prazosin was without any significant effect on modafinil maintained behavior (Figure 7, as copied from the sponsor's submission).

CONCLUSION. Modafinil functioned as a positive reinforcer in primates and was psychoactive in rats. Modafinil substituted for cocaine in rats trained to discriminate cocaine from saline.

FIGURE 3. Reinforcing Effects of Modafinil in Primates.

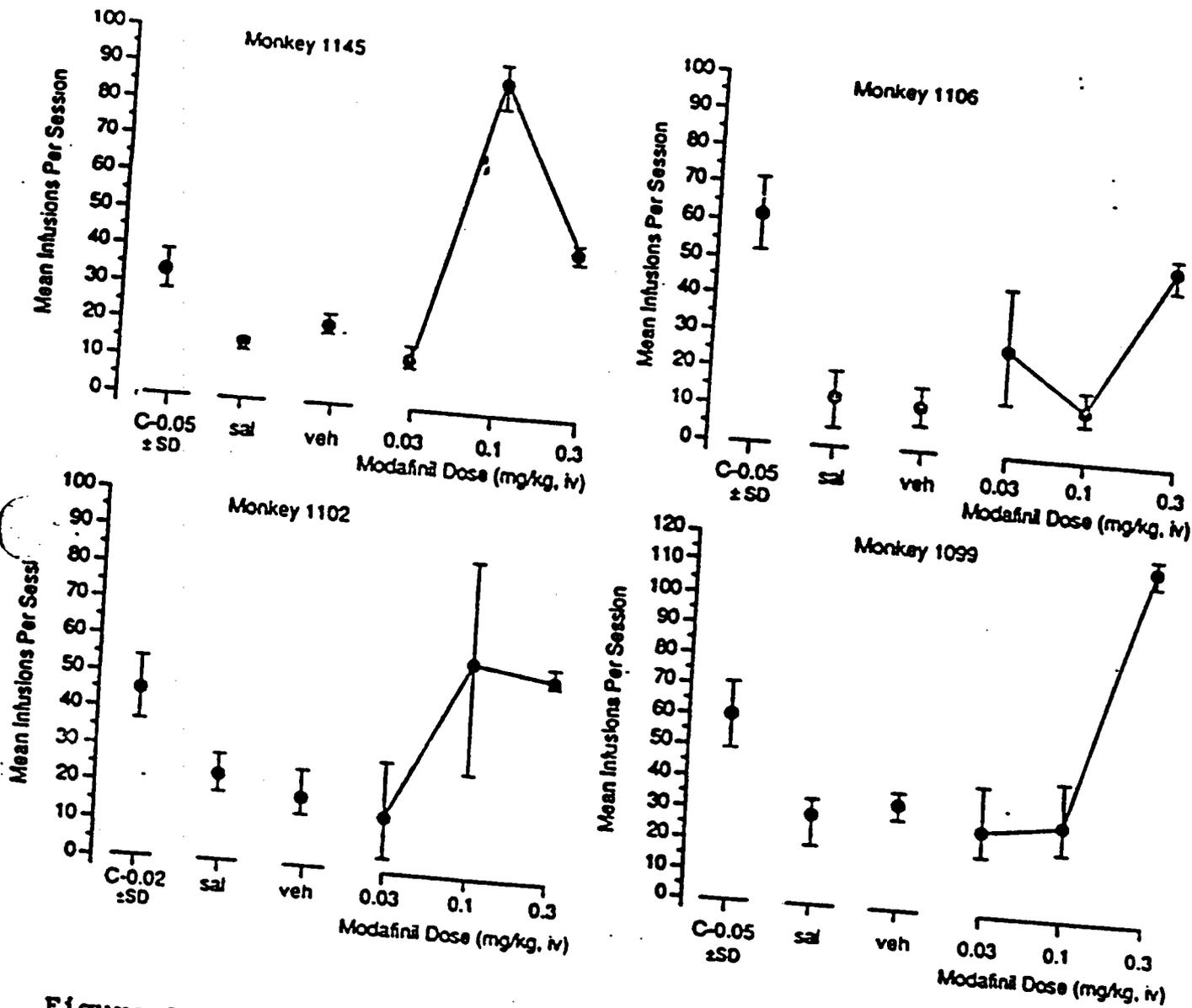


Figure 3. Results of substitution tests with saline, vehicle and three doses of modafinil in four individual rhesus monkeys trained to self-administer intravenous cocaine injections (0.02 or 0.05 mg/kg/infusion). Shown above C are the mean (\pm SD) rates of cocaine self-administration for the three sessions preceding all substitution tests. Other values represent the mean (\pm range) of the last three days of substitution tests with saline (sal), vehicle (veh) and various doses of modafinil. Note the difference in the ordinate scale for monkey 1099 (lower right).

FIGURE 4. Modafinil's Pattern of Responding in Cocaine Maintained Primates.

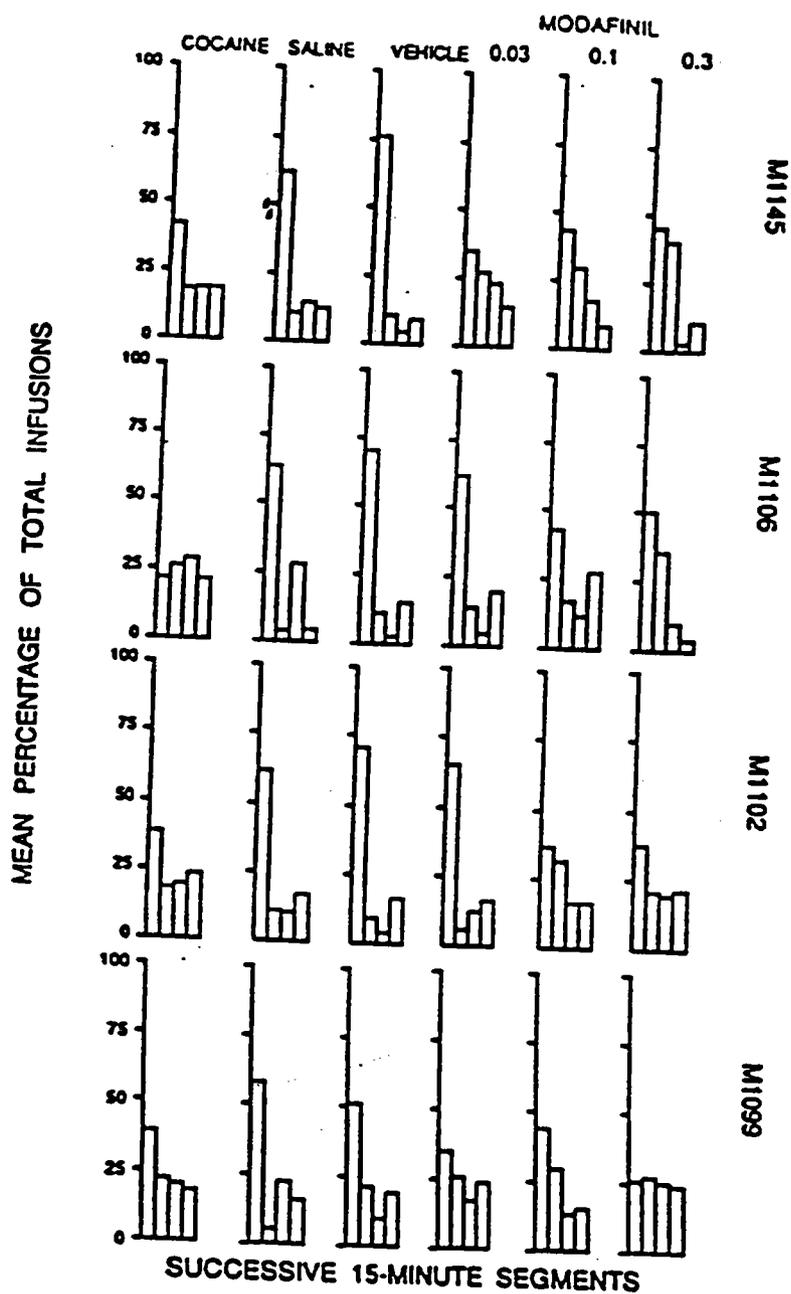


Figure 4. The within-session distribution of cocaine [0.02 mg/kg/infusion (M1102) or 0.05 mg/kg/infusion (M1145, M1106, M1099), saline, vehicle and modafinil (0.03, 0.1, 0.3 mg/kg/infusion) infusions for each of the 4 monkeys. Each bar represents the mean percentage of the total number of infusions obtained during each 15-min segment of the last three 1-hour sessions of each condition. Bars representing cocaine infusions are the mean for the last 3 days of all cocaine baseline sessions.

Study Report N° DRR-96-2: Study of the addictive properties of modafinil by intravenous drug self-administration.

Objective: To determine if modafinil can initiate and maintain self-administration behavior in rats.

The ability of modafinil, cocaine and vehicle (cyclodextrine) to initiate self-administration was evaluated in drug naive rats. Drug-naive rats were randomly assigned to one of six experimental groups:

GROUPS	TRAINING DRUG (DOSE)
1	Vehicle (cyclodextrine)
2	Modafinil (0.1 mg/injection)
3	Modafinil (0.2 mg/injections)
4	Modafinil (0.4 mg/injection)
5	Modafinil (0.6 mg/injection)
6	Cocaine (0.275 mg/injection)

The rats were surgically prepared with siliastic catheter (0.28 mm i.d.; 0.61 mm o.d.) under ether anesthesia. The external jugular vein was catheterized. Catheters were routed subcutaneously from the catheterized vein and exited in the mid scapular area.

The rats were trained to self-administer their respective training drug during daily 1-hr experimental sessions. Animals obtained infusions by poking their nose into the active hole within the operant chamber. During the acquisition phase (Day 1 to 11) of the study, a FR 1 schedule of reinforcement resulted in drug delivery. During day 11 to day 10, an inter-session progressive ratio schedule was initiated. During this period the FR requirement for drug infusion was progressively increased. The progressive ratio schedule was as follows: 2 days (Days 11 and 12) at FR 3; 3 days (Days 13 -16) at FR 6; and 3 days (Days 17-19) at FR 10.

Results presented in Figure 1 and 2 have shown that in comparison to cocaine, modafinil did not initiate self-administration during the acquisition phase of the study. As shown in figure 1, the number of injections significantly increased over the days and by the fifth day of acquisition, stable responding was observed. During the progressive ratio phase of the study, stable responding for modafinil was not observed. In contrast, as the FR value was increased in the cocaine group, the animals increased their responding in order to maintain a constant number of injections per session.

CONCLUSION. Modafinil did not initiate or maintain self-administration behavior in rats.

Study Report N° DRR-96-18: Study of the addictive potential of modafinil by drug-induced place conditioning.

Objective: To evaluate the abuse potential of modafinil in the drug-induced place preference model.

Drug-induced place conditioning is proposed to be a test that predicts the addictive potential of drugs since some drugs of abuse has been reported to induce a preference for the drug paired environment. This behavioral paradigm is conducted in an apparatus consisting of two boxes connected by a central alley. The two boxes differ in shape only. During conditioning, animals are injected, over alternative days, either with drugs or with vehicle. Drug injections are paired with one environment and vehicles injection are paired with the other environment. Animals that spend more time in drug-paired environment during testing phase are considered to have developed place preference.

Modafinil, at doses of 0, 32, 64, 128, and 256 mg/kg, was compared to d-amphetamine (0, and 2.0 mg/kg). Results from this study demonstrated that in contrast to d-amphetamine, modafinil was unable to induce a significant place preference.

CONCLUSION. In the conditioned place preference model for addictive potential, modafinil did not induce place preference.

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Overall Conclusion. Results from the preclinical studies conducted by Dr. Robert Balster suggest that modafinil does possess effects which potentially could lead to its abuse. Modafinil functioned as a positive reinforcer in primates and produced partial cocaine-like discriminative stimulus effects in rats. Modafinil, at doses of 0.1 and 0.3 mg/kg/infusion, maintained self-administration behavior. The rates and patterns of responding closely resembled those of the training dose of cocaine. Modafinil substituted for cocaine in 5 of 6 rats trained to discriminate 10 mg/kg of cocaine from saline. One rat treated with 150 mg/kg of modafinil generalized to cocaine; 4 of 6 rats generalized to the cocaine cue after receiving 250 mg/kg of modafinil. However, the rate of responding was suppressed at this high dose.

In contrast to the results from Dr. Balster's laboratory, preclinical studies conducted by Dr. Michel LeMoal did not suggest that modafinil has abuse potential. Modafinil did not initiate self-administration behavior in rats nor did it induce place preference. It is important to point out that despite the negative results from these studies, the potential of abuse of modafinil should not be ruled out. Negative results from the conditioned place preference model should be viewed with skepticism. This animal model of addictive properties of a drug is not a universal accepted model as a measure of the reinforcing effects of a drug. There are only a few laboratories that have been able to get this model to work with known drug of abuse; and some times these laboratories can not replicate their own work. Also, the fact that modafinil did not initiate self-administration behavior does not imply that it does not possess dependence-producing properties. Modafinil may be a potential drug of abuse in people with a history of stimulant abuse; as implied in the results from the self-administration study conducted in primates.

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CLINICAL ABUSE LIABILITY ASSESSMENT

The abuse potential of modafinil was evaluated in the following clinical trial.

Study N°: 1538a/201/AB/US

Title: AN EVALUATION OF POTENTIAL ABUSE LIABILITY OF ORALLY ADMINISTERED MODAFINIL USING METHYLPHENIDATE AS A REFERENCE AGENT (Phase B)

Clinical Investigators: [REDACTED]

Site: [REDACTED]

Objectives: To evaluate the potential abuse liability of orally administered modafinil using methylphenidate as a reference agent.

Study Design. Double blind, placebo controlled, 6x 6 latin square crossover, inpatient. Each drug evaluation session was separated by two washout days. Doses were chosen on the basis of the results of phase A, the dose ranging segment of the protocol. Each subject received two doses of methylphenidate (45 mg and 90 mg), three doses of modafinil (200, 400 and 800 mg), and placebo in a randomized, double-blind manner.

Each treatment was administered as one dose on the morning of the first day of each treatment session followed by a two day washout period.

Subjects. Male (n = 24; 30-46 years old) and female (n = 12; 30-40 years old) subjects with a history of polysubstance abuse that included cocaine.

Study Medication. Modafinil 100 mg tablets; modafinil placebo tablets; methylphenidate 45 mg capsules and methylphenidate placebo capsules. Patients received tablets and capsules during the study (combinations of 8 tablets plus 2 capsules per day).

SUBJECTIVE SCALE - SUBJECT RATING

1. **Addiction Research Center Inventory (ARCI):** 49 Item questionnaire contains 5 overlapping subscales derived from the original 102-item ARCI. Subject is instructed to select which 5 responses best describes how he feels right now. Response for each item was scored as follows: (= 1) "not at all", (= 2) "maybe", (= 3) "a little", (= 4) "moderately", (= 5) "an awful lot"

The subscales of the ARCI were:

- **Amphetamine Scale** consisting of 11 items that measure amphetamine-like effects (i.e., stimulant).
- **Benzedrine Group (BG)** consisting of 13 items that identify drugs with amphetamine-like properties.
- **Morphine-Benzedrine Group (MGB)** consisting of 16 items that identify drugs with euphoric properties.
- **Pentobarbital-Chlorpromazine-Alcohol Group (PCAG)** consisting of 15 items that identify drugs with sedative properties.
- **LSD-Specific Group** consisting of 14 items that identify drug with hallucinogenic and dysphoric properties.

2. **Drug Rating Questionnaire:** A 4-item questionnaire which ask the subject if she/he:

- Feel the drug
- Likes the drug
- Dislikes the drug
- Feel high

For each item the subject was to indicate how she/he felt at the time by darkening a circle along a continuous line of 42 circles (equivalent to a 100-mm visual scale). The scale was anchored with descriptors "not at all" and "awful a lot"

3. **Drug Identification Questionnaire:** This is a ten-item questionnaire where the subject is asked if the drug felt like that of other drugs (i.e., morphine, chlorpromazine, LSD, amphetamine, PCP, valium, barbiturate, etc). For each item, the subject is instructed to select which of 5 responses best describes how he feels right now. Response for each item is scores as follows; "not at all" (= 1), "maybe" (= 2), "a little" (= 3), "moderately" (= 4), and "an awful lot" (= 5).

4. **Specific Drug Effect Questionnaire:** This is a 22-item questionnaire that ask the subject if the drug is producing certain drug effects (i.e., skin itching, sleepiness, nervousness, dizziness, depression, hallucinations, etc.). For each item the subject and the observer were instructed to select one of five responses that best described how she/he felt at the time of assessment. The responses were scored as follows: not at all (= 1); maybe (= 2); a little (= 3), moderately (= 4) and a lot (= 5).

SUBJECTIVE SCALES - OBSERVER RATING:

1. **Drug Rating Questionnaire:** A 4-item questionnaire asks the observers if subject feel the drug, likes the drug, dislikes the drug, or feel high. For each item the subject was to indicate how she/he felt at the time by darkening a circle along a continuous line of 42 circles (equivalent to a 100-mm visual scale). The scale was anchored with descriptors "not at all" and "awful a lot".
2. **Specific Drug Effect Questionnaire:** A 22-item questionnaire that ask the observer if the subject has certain drug effects (i.e., skin itching, sleepiness, nervousness, dizziness, depression, hallucinations, etc.). For each item the subject and the observer were instructed to select one of five responses that best described how she/he felt at the time of assessment. The responses were scored as follows: not at all (= 1); maybe (= 2); a little (= 3), moderately (= 4) and a lot (= 5).

OTHER MEASURES:

1. **Sleep Log:** The actual (observed) and estimated (subject) hours of sleep on the day of dosing were determined between 6:00 pm of each dosing day until 6:00 am the following day.
2. **Calorie Count:** Total estimated calories for the noon meal and evening meal.
3. **Physiologic Measures:** The following measures were obtained prior and following drug administration:
 - Pupil size
 - Supine and standing blood pressure and pulse rate
 - Body temperature
 - Respiratory rate
4. **Safety Assessments**
5. **Adverse Events**

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RESULTS.

On the Amphetamine (Stimulant) Subscale in the males group, maximal response for modafinil 800 mg was observed at 1 hour, being greater than that of modafinil 200, modafinil 400 and placebo and a short stimulant effect is noticed within the first hour after the administration of 800 mg of modafinil (Table 1, Fig. 1). On the same Scale in the female group the maximal responses for modafinil 200 mg and 800 mg were greater than that of placebo (Table 2, Fig.2).

Table 1. Changes from baseline score for the amphetamine scale (n = 24, males).

Hour	MEAN CHANGE FROM BASELINE					
	Placebo	ME 45 mg	ME 90 mg	MO 200 mg	MO 400 mg	MO 800 mg
0	20.1	19.9	19.9	21.5	21	20.6
0.5	-0.4	1.5	1.8	-0.7	0.9	2.3
1	0.4	2.5	5.1	0	0.6	2.1
1.5	0.1	2.7	2.9	-0.5	0.3	0.6
2.5	0.3	2.4	2.9	-1	-0.3	0.8
4	0.1	0.8	2.2	-0.3	-0.9	0.1
6	-0.1	0.6	1.5	-1.2	-0.9	-0.3
11	0.1	1.1	0.6	-1.3	-1.8	-0.4
23	-0.2	0.8	2.6	-1.3	-0.8	-1.3

FIGURE 1.

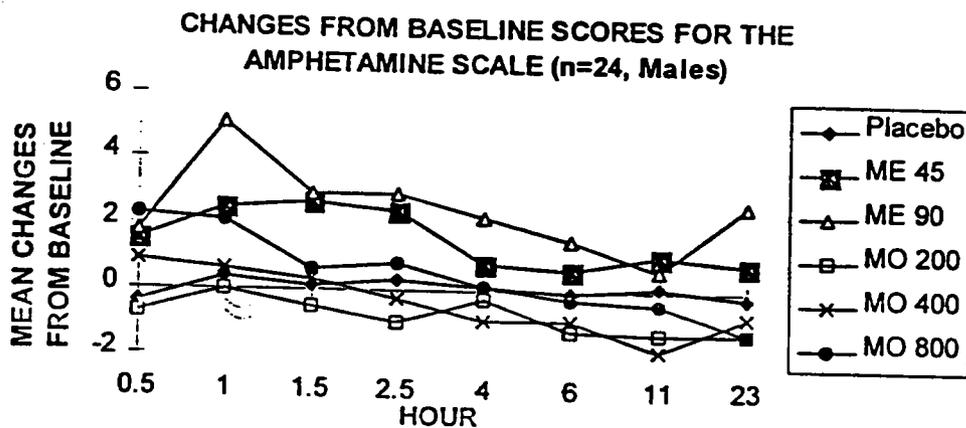
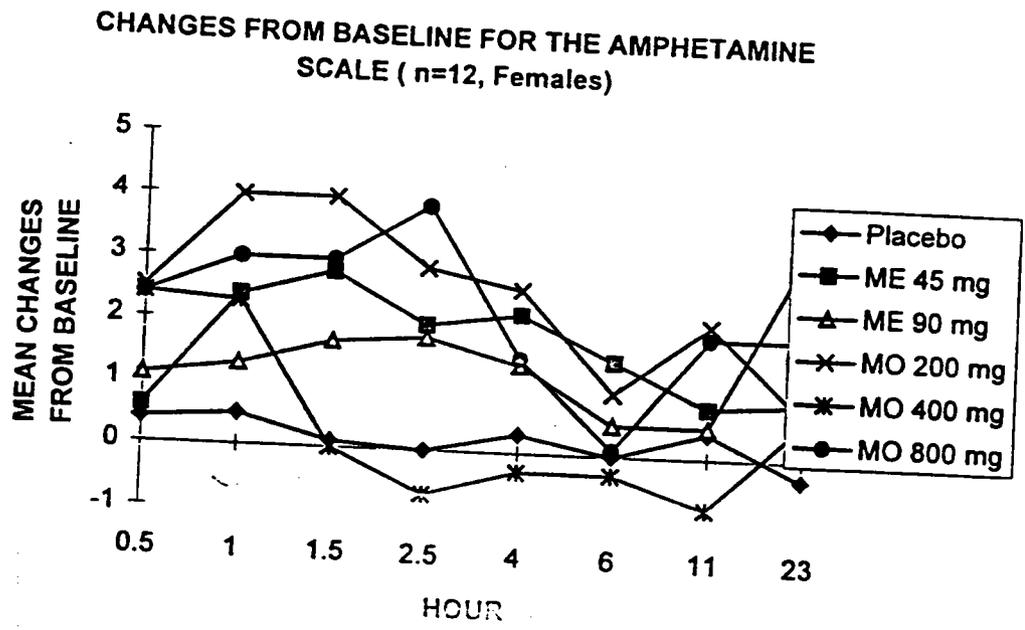


Table 2. Changes from baseline score for the amphetamine scale (n = 12, females)

Hour	MEAN CHANGE FROM BASELINE					
	Placebo	ME 45 mg	ME 90 mg	MO 200 mg	MO 400 mg	MO 800 mg
0	18.4	17	17.6	17.5	17.8	17.6
0.5	0.4	0.6	1.1	2.5	2.4	2.4
1	0.5	2.4	1.3	4	2.3	3
1.5	0.1	2.8	1.7	4	0	3
2.5	0	2	1.8	2.9	-0.7	3.9
4	0.3	2.2	1.4	2.6	-0.3	1.5
6	0	1.5	0.5	1	-0.3	0.1
11	0.4	0.8	0.5	2.1	-0.8	1.9
23	-0.3	0.9	3.3	0.7	0.6	1.9

FIGURE 2.



On the Benzedrine (Stimulant) Subscale of the ARCI, modafinil was not identified as an amphetamine-like by the male subjects (Table 3, Fig. 3). Methylphenidate 90 mg was identified as a stimulant within 1 hour post-dosing. In contrast, the female subjects, identified modafinil 200 mg as a stimulant (Table 4, Fig. 4). The maximal response for modafinil 200 mg was observed at 1.5 hours and it was greater than that of modafinil 400 mg.

Table 3. Changes from baseline score for the benzedrine scale (n = 24, males)

Hour	MEAN CHANGE FROM BASELINE					
	Placebo	ME 45 mg	ME 90 mg	MO 200 mg	MO 400 mg	MO 800 mg
0	11.3	12.1	11.5	13.5	12.3	12.6
0.5	-1.6	0.1	0.1	-2.1	-1	-0.4
1	-0.1	-0.3	1.4	-1.8	-0.5	-0.2
1.5	-0.1	0.2	-0.9	-1.9	-0.8	-1.6
2.5	0.9	0.1	-0.3	-2.4	-1	-1.4
4	0.2	-1.5	0.3	-0.8	-1.1	-2.1
6	-0.3	-0.3	-0.7	-2.2	-1.5	-2.4
11	0.1	0.8	0.6	-1.5	-2	-2.8
23	-0.5	-0.3	2.5	-2.5	-0.9	-2.4

FIGURE 3.

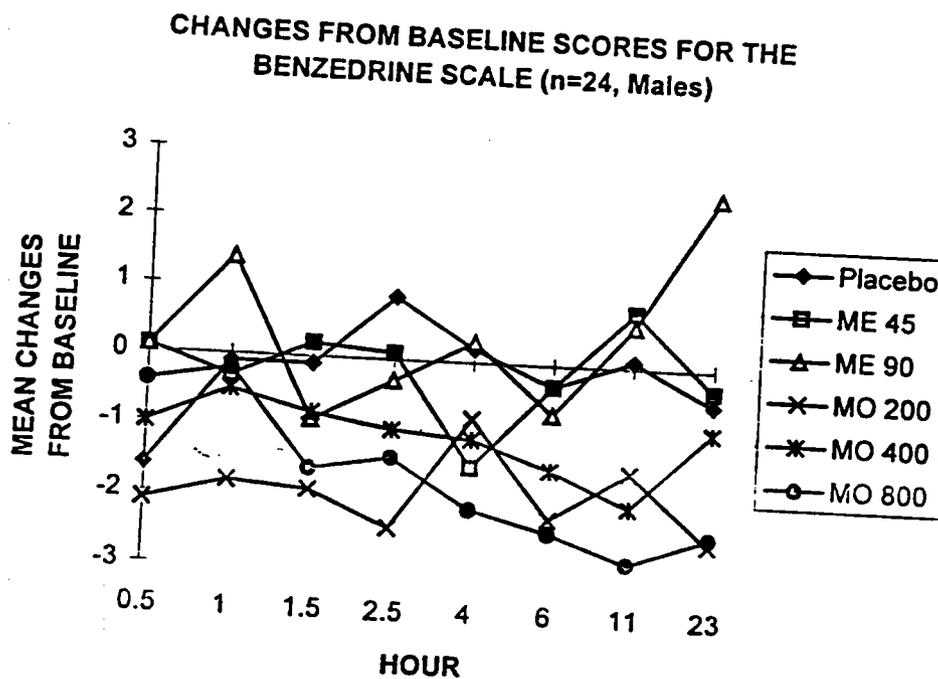
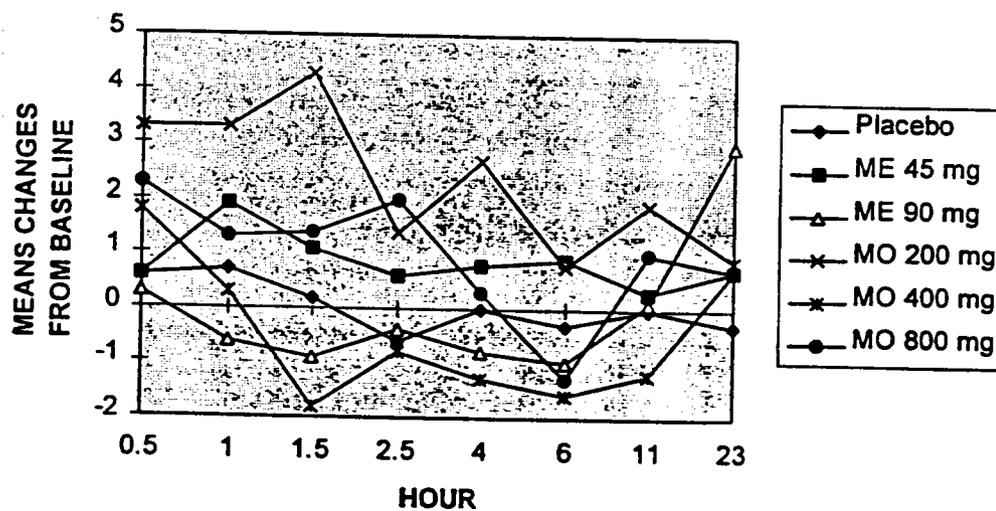


Table 4. Changes from baseline score for the benzedrine scale (n = 12, females)

Hour	MEAN CHANGE FROM BASELINE					
	Placebo	ME 45 mg	ME 90 mg	MO 200 mg	MO 400 mg	MO 800 mg
0	11.6	10.1	10.4	10.6	10.9	10.2
0.5	0.6	0.6	0.3	3.3	1.8	2.3
1	0.7	1.9	-0.6	3.3	0.3	1.3
1.5	0.2	1.1	-0.9	4.3	-1.8	1.4
2.5	-0.6	0.6	-0.4	1.4	-0.8	2
4	0	0.8	-0.8	2.7	-1.3	0.3
6	-0.3	0.9	-1	0.8	-1.6	-1.3
11	0	0.3	0.1	1.9	-1.2	1
23	-0.3	0.7	3	0.9	0.7	0.7

FIGURE 4.

CHANGES FROM BASELINE SCORES FOR THE BENZEDRINE SCALE (n = 12, Females)



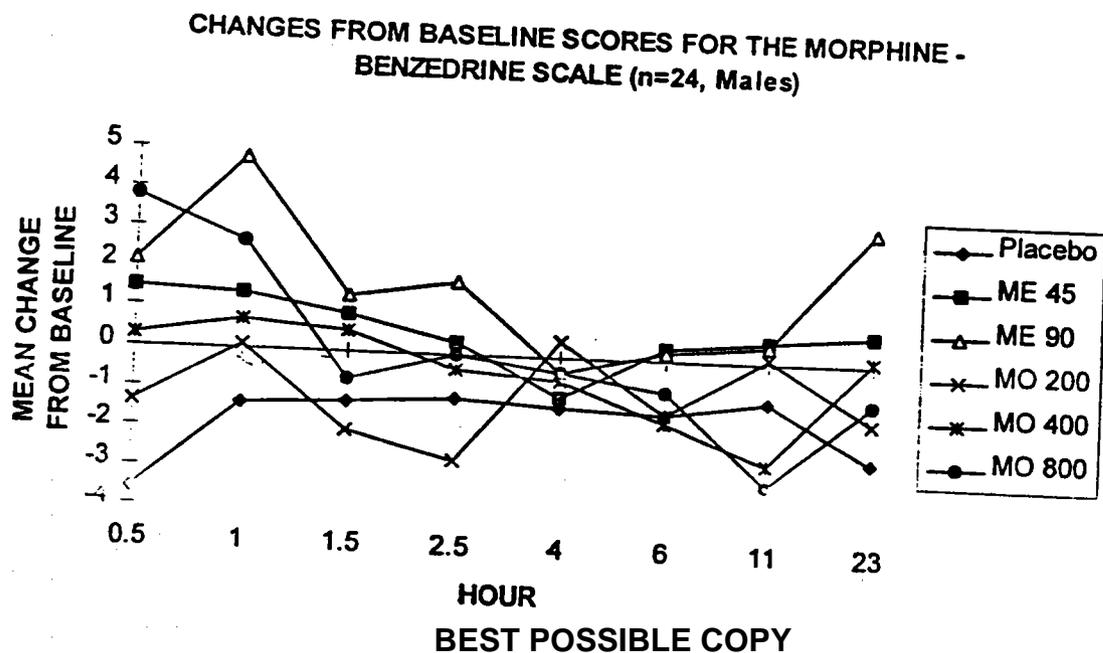
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On the Morphine -Benzedrine (Euphoria) Scale of the ARCI, in the male group modafinil 200 and modafinil 400 mg produced negative responses (Table 5, Fig.5). A dose-dependent effect for this measure was apparent for both methylphenidate and modafinil. As observed in the amphetamine scale the peak effect for modafinil 800 mg occurred within 1 hr. The response for modafinil 800 mg was between that of methylphenidate 45 mg and methylphenidate 90 mg. In the female group, the response for modafinil 800 mg was greater than both methylphenidate doses and modafinil 400 mg. (Table 6, Fig. 6). Consistent with the results on the Benzedrine and Amphetamine Scales, no dose-dependent pattern of effects was apparent for modafinil in this scale.

Table 5. Changes from baseline score for the morphine-benzedrine scale (n = 24, males).

Hour	MEAN CHANGE FROM BASELINE					
	Placebo	ME 45 mg	ME 90 mg	MO 200 mg	MO 400 mg	MO 800 mg
0	33.1	32.3	31.8	33.6	31.5	32.9
0.5	-3.6	1.5	2.2	-1.4	0.3	3.8
1	-1.4	1.4	4.8	0.1	0.7	2.7
1.5	-1.3	0.9	1.4	-2	0.5	-0.7
2.5	-1.1	0.3	1.8	-2.7	-0.4	0
4	-1.3	-1	-0.4	0.4	-0.6	-0.4
6	-1.4	0.3	0.2	-1.4	-1.6	-0.8
11	-1	0.5	0.4	0.1	-2.6	-3.1
23	-2.5	0.7	3.3	-1.5	0.1	-1

FIGURE 5.



On the Pentobarbital-Chlorpromazine-Alcohol (Sedation Scale of the ARCI), in both males and females the maximum responses for all doses of methylphenidate and modafinil were similar to that of placebo.

On the Lysergic Acid Diethylamine (Dysphoria or hallucinogenic) Scale in males, both modafinil 800 mg and methylphenidate 90 mg produced similar dose-response curves (Table 7, Fig. 7). The response for methylphenidate 90 mg was greater than that of modafinil 800 mg. In females, the response for modafinil 800 mg was greater than that of methylphenidate 45 mg (Table 8, Fig. 8).

Table 7. Changes from baseline score for the lysergic acid diethylamide scale (n = 24, males)

Hour	MEAN CHANGE FROM BASELINE					
	Placebo	ME 45 mg	ME 90 mg	MO 200 mg	MO 400 mg	MO 800 mg
0	0.8	0	0.5	-0.5	0.3	0.1
0.5	0.5	1.8	2.3	3.3	3.8	3.2
1	0.1	4.7	8.1	3.1	2.4	3.5
1.5	-0.1	5.5	10.2	4	3	5.4
2.5	0.2	5	8.8	2.9	2.1	6
4	-0.7	2.3	7.1	1.2	2.4	5.1
6	-0.3	0.2	3.3	1.5	2.3	4.9
11	-0.4	-0.2	1	0.6	1.7	4.8
23	-0.4	-0.8	-1.1	0.8	0.8	1

FIGURE 7.

CHANGES FROM BASELINE SCORE FOR THE LSD SCALE
(n=24, Males)

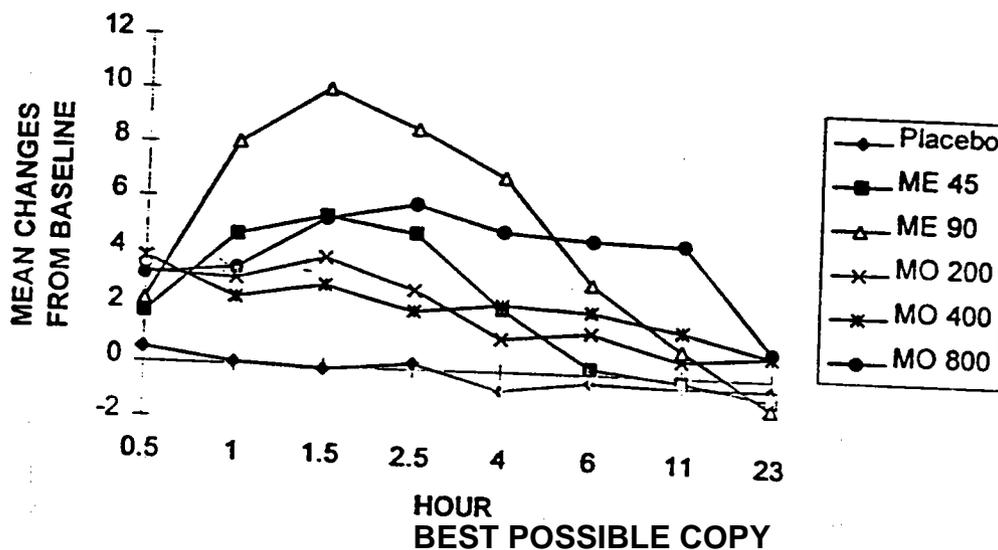
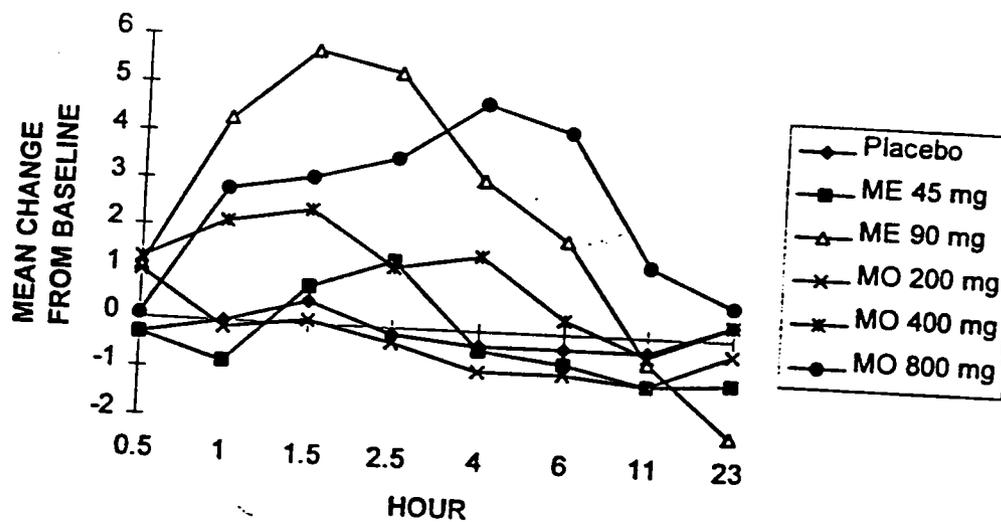


Table 8. Changes from baseline score for the lysergic acid diethylamide scale (n = 12, females)

Hour	MEAN CHANGE FROM BASELINE					
	Placebo	ME 45 mg	ME 90 mg	MO 200 mg	MO 400 mg	MO 800 mg
0	2.2	3.3	3.1	2.3	2.4	2.6
0.5	-0.3	-0.3	1.1	1	1.3	0.1
1	0	-0.8	4.3	-0.1	2.1	2.8
1.5	0.5	0.8	5.8	0.1	2.4	3.1
2.5	-0.1	1.4	5.4	-0.3	1.3	3.6
4	-0.3	-0.4	3.2	-0.8	1.6	4.8
6	-0.3	-0.6	2	-0.8	0.3	4.3
11	-0.3	-1	-0.5	-1	-0.4	1.5
23	0.3	-0.9	-2	-0.3	0.3	0.7

FIGURE 8

CHANGES FROM BASELINE SCORE FOR THE LSD SCALE
(n = 12, Females)



The Drug Rating Questionnaire is a 4-item questionnaire in which the subject indicates "drug liking", "drug disliking" and if "felt the drug's effect" and whether "felt high". To the question "Feel the drug", in males, both doses of methylphenidate and the 800 mg dose of modafinil were discriminated from placebo and the maximum effect for modafinil 800 mg which is achieved at 1 hour was intermediate to that of methylphenidate 45 mg and 90 mg (Fig.9). In the female group the response observed for modafinil 800 mg was greater than that of methylphenidate 45 mg and 90 mg and a dose-dependent effect was observed for modafinil and methylphenidate (Fig.10).

FIGURE 9.

**CHANGES FROM BASELINE SCORES FOR
DRUG RATING- 'Feel the Drug'- (n=24, Males)**

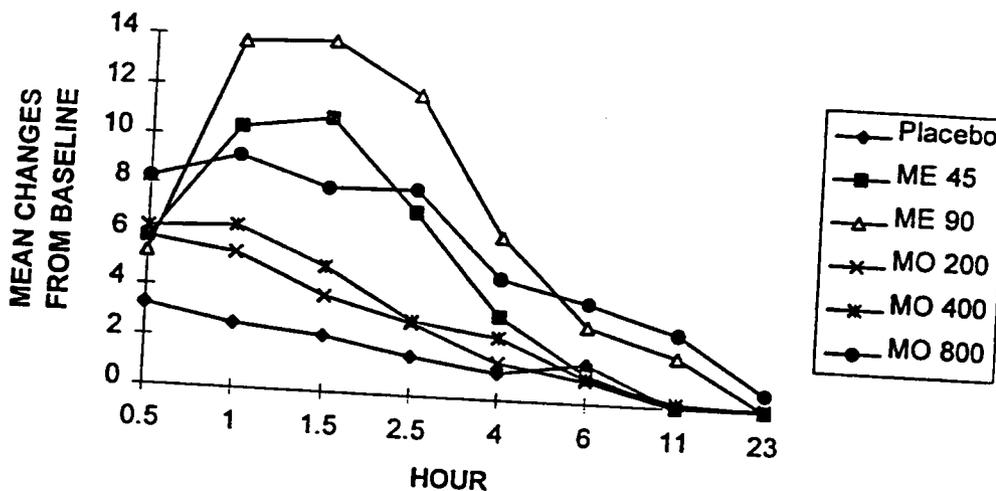
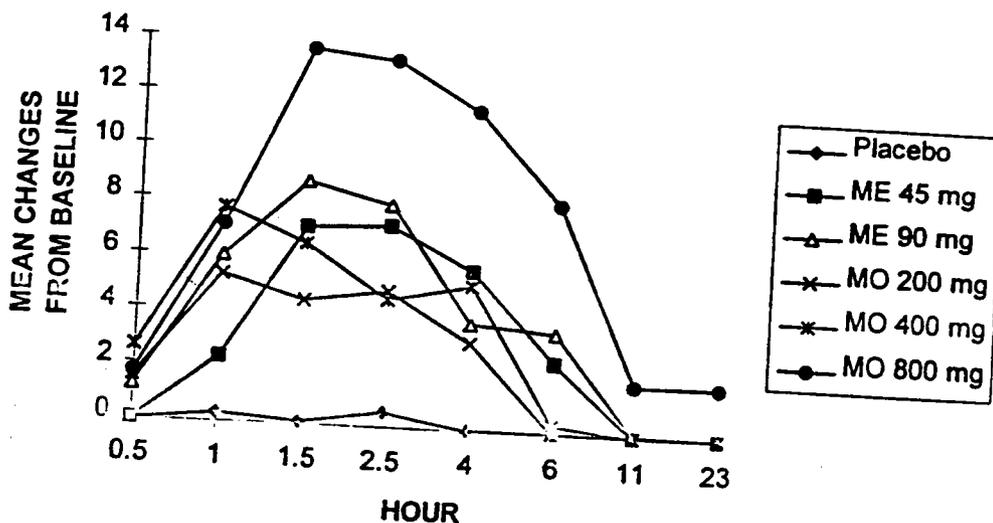


FIGURE 10.

**CHANGES FROM BASELINE SCORE FOR DRUG RAITING- "
Feel the Drug"- (n =12, Females)**



To the question "Like the drug effect", in males, a dose-dependent effect for this measure was apparent for both methylphenidate and modafinil and the response for modafinil 800 mg was similar to that of methylphenidate 90 mg and the maximal response was achieved at 1 hr (Fig. 11). In the female group, the maximum responses for modafinil 200 and 400 mg were slightly higher than those of both dose of methylphenidate (Fig. 12). The maximal response for modafinil 800 mg was higher than the response produced by methylphenidate 90 mg and occurred at 2.5 hours.

FIGURE 11.

CHANGES FROM BASELINE SCORE FOR DRUG RATING - Like
the Drug Effect- (n= 24, Males)

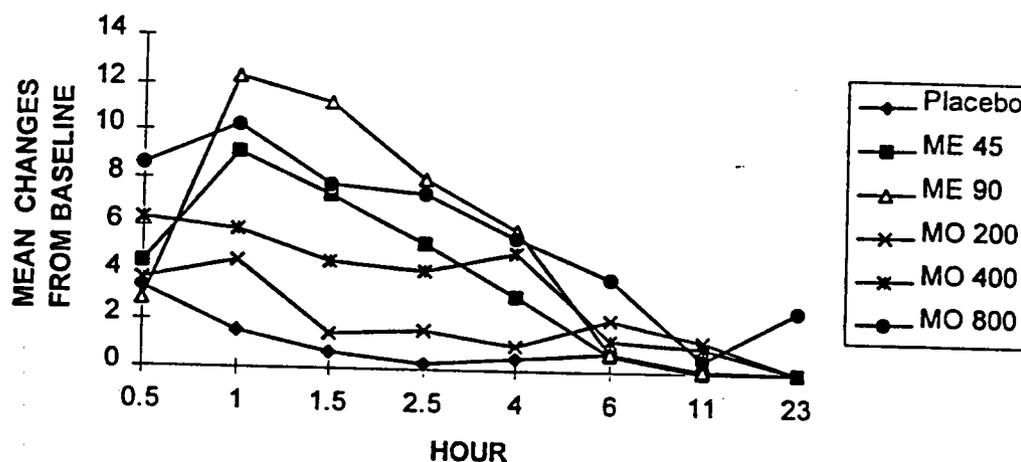
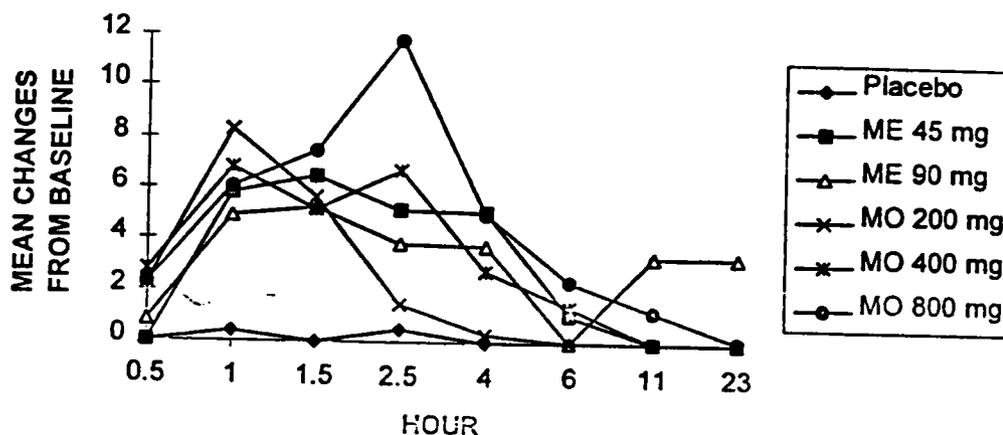


FIGURE 12

CHANGES FROM BASELINE SCORE FOR DRUG RATING - "
Like the Drug Effect"- (n=12, Females)



To the question "Dislike the drug effect", in males, the response obtained for modafinil 800 mg was similar to that of methylphenidate 90 mg and the maximum responses for all modafinil doses were lower than those produced by both methylphenidate doses (Fig. 13). In females, the responses for modafinil 400 mg and 800 mg were similar to those of methylphenidate 45 and 90 mg respectively (Fig. 14).

FIGURE 13.

CHANGES FROM BASELINE SCORE FOR DRUG RAITING-
"Dislike the drug effect"- (n=24, Males)

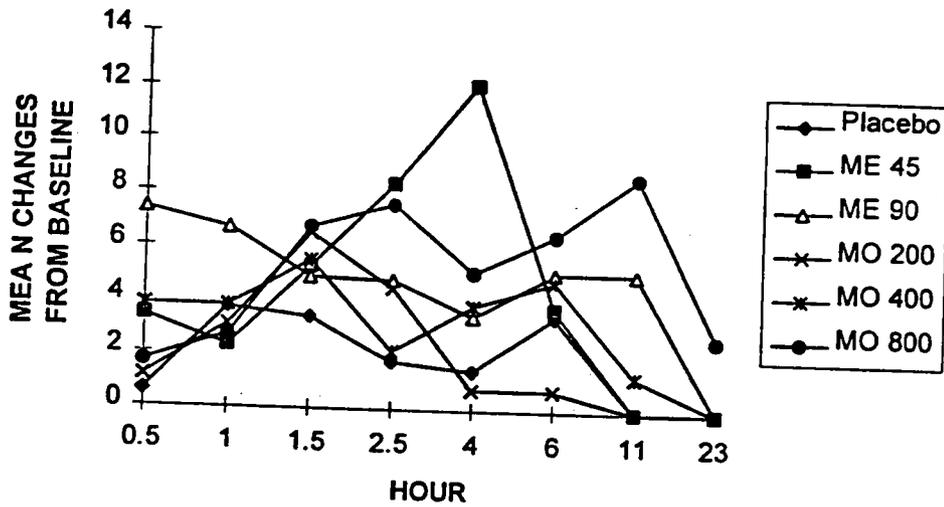
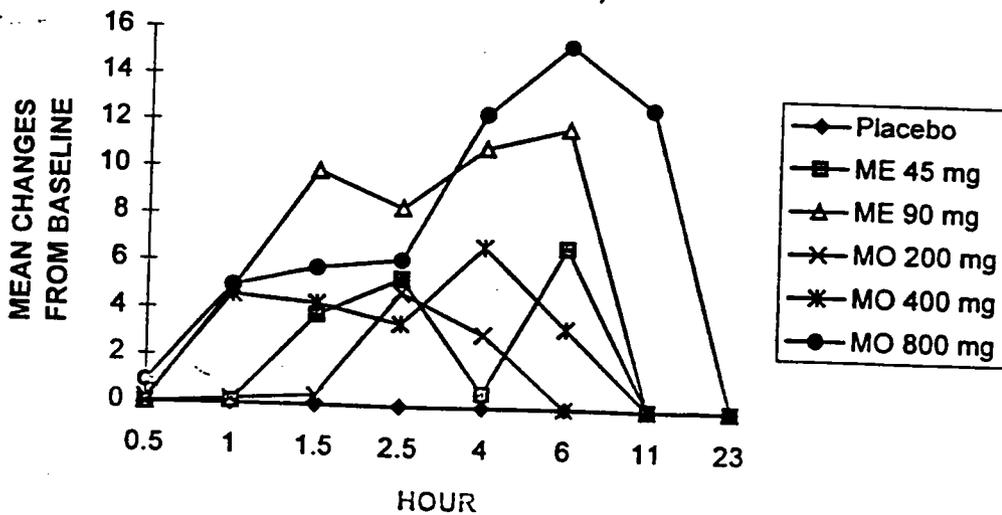


FIGURE 14.

CHANGES FROM BASELINE SCORE FOR DRUG RAITING-
"Dislike the drug effect"-
(n =12, Females)



To the question "Do you feel high", in males, a dose-dependent effect for this measure was apparent for both methylphenidate and modafinil. Both doses of methylphenidate and the 800 mg dose of modafinil produced statistically significant elevations compared to placebo (Fig. 15). The response for modafinil 800 mg was intermediate to that of methylphenidate 45 mg and 90 mg and greater than modafinil 200 mg. In females, also a dose-dependent effect for this measure was apparent for both methylphenidate and modafinil and the response for modafinil 800 mg was greater than both methylphenidate doses and modafinil 200 and 400 mg (Fig.16).

FIGURE 15.

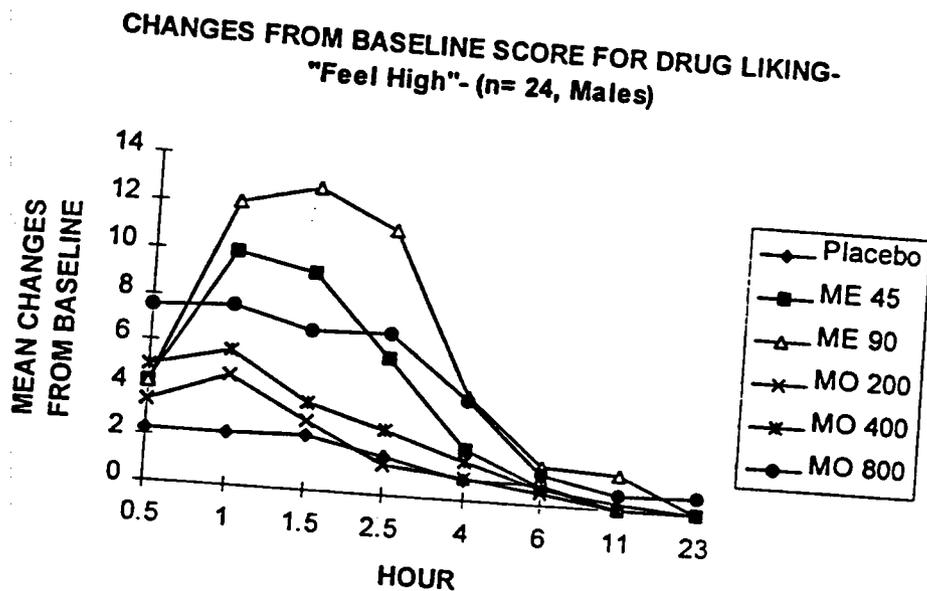
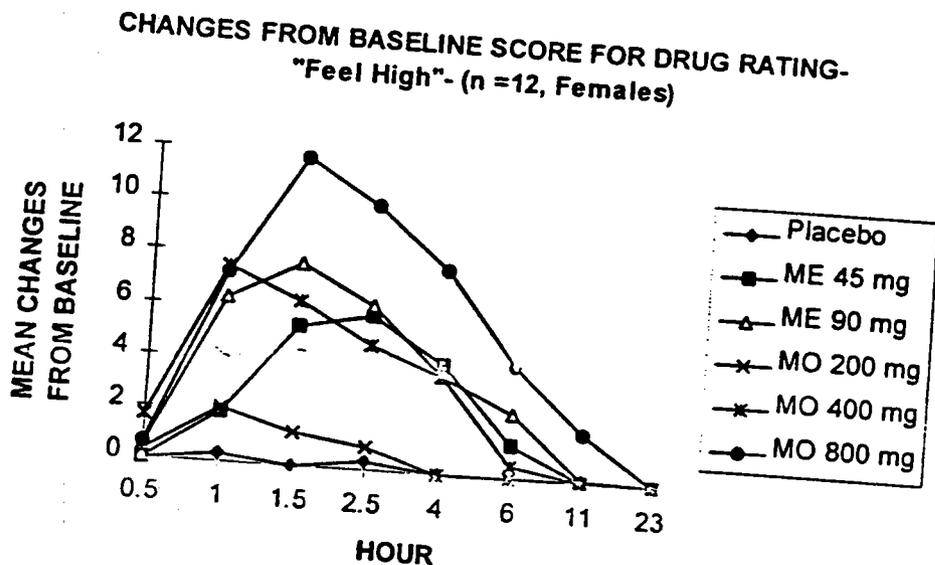


FIGURE 16.



Drug Identification. In the male subjects, the effects of both methylphenidate and modafinil were predominantly identified as stimulant-like, with positive identifications reported by the majority of subjects for both doses of methylphenidate and for modafinil 400 mg and 800 mg. 17 subjects (71%) out of 24 recognized modafinil 800 mg as stimulant; 14 (58%) out of 24 recognized modafinil 400 mg as stimulant and 10(42%) out of 24 recognized modafinil 200 mg as stimulant. For methylphenidate 90; 20 subjects (83%) recognized this dose as stimulant and for methylphenidate 45 mg, 19 (79%) recognized it as an stimulant dose. The second most common identification of both methylphenidate and modafinil was as "downers", although these identifications were only slightly greater than placebo.

Drug Response Questionnaire. In drug response questionnaire, male and female subjects reported "body feels different, changed", "nervous" and "stomach turning" following administration of methylphenidate and modafinil compared to placebo. Subjects also reported a "need to talk" following all active doses with the exception of modafinil 200 mg. Fewer male subjects reported feeling "sleepy" or "relaxed" following modafinil dosing compared to placebo and methylphenidate. In females, modafinil 400 mg and 800 mg resulted in a greater number of reports of "full of energy" and modafinil 200 mg had increased reports of "stomach turning" and modafinil 800 mg had increased reports of "afraid". In the same questionnaire the observer evaluation differ from the male subjects in that included more reports of "talking", "nervous" and "anxious" and fewer reports of "nodding" for methylphenidate and modafinil; and fewer reports of "sleepy" and greater responses of "active" occurred for modafinil compared to methylphenidate and placebo. The observer, also reported for the female group a greater number of "talking" responses and fewer "sleepy and "nodding" for methylphenidate and modafinil. More "active" responses were observed following administration of modafinil.

Both methylphenidate and modafinil produced dose-dependent reductions in the number of observed and reported hours of sleep relative to placebo in male and female subjects. Also, reduction of appetite was assessed by caloric intake count. In both groups, all doses of methylphenidate and modafinil reduced caloric intake at the noon meal relative to placebo, and methylphenidate 90 mg and modafinil 400 and 800 mg produced statistically significant reduction on combined caloric consumption at the noon and evening meals compared to placebo.

Physiological Measures. For both groups no notable changes in pupil size were observed following administration of methylphenidate or modafinil compared to placebo. Both methylphenidate and modafinil produced dose-dependent increases in supine and in standing diastolic and systolic blood pressure. In supine systolic and diastolic blood pressure, the effects produced by modafinil 400 and 800 mg were generally similar to those produced by methylphenidate 45 mg. The increases produced by methylphenidate 90 mg were consistently higher than those produced by modafinil, with statistically significant greater values than modafinil 200 and 400 mg. A positive correlation between blood pressure and standing pulse rate was observed for methylphenidate and modafinil.

CONCLUSION.

Results from this clinical study demonstrated that modafinil produced psychoactive and euphoric effects and feelings consistent with other scheduled CNS stimulants. Also, a gender difference was observed on some of the subjective measures following modafinil treatment. On the Amphetamine Subscale, both males and females reported that modafinil elicited stimulant-like responses. In male subjects, modafinil produced stimulant and euphoric effects with a very rapid onset in a dose-dependent manner. The responses of 800 mg of modafinil were in general intermediate to methylphenidate 45 and 90 mg. Females reported that 200 and 800 mg of modafinil elicited stimulant effects. The responses elicited by 200 and 800 mg of modafinil were greater than those observed with placebo and methylphenidate 45 and 90 mg. On the Benzedrine (Stimulant) Subscale, only the females reported that modafinil elicited stimulant-like effects at a dose of 200 mg. The peak time of stimulant effects were similar to methylphenidate (90 mg); The maximal response for modafinil (200 mg) was observed at 1.5 hours, while the maximal response for methylphenidate (90 mg) was 1.0 hours post-dosing.

Results from the Pentobarbital-Chlorpromazine-Alcohol (Sedation Scale) Subscale were similar to those observed with placebo. Modafinil and methylphenidate did not elicit sedative-like effects.

Some dysphoric effects were associated with modafinil. On the Lysergic Acid Diethylamine (Dysphoric or Hallucinogenic) Subscale, both 800 mg of modafinil and 90 mg of methylphenidate produced elicited similar dose-response curves.

These studies demonstrated that on subjective measures of abuse liability in male subjects, modafinil produced stimulant and euphoric effects with a very rapid onset in a dose-related manner. Also, in this group, the responses for modafinil 800 mg were in general intermediate to methylphenidate 45 and 90 mg. Although, in female subjects, no dose related effects were observed for modafinil 200 mg and 400 mg on subjective measures of abuse liability, modafinil produced stimulant and euphoric effects; and it was recognized as a stimulant by the majority of subjects.

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EVALUATION OF MODAFINIL'S ADVERSE EFFECTS

Adverse Events Following Withdrawal of Therapy:

Effects of discontinuation from modafinil were assessed in pivotal efficacy and safety studies, wherein patients were taken off drug during a 2-week period before the open label extension period. Frequency of new AEs was comparable between subjects discontinued from placebo (2 subjects), 200 mg/d modafinil (3 subjects), and 400 mg/d modafinil (2 subjects). Patients who completed the 9 week double-blind phase, or who terminated for reasons other than noncompliance or a medication related AE, then participated in a 2-week double-blind withdrawal phase before entering the open label phase. Patients were randomized to a withdrawal period as follows: 20% in the 400 mg/d group; and 20% in the 200 mg/d group.

The Adverse Event profile for the withdrawal phase was not significantly different for patients who were withdrawn from modafinil treatment compared to those who continued to receive placebo. There was no specific evidence of an amphetamine-type withdrawal syndrome. However, there was an indication of slight worsening excessive daytime sleepiness, based on MWT results, for patients withdrawing from either dose of study drug.

Effects of discontinuation from modafinil were also assessed in Parkinson's disease patients (Study 917) and normal subjects (Study p1424). As seen in the pivotal efficacy and safety studies, no withdrawal syndrome was associated with modafinil. Parkinson's disease patients treated with 200 or 300 mg/d of modafinil for 21 days experienced no withdrawal symptoms during a 7-day observation period. Likewise, normal subjects treated with 200 to 1000 mg of modafinil for 7 days were observed during a withdrawal period of 3 days. The only AE possibly related to withdrawal was drowsiness occurring in 7/8 patients who completed dosing in the 1000 mg/d group.

Adverse reactions reported in the postmarketing surveillance database mainly from France and a few (very) from Belgium and Italy that are deemed by the reviewer to be either likely or possibly related to the administration of modafinil as listed in Table 3. The vast majority of these subjects were using modafinil for the treatment of narcolepsy. No deaths or withdrawal reactions were reported in the database.

Denominator data estimated by the sponsor at the time of this review are approximately 1800 patients since its restricted marketing in France 1994. Forty-seven (47) total events were reported, 28 occurring in men, and 19 in women (the disease tends to affect more men than women). There were no reports of death or withdrawal reactions. Information regarding concomitant medicines are often incomplete. The vast majority of events were reported in the 100 to 400 mg range for modafinil (2 events at 500 mg, and one at 600 mg).

The body system with the greatest number of adverse events was the CNS with 16 likely/possible. Eight of these 16 were either nervousness/anxiety/agitation. The body system with the next most frequent mention was the gastrointestinal system, with 9 likely/possible, 4 of these 9 being dry mouth. The systems in diminishing order of frequency follows: cardiovascular with 6 events (4 of the 6 being tachycardia); dermatologic with 4 events (all 4

being rashes of various sorts); endocrine/metabolic with 4 events; musculoskeletal with 3 events; and various miscellaneous events comprising 5 events (including 2 cases of increased sweating). Additionally, although not mentioned in the firm's NDA database of possible adverse reactions, there was one interesting case of an apparent decrease in the effect of cyclosporine due to modafinil.

WHO Adverse Reactions database, up to July 1997, was reviewed as well. There appears to be no discernible pattern of events from this table and causation was difficult to establish. The only "new" events listed that were not in the firm's own database are: urinary incontinence, dyskinesia, malaise, hypertension, and tinnitus.

ADVERSE EVENTS ASSOCIATED WITH DROPOUTS.

The most commonly observed AE's in modafinil-treated subjects (not seen at an equivalent incidence in placebo-treated subjects) were: headache, nausea, diarrhea, dry mouth, anorexia, nervousness, dizziness, rhinitis, and pharyngitis (Table 5). Most frequent AEs in modafinil-treated subjects compared to subjects on placebo were headache and nausea. AEs of clinical concern that resulted in discontinuation from study were primarily cardiovascular related.

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Table 5 . AEs in Subjects Who Discontinued Due to AEs - By COSTART Terms

Body System COSTART Term	Subjects Discontinued Due to Specified AE N (%)							
	Cephalon Phase 3 DB		Cephalon Phase 1/ 2		Foreign NA/HS		Foreign non-NA/HS	
	M N=369	P N=185	M N=232	P N=61	M N=533	P N=103	M N=1171	P N=701
NERVOUS SYSTEM	109(30)	41 (22)	109 (47)	20 (33)	86 (16)	8 (8)	419 (36)	167 (24)
Nervousness	30 (8)	12 (6)	33 (14)	3 (5)	23 (4)	1 (<1)	86 (7)	31 (4)
Insomnia	11 (3)	2 (1)	25 (11)	1 (2)	19 (4)	2 (2)	123 (11)	32 (5)
Anxiety	13 (4)	1 (<1)	10 (4)	1 (2)	6 (1)	1 (<1)	87 (7)	20 (3)
Somnolence	7 (2)	4 (2)	27 (12)	16 (26)	6 (1)	2 (2)	26 (2)	29 (4)
CNS Stim	0(0)	0 (0)	4 (2)	0 (0)	7 (1)	0 (0)	78 (7)	22 (3)
Sleep Disorder	2 (<1)	3 (2)	0 (0)	0 (0)	9 (2)	1 (<1)	52 (4)	21 (3)
BODY AS A WHOLE	247 (67)	121 (65)	113 (49)	8 (13)	53 (10)	11 (11)	209 (18)	81 (12)
Headache	183 (50)	74 (40)	95 (41)	6 (10)	23 (4)	3 (3)	101 (9)	33 (5)
Asthenia	6 (2)	3 (2)	17 (7)	1 (2)	9 (2)	2 (2)	57 (5)	27 (4)
Infection	51 (14)	29 (16)	2 (<1)	0 (0)	0 (0)	2 (2)	6 (<1)	1 (<1)
Abdominal Pain	16 (4)	7 (4)	7 (3)	1 (2)	5 (<1)	1 (<1)	41 (4)	6 (<1)
DIGESTIVE	143 (39)	45 (24)	85 (37)	5 (8)	32 (6)	3 (3)	143 (12)	50 (7)
Nausea	47 (13)	7 (4)	47 (20)	2 (3)	8 (2)	0 (0)	46 (4)	14 (2)
Anorexia	17 (5)	2 (1)	25 (11)	1 (2)	6 (1)	0 (0)	32 (3)	4 (<1)
Dry Mouth	19 (5)	1 (<1)	20 (9)	1 (2)	7 (1)	0 (0)	30 (3)	9 (1)

Aes ASSOCIATED WITH LONG TERM USE: Forty of 478 (8%) subjects discontinued due to AEs in the Phase 3 open label studies compared to 5% in the Phase 3 db studies. This small difference is likely due to the significantly longer duration of the open label trials (52 weeks vs 9 weeks). AEs leading to discontinuation were similar in the double blind and open label studies. 17 of the 478 (4%) subjects in the open label studies discontinued because of nervous system AEs: including nervousness (7 subjects), anxiety (4), depression (3) and

cataplexy (2 subjects). Other long term studies (1 year or longer) resulted in 7 of 10 subjects withdrawing or being discontinued due to the following AEs: salivation disorders, restless legs, nausea, anxiety and "internal tension".

In another study, 319 subjects received 50 to 600 mg per day, and readjusted most commonly to a maintenance dose in the 100 to 300 mg/d range. Duration of treatment ranged from 1 month to 10 years. 81 subjects received modafinil for 1 year or greater and 37 subjects received modafinil for 3 years or greater. 67 Subjects reported a total of 319 AEs: including irritability, sleep disorders, headaches, and gastric pain. 10 Subjects withdrew for the following Aes: depression, gastric pain, asthenia, dyspnea, nervousness, cutaneous eruption, anorexia and "poor tolerance." There were 3 serious AEs: myocardial infarction, cranial trauma and abdominal surgery for stenosis.

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