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Reinforcing Effects of Extended Inhalation of a Low Nitrous Oxide Concentration in Humans

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DOHRN, C. S., J. L. LICHTOR, D. W. COALSON, D. FLEMMING AND J. P. ZACNY. *Reinforcing effects of extended inhalation of a low nitrous oxide concentration in humans.* PHARMACOL BIOCHEM BEHAV 46(4) 927–932, 1993.—The reinforcing, subjective, and psychomotor effects of 30 min of inhalation of 20% nitrous oxide were determined in 12 healthy volunteers using a choice paradigm with 100% oxygen as placebo. Nitrous oxide was chosen on only 22% of choice occasions, indicating that, in general, this concentration did not function as a reinforcer. Nitrous oxide produced changes in mood, but had no effect on psychomotor performance. Three out of the 12 subjects chose nitrous oxide on at least two out of the three choice sessions, and during a poststudy debriefing interview, reported pleasant effects of the drug. The other nine subjects reported unpleasant acute effects of the drug (e.g., drowsiness) or residual (postsession) effects of the drug which, they said, influenced their drug choice. The present results are compared to those results obtained in a previous study in which higher concentrations of nitrous oxide (30 and 40%) also produced relatively low choice rates. The apparent lack of reinforcing effects of extended inhalation of nitrous oxide is discussed.

Nitrous oxide Reinforcer Subjective effects Psychomotor performance Mood Human

NITROUS oxide (N_2O) is an inhaled drug that is commonly used in medical and dental practice for its anesthetic, amnestic, analgesic, and anxiolytic effects. It produces a spectrum of subjective effects that can differ among individuals and includes euphoria, dysphoria, confusion, stimulation, relaxation/sedation, a dreamy-like, reverie state, disorientation, derealization, and increased body awareness (2,5,6,13–15,19,26,28,30). Nitrous oxide is used recreationally by some humans (16,21), and serves as a reinforcer in nonhumans (18,33). Previous studies in our laboratory have examined the reinforcing effects of 30% and 40% nitrous oxide in humans (13). Forty percent N_2O was chosen on only 22% of all possible choice occasions, whereas 30% N_2O was chosen on 42% of all possible choice occasions. Although choice rates were generally low with both of these concentrations, the 30% N_2O choice rate was significantly higher than the 40% N_2O choice rate. It is conceivable, then, that choice rates would be even higher with a still lower dose of N_2O.

The present study was designed to examine the reinforcing efficacy of 20% N_2O, compared to oxygen (placebo). Such a study, in conjunction with our previous study, would allow us to determine if the reinforcing effects of N_2O are concentration related. Twenty percent is a low concentration by clinical standards: a survey of over 1000 dental cases in which N_2O was used revealed that the mean concentration delivered to patients was 38% (20). The effects of 20% N_2O on mood and psychomotor performance have been investigated in a number of studies: most studies have documented that it alters mood (7,14,23) and psychomotor performance (4,8,17,23,32), although several studies have failed to detect an effect on one or both parameters (14,15,17).

METHOD

Subjects

Twelve healthy volunteers (six females, six males) were recruited. Candidates, aged 21–35 years old, who consumed at least one alcoholic drink per week, were scheduled for a screening interview with one of the research personnel. At the interview, potential subjects completed the SCL-90 (10) and a health questionnaire to judge their psychiatric and medical status. During the psychiatric interview, if it was ascertained that candidates had any significant psychiatric problems [including any history of drug- or alcohol-related problems or

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Axis I psychiatric disorders (1)], they were excluded. The subjects underwent a physical exam and resting electrocardiogram (EKG). Volunteers with significant medical disorders (including past adverse reaction to general anesthesia) and females who were pregnant or were planning to become pregnant during the course of the study were excluded (pregnancy tests were administered as a screening procedure in females prior to the study). Subjects were paid for their participation upon completion of the study. The study was approved by the local institutional review board. Informed consent was obtained during a practice session. The consent form described details of the study. To keep subjects blind as to the compound being studied, subjects were told in the consent form that the agents being studied might come from one of six classes, in gaseous or aerosol form—sedative, stimulant, general anesthetic (at subanesthetic concentrations), opiate, alcohol, or placebo.

Experimental Procedures

There were seven sessions in this experiment, and sessions were separated from each other by at least 48 h. Subjects were instructed to abstain from all drugs (excluding their normal amounts of caffeine and nicotine) for 24 h prior to sessions. The first four sessions were sampling sessions, and the last three were choice sessions. Each of the seven experimental sessions consisted of three periods: baseline (BL), inhalation (INH), and recovery (REC). Mood and psychomotor performance were assessed at fixed times throughout each period. Upon arrival in the laboratory on each session, noninvasive monitoring apparati were placed on the subject so that we could measure pulse, blood pressure, EKG, and arterial oxygen saturation during the session. An anesthesia mask was then placed over the subject's nose and mouth by the anesthesiologist, and the BL period began. Subjects were told that the air they were breathing was drug free. Subjects breathed oxygen during this period, which rarely exceeded 5 min. The 30-min INH period then commenced. During the four sampling sessions, half the subjects were randomly assigned to inhale 20% N_2O on days 1 and 3 and 100% oxygen on days 2 and 4. The order was reversed for the other subjects. At the start of the INH period of the sampling sessions, subjects were informed that the air they would be inhaling for the next 30 min may or may not contain drug. For each subject, the mood forms that they filled out in the study were color coded and remained consistent for each agent. The subjects were instructed during the sampling sessions to note the form colors and to try to associate each of the two colors with the effects of the agents inhaled. Prior to the BL measurement period of the three choice sessions, subjects chose which agent they wished to inhale during the INH period based on the color. In both the sampling and choice sessions, following the INH period, the anesthesiologist took the mask off the subject, and the 60-min REC period commenced. During this time the subject remained seated.

Dependent Measures

Choice. The agent that the subject chose, i.e., drug or placebo, was the primary dependent measure in this study.

Subjective effects. The Addiction Research Center Inventory (ARCI) is a true-false questionnaire (49 items) designed to differentiate among different classes of psychoactive drugs (24). The 49 items yielded scores for five different scales: PCAG (pentobarbital-chlorpromazine-alcohol group), a measure of sedation; BG (benzedrine group), and A (amphetamine), measures of stimulant effects; LSD (lysergic acid diethylamide), a measure of somatic and dysphoric effects; and MBG (morphine-benzedrine group), a measure of euphoria. The ARCI was completed at BL, 15 min into the INH period, and 5, 30, and 60 min after the REC period had commenced.

The Visual Analog Scale (VAS) measured mood states on a form that had 10 100-mm lines, each labeled with an adjective (stimulated, high, dizzy, nauseous, down, tingling, hungry, anxious, happy, and sedated). Subjects were instructed to place a mark on each line indicating how they felt at the moment, ranging from 'not at all' to 'extremely.' The VAS was completed at BL, 2, 15, and 29 min into the INH period, and 5, 30, and 60 min after the REC period had commenced.

On the Intrasession Drug Effects/Liking questionnaire, subjects were asked to rate the intensity of the agent's effect as they were currently feeling it on a scale of 1 to 5 (from 1 = "I feel no effect at all" to 5 = "I feel a very strong effect"), and to indicate their current degree of liking of the drug effects on a 100-mm line (0 = dislike a lot; 50 = neutral; 100 = like a lot). Liking was arbitrarily defined as ≥ 60 mm on this scale, neutrality was defined as ≥ 41 mm and ≤ 59 mm, and disliking the agent was defined as ≤ 40 mm. These ranges were defined by previous observations (13,14) that liking ratings for placebo substances rarely exceeded the 40–60 mm limits. The Intrasession Drug Effects/Liking questionnaire was completed at BL, 2, 15, and 29 min into the INH period, and 5, 30, and 60 min after the REC period had commenced.

Psychomotor/cognitive performance. The Digit Symbol Substitution Test (DSST) is a simple pen-and-paper test that provides a general measure of psychomotor performance (31). It has also been shown to be sensitive to the effects of a number of CNS-active drugs (11,12). In this 1-min test, subjects replaced digits with an appropriate symbol. The appropriate symbols for each digit were changed for each administration of the test to reduce any learning effect. The score was the number of symbols drawn by the subject. In the eye-hand coordination test, the subjects traced a randomly moving target on a computer screen with a small cross for 1 min (25). The cross was controlled by a computer mouse, operated by the dominant hand. The dependent measure was coordination mistakes, which was assessed by counting the number of times the cross exceeded a certain distance (1 cm) from the target. These two psychomotor tests were completed at BL, 15 min into the INH period, and 5, 30, and 60 min after the REC period had commenced.

Debriefing comments. At the end of the study, a debriefing session was held in which subjects were asked to characterize the effects of the different agents they had inhaled during sampling sessions, and more importantly, to tell us in their own words what prompted their choices.

Data Analysis

Chi-square analyses were performed to determine whether subjects chose nitrous oxide significantly more or less often than chance. Data from the four sampling sessions of the experiment were analyzed using a repeated measures analysis of variance (ANOVA). Separate ANOVAs were used for each of the subjective effects scales and the psychomotor tests (DSST and eye-hand coordination). The three factors were concentration (i.e., drug vs. placebo), replications (first vs. second exposure to an agent), and time. An effect was considered significant if $p \leq 0.05$. Huynh-Feldt adjustments of

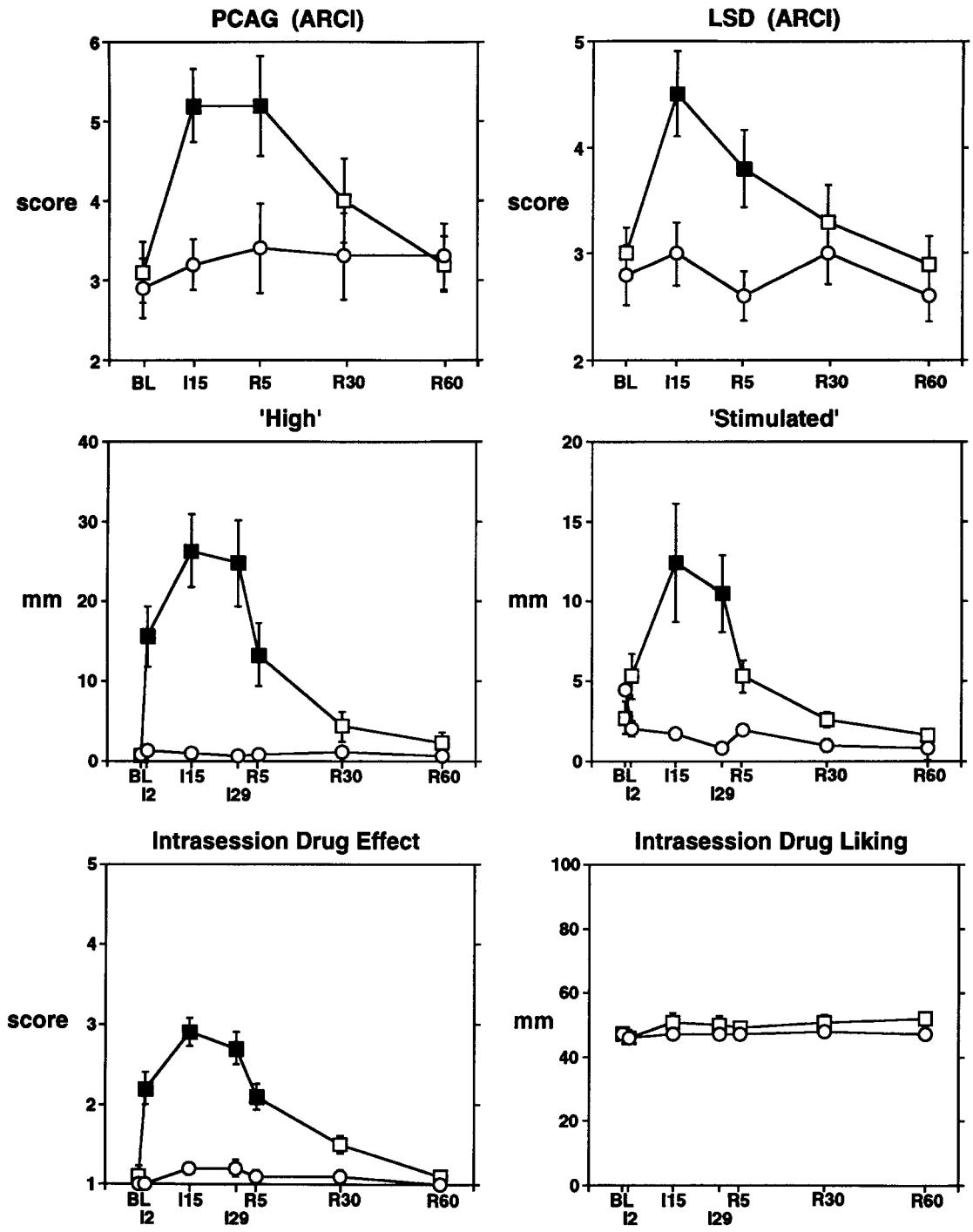

FIG. 1. Time course of the effects of oxygen (circle) and 20% N_2O (□) on scores from the PCAG (top left frame) and LSD (top right frame) scales from the ARCI, ratings from the 'high' (middle left frame) and 'stimulated' (middle right frame) visual analog scales, and scores from the drug effect question (bottom left frame) and ratings from the drug liking scale (bottom right frame) of the Intrasession Drug Effects/Liking questionnaire. Each point is the mean across 12 subjects. Time point BL refers to baseline; I2, I15, and I29, respectively, refer to 2, 15 and 29 min after inhalation began; R5, 30 and 60, respectively, refer to 5, 30, and 60 min after the INH period had ceased. Solid symbols indicate that 20% N_2O is significantly different from placebo (i.e., oxygen) at a given time point (using a Tukey post hoc comparison test). Brackets indicate SEM.

within-factors degrees of freedom were used to protect against violations of symmetry assumptions. For the sake of brevity, Time effects will not be reported. When significant (e.g., $p \leq 0.05$) concentration × time interactions were obtained, Tukey post hoc comparisons of oxygen responses vs. drug responses were made at each time point in a session.

RESULTS

Six females and six males (mean age: 26.7; range: 21-31) completed the experiment. Subjects consumed an average of 4.7 (± 3.2) alcoholic beverages per week. Three subjects smoked tobacco daily and two subjects had smoked marijuana within the last month. Lifetime drug use of our subjects included use of stimulants (one subject), sedatives (three subjects), hallucinogens (five subjects), prescribed opiates (nine subjects), and cannabis (nine subjects). One subject had previously used N_2O recreationally (via Whippets®).

Drug choice. On the majority of choice occasions, placebo was chosen over 20% N_2O. Out of 36 choice occasions, subjects chose nitrous oxide only eight times (22% choice rate), which is significantly lower than chance levels ($\chi^2 = 5.6$, $p < 0.05$). Only 1 out of 12 subjects chose nitrous oxide three times, 2 subjects chose it twice, and 1 subject chose it once. It is interesting to report that two of the three subjects who chose N_2O at least twice were those subjects who were current marijuana users. The subject who had used N_2O recreationally in the past did not choose N_2O in the present study.

Subjective effects. Scores on the PCAG [concentration × time: $F(4, 44) = 3.8$, $p < 0.05$] (Fig. 1, top left frame) and LSD [concentration × time: $F(4, 44) = 5.6$, $p < 0.005$] (Fig. 1, top right frame) scales of the ARCI increased during inhalation of 20% N_2O and gradually returned to baseline levels during the recovery period.

Ratings of 'dizzy' [concentration × time: $F(6, 66) = 4.2$, $p < 0.05$]; 'high' [concentration × time: $F(6, 66) = 13.0$, $p < 0.001$] (Fig. 1, middle left frame); 'sedated' [concentration × time: $F(6, 66) = 3.5$, $p < 0.05$]; 'stimulated,' $F(6, 66) = 5.6$, $p < 0.01$ (Fig. 1, middle right frame); and 'tingling' [concentration × time: $F(6, 66) = 3.9$, $p < 0.01$] increased during inhalation. Except for 'dizzy' ratings which peaked 2 min after onset of gas inhalation, ratings peaked 15 min after onset of gas inhalation and remained at that level for the duration of the INH period. All subjective effects of N_2O returned to baseline levels by the end of the REC period.

Subjects reported an increase in strength of drug effect during inhalation of N_2O [concentration × time: $F(6, 66) = 27.3$, $p < 0.001$] (Fig. 1, bottom left frame). Ratings increased 2 min after onset of gas inhalation, peaked 13 min later, and remained at the peak level for the rest of the INH period before declining gradually during the REC period. Overall ratings of 'liking' did not change significantly during or after inhalation of 20% N_2O (Fig. 1, bottom right frame). However, the three subjects who chose N_2O at least two times in the choice sessions reported liking N_2O during the sampling session.

Psychomotor effects. Subjects' performance was not impaired by 20% N_2O on either the eye-hand coordination test or the DSST.

Debriefing comments. Table 1 summarizes comments subjects made during the debriefing session when asked about their choices during choice sessions. What is evident is the striking degree of concordance between subjects' description of N_2O (either its acute or residual effects) and whether they were likely to choose it during choice sessions.

TABLE 1

SUBJECTS' DEBRIEFING COMMENTS REGARDING DRUG CHOICE

Subject	
1 (1)	Chose oxygen 2/3 times because the other agent made her feel tired.
2 (0)	Chose oxygen because he would always prefer to feel straight.
3 (0)	N_2O made him feel less than 100% for the rest of the day.
4 (2)	N_2O felt like alcohol, he liked it, and found it to be pleasant.
5 (0)	N_2O had a strong disorienting effect and she did not want to feel anything during the sessions.
6 (2)	N_2O had pleasant effects.
7 (3)	N_2O felt okay, made him feel lightheaded and good.
8 (0)	Didn't want to feel sleepy and N_2O made her feel sleepy.
9 (0)	N_2O was sort of pleasant but he preferred to feel clear headed. Also, he didn't like the environment and the fact that he was being studied and nobody else was doing it.
10 (0)	N_2O produced an uncomfortable feeling, she did not feel in control of her thoughts.
11 (0)	N_2O made her want to sleep for the rest of the day.
12 (0)	Doesn't like getting stoned, which is how N_2O made her feel. Compared it to alcohol except N_2O had a much quicker onset.

In parentheses are the number of times 20% N_2O was chosen during the three choice sessions.

DISCUSSION

Over the course of three experiments, N_2O ranging in concentrations from 20-40% did not function as a reinforcer in the majority of healthy volunteers tested. There was a subpopulation of subjects tested in both this and a previous study (13) in which N_2O appeared to function as a reinforcer. Subjective effects indicated that these subjects liked the effects of the agent. On the other hand, the majority of subjects did not like, nor choose N_2O. Further, in the present study, the debriefing comments of the subjects who did not choose N_2O were concordant with their choice of placebo in that they self-reported experiencing acute or residual dysphoric effects of the drug during the sampling sessions.

What might account for this discrepancy between our laboratory results and a) results obtained in animal studies in which N_2O does function as a reinforcer (18,33), b) N_2O's known abuse liability in humans (16,21), c) N_2O's acceptance by dental patients (20,29), and d) those laboratory studies that have focused on the subjective effects of N_2O and have found predominantly a spectrum of "pleasant" subjective effects [e.g., (3,6,15)]. Admittedly, it is not clear why there is this discordance, although we have several speculations. First, although N_2O does function as a reinforcer in animals, factors in the human milieu can attenuate drug choice. For example, setting is a powerful modulating variable in the subjective effects of some drugs in that a social setting promotes a more positive spectrum of subjective effects of the drug than does an isolated setting (9,22). Time of day is another factor to consider because most nondrug-abusing humans tend to self-administer recreational drugs in the evening (i.e., at the end of the day). Because of practical considerations, we could not conduct sessions in the evening. It is possible that N_2O choice would have

been increased in our studies had the drug been administered in a social environment and/or in the evening. In fact, one of our subjects stated that the setting was not conducive to taking N_2O. Also, had the drug been given in the evening, fatigue may not have been an issue to those subjects who reported acute or residual fatigue from the gas. In regards to the widespread acceptance of N_2O in dental settings, dental patients may find the effects of N_2O to be tolerable, if not pleasant, because it functions as a means to escape or avoid aversive stimulation (e.g., anxiety engendered by dental procedures). In our study, aversive stimulation was not present, but perhaps if it had (e.g., some sort of stressor presented periodically during the INH period), higher choice rates would have been obtained. Finally, while there are some studies demonstrating predominantly "pleasant" effects from the drug in healthy normals, there are as many studies, if not more, which demonstrate there are individual differences in how subjects react to N_2O, with some subjects showing dysphoric or unpleasant effects from the drug [e.g., (5,23,26,28,30)].

In conclusion, we have shown that extended inhalation of 20% N_2O did not function as a reinforcer in the majority of healthy normal volunteers tested. This result systematically replicates findings obtained from a previous study in which concentrations of 30 and 40% N_2O were tested (13). Apparently, decreasing N_2O concentrations from 30% to lower concentrations does not increase the reinforcing effects of N_2O, as we had originally surmised. Future studies should be directed at examining whether there are variables that would increase the reinforcing effects of extended inhalations of N_2O (e.g., drug history, instructional set, subject's ability to titrate concentration), as well as examining the effects of briefer exposures to N_2O across a wider range of concentrations. This latter study would be especially relevant to conduct because N_2O is often used recreationally via procedures (e.g., Whippets®), which involve very brief inhalations of the drug (21,27).

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REFERENCES

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (DSM-III-R), 4th ed. Washington, DC: American Psychiatric Association; 1987.
2. Atkinson, R. M.; Morozumi, P.; Green, J. D.; Kramer, J. C. Nitrous oxide intoxication: Subjective effects in healthy young men. J. Psychedel. Drugs 9:317–328; 1977.
3. Atkinson, R. M.; Green, J. D.; Chenoweth D. E.; Atkinson, J. H. Subjective effects of nitrous oxide: Cognitive, emotional, perceptual and transcendental experiences. J. Psychedel. Drugs 11:317–330; 1979.
4. Berry, C.; Gelder, M.; Summerfield, A. Experimental analysis of drug effects on human performance using information theory concepts. Br. J. Psychol. 56:255–259; 1965.
5. Block, R. I.; Ghoneim, M. M.; Hinrichs, J. V.; Kumar, V.; Pathak, D . Effects of a subanaesthetic concentration of nitrous oxide on memory and subjective experience: Influence of assessment procedures and types of stimuli. Hum. Psychopharmacol. 3:257–265; 1988.
6. Block, R. I.; Ghoneim, M. M.; Kuman, V.; Pathak, D. Psychedelic effects of a subanesthetic concentration of nitrous oxide. Anesth. Prog. 37:271–276; 1990.
7. Chapman, W. P.; Arrowood, J. G.; Beecher, H. K . The analgetic effects of low concentrations of nitrous oxide compared in man with morphine sulphate. J. Clin. Invest. 22:871–875; 1943.
8. Cook, T. L.; Smith, M.; Starkweather, J. A.; Winter, P. M.; Eger, E. I. Behavioral effects of trace and subanesthetic halothane and nitrous oxide in man. Anesthesiology 9:419–424; 1978.
9. del Porto, J. A.; Masur, J. The effects of alcohol, THC, and diazepam in two different social settings. A study with human volunteers. Res. Commun. Psychol. Psychiatr. Behav. 9:201–212; 1984.
10. Derogatis, L. R.; Lipman, R. S.; Cozi, L. HSCL-90: An outpatient psychiatric rating scale—Preliminary report. Psychopharmacol. Bull. 9:13–17; 1973.
11. de Wit, H.; Pierri, J.; Johanson, C. E. Reinforcing and subjective effects of diazepam in nondrug-abusing volunteers. Pharmacol. Biochem. Behav. 33:205–213; 1989.
12. de Wit, H.; Pierri, J.; Johanson, C. E. Assessing pentobarbital preference in normal volunteers using a cumulative dosing procedure. Psychopharmacology (Berlin) 99:416–421; 1989.
13. Dohrn, C. S.; Lichtor, J. L.; Coalson, D. W.; Uitvlugt, A.; de Wit, H.; Zacny, J. P. Reinforcing effects of extended inhalation of nitrous oxide in humans. Drug Alcohol Depend. 31:265–280; 1993.
14. Dohrn, C. S.; Lichtor, J. L.; Finn, R. S.; Uitvlugt, A.; Coalson, D. W.; Rupani, G.; de Wit, H.; Zacny, J. P. Subjective and psychomotor effects of nitrous oxide in healthy volunteers. Behav. Pharmacol. 3:19–30; 1991.
15. Garfield, J. M.; Garfield, F. B.; Sampson, J. Effects of nitrous oxide on decision strategy and sustained attention. Psychopharmacologia 42:5–10; 1975.
16. Gillman, M. A. Nitrous oxide abuse in perspective. Clin. Neuropharmacol. 15:297–306; 1992.
17. Greenberg, B. D.; Moore, P. A.; Letz, R.; Baker, E. L. Computerized assessment of human neurotoxicity: Sensitivity to nitrous oxide exposure. Clin. Pharmacol. Ther. 38:656–660; 1985.
18. Grubman, J.; Woods, J. H. Schedule-controlled behavior maintained by nitrous oxide delivery in the rhesus monkey. In: Proceedings of a symposium on drugs as reinforcers: Tokyo, July 25. Excerpta Medica, International Congress Series 620; 1981: 259–274.
19. Henrie, J. R.; Parkhouse, J.; Bickford, R. G. Alteration of human consciousness by nitrous oxide as assessed by electroencephalography and psychological tests. Anesthesiology 22:247–259; 1961.
20. Jastak, J. T.; Paravecchio, R. An analysis of 1,331 sedations using inhalation, intravenous, or other techniques. J. Am. Dental Assoc. 91:1242–1249; 1975.
21. Layzer, R. B. Nitrous oxide abuse. In: Eger, E. I., ed. Nitrous oxide/N_2O. New York: Elsevier Press; 1985:249–257.
22. Lindman, R. Social and solitary drinking: Effects on consumption and mood in male social drinkers. Physiol. Behav. 28:1093–1095; 1982.
23. Mahoney, F. C.; Moore, P. A.; Baker, E. L.; Letz, R. Experimental nitrous oxide exposure as a model system for evaluating neurobehavioral tests. Toxicology 49:449–457; 1988.
24. Martin, W. R.; Sloan, J. W.; Sapira, J. D.; Jasinski, D. R. Physiologic, subjective, and behavioral effects of amphetamine, methamphetamine, ephedrine, phenmetrazine, and methylphenidate in man. Clin. Pharmacol. Ther. 12:245–258; 1971.
25. Nuotto, E. J.; Korttila, K. T. Evaluation of a new computerized

psychomotor test battery: Effects of alcohol. Pharmacol. Toxicol. 68:360–365; 1991.
26. Rosenberg, P. The effect of N_2O—Oxygen inhalation on subjective experiences of healthy young adults. Ann. Chir. Gynaecol. 63:500–504; 1974.
27. Sharp, C. W. It's no laughing matter. Anesth. Analg. 58:73–75; 1979.
28. Steinberg, H. 'Abnormal behaviours' induced by nitrous oxide. Br. J. Psychol. 47:183–184; 1956.
29. Sundin, R. H.; Adriani, J.; Alam, S.; Butler, J.; Hatrel, P.; Hyde, P.; Mangum, F.; Nicoletti, J.; Wallace, C. J. Anxiolytic effects of low dosage nitrous oxide mixtures administered continuously in apprehensive subjects. South. Med. J. 74:1489–1492; 1981.
30. Timsit-Berthier, M.; de Thier, D.; Timsit, M. Electrophysiological and psychological aspects of the derealization state induced by nitrous oxide in nine control subjects. Adv. Biol. Psychiatry 16:90–101; 1987.
31. Wechsler, D. The measurement and appraisal of adult intelligence. Baltimore, MD: Williams and Wilkins; 1958.
32. Wernberg, M.; Neilsen S. F., Hommelgaard, P. A comparison between reaction time measurement and critical flicker fusion frequency under rising nitrous oxide inhalation in healthy subjects. Acta Anaesth. Scand. 24:86–89; 1980.
33. Wood, R. W.; Grubman, J.; Weiss, B. Nitrous oxide self-administration in the squirrel monkey. J. Pharmacol. Exp. Ther. 202:491–499; 1977.