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Effects of Naloxone on the Subjective and Psychomotor Effects of Nitrous Oxide in Humans

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ZACNY, J. P., D. W. COALSON, J. L. LICHTOR, S. YAJNIK AND P. THAPAR. *Effects of naloxone on the subjective and psychomotor effects of nitrous oxide in humans.* PHARMACOL BIOCHEM BEHAV 49(3) 573-578, 1994.– The effects of naloxone on the mood-altering and psychomotor-impairing effects of nitrous oxide were examined in two studies. Each of the double-blind, randomized trials tested effects of three doses of naloxone or saline placebo during inhalation of 30% nitrous oxide in oxygen or 100% oxygen placebo. Experiment 1 tested a range of naloxone doses used clinically to reverse opiate-induced respiratory depression (0, 0.01, 0.1, 1.0 mg/70 kg) and Experiment 2 included a dose approximately 25 times higher than that needed to reverse opiate-induced respiratory depression (0, 1.0, 3.0, 10 mg/70 kg). Nitrous oxide increased subject-rated reports of "feel drug effect," "carefree," "drunk," "sedated," and "high," and decreased psychomotor performance in both experiments. Naloxone had no effects by itself in either experiment, and, for the most part, did not significantly interact with nitrous oxide-induced changes in mood or psychomotor performance. Naloxone, in doses of 10 mg or less, does not appear to affect the subjective and psychomotor effects of nitrous oxide.

Nitrous oxide Naloxone Subjective Psychomotor Human Volunteer Antagonist Opiate Opioid

A NUMBER of studies, both animal and human, have provided evidence that the analgesic effects of nitrous oxide are mediated in part by the endogenous opioid system (EOS). Most of the studies have involved a challenge with an opiate antagonist prior to nitrous oxide inhalation, during which a nociceptive stimulus is being applied. In the majority of these studies, an opiate antagonist challenge reverses, in part, or totally, the analgesia that is produced by nitrous oxide (2,3, 22,28,33,37). An exception to this finding was obtained in a study conducted in humans in which 10 mg of naloxone (IV) did not reduce the analgesic effects of nitrous oxide on dental postoperative pain (23).

Whether other effects of nitrous oxide are mediated by the EOS is not clear. The anesthetic effects of nitrous oxide, for example, are at best only weakly antagonized by naloxone (15,34). The purpose of our study was to assess the degree to which the mood-altering and psychomotor-impairing effects of nitrous oxide are mediated by the EOS, and hence reversed by the opiate antagonist, naloxone. Naloxone is a nonspecific opiate antagonist that has affinity at the mu, kappa, and delta receptors (13,19,27). In our study, naloxone, in the clinically effective range for reversing respiratory depression and in a range roughly 10 times higher, was studied. We tested the higher range because there is evidence that blockade of nitrous oxide effects by an opiate antagonist (2) occurs at much higher doses than that needed to reverse opiate-induced respiratory depression.

METHOD

Subjects

Subjects were recruited from the local university community via newspaper and bulletin board advertisements. Candidates who met screening criteria (i.e., 21-35 years old, within

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25% of ideal body weight, reporting at least one alcoholic beverage consumed per week, and no current medical problems) were scheduled for a screening interview. At the interview, they completed the SCL-90 (8) and a locally developed health questionnaire, and they were interviewed in a semi-structured fashion to determine their psychiatric and medical status. Candidates with any history of significant psychiatric disorders or substance use disorder (1), except for tobacco dependence, were excluded. An anesthesiologist performed a medical history and physical examination. An electrocardiogram was performed to assess cardiac function. The studies were approved by our institutional review board. Informed written consent was obtained from subjects before the first session. In the consent form subjects were told that the drugs they would receive in the experiment may come from one or more of the following classes of drugs in gaseous or intravenous form: sedative, stimulant, general anesthetic (at subanesthetic doses), alcohol, opiate, opiate antagonist, or placebo. Subjects were paid for their participation, upon study completion. During an initial practice session, subjects were exposed to the different tests in the battery to gain familiarity with them.

Experiment 1 utilized nine volunteers [six males, three female; mean age 23.8 ± 3.8 (± SD) years] and Experiment 2 utilized eight volunteers (five males, three females; mean age 28.1 ± 4.5 years). Subjects for Experiment 1 had a history of consuming 3.6 ± 2.1 alcoholic drinks per week and subjects for Experiment 2 had a history of consuming 3.3 ± 2.6 drinks per week.

Experimental Design and Drugs Tested

Two separate studies were conducted in which different naloxone dose ranges were tested in conjunction with nitrous oxide. Each study was performed as a double-blind, randomized trial using a within-subjects 4 × 2 design (four levels of drug antagonist and two levels of drug). Each subject was tested in eight different test sessions, with a minimum of 48 h between each session. In the first study, subjects received 0, 0.01, 0.1, or 1.0 mg/70 kg naloxone, along with nitrous oxide at concentrations of 0% or 30%. In the second study, subjects received 0, 1.0, 3.0, or 10 mg/70 kg naloxone along with 0% or 30% nitrous oxide. Duration of nitrous oxide or oxygen inhalation was 35 min. Subjects received challenge injections of naloxone or placebo 10 min after initiation of nitrous oxide or placebo inhalation.

Session Procedures

Each experimental session was approximately 120 min in duration and took place in the morning. Female subjects had to have a negative urine pregnancy test each week that they participated in the study. On testing days, subjects were not allowed to eat for 6 h or drink for 2 h before the tests. Subjects were instructed to refrain from drinking alcohol for 24 h before sessions. Alcohol abstinence was verified by measuring the blood alcohol level when subjects arrived for the session. Subjects were told not to drive a car, operate heavy machinery, or cook until the day after the study, and were transported home by a university transportation service.

Subjects were seated in a chair during the entire testing period. Nitrous oxide and/or oxygen were delivered via a semiclosed circuit from an anesthetic machine (Narkomed, Draeger, Inc.), and subjects inhaled through a clear anesthesia facial mask. Oil of peppermint was placed in the circuit in an attempt to mask any differential odors between nitrous oxide and oxygen. A catheter was inserted into a forearm vein prior to inhalation and was removed immediately following the end of inhalation. Noninvasive measurements of heart rate, electrocardiogram, peripheral oxygen saturation, and blood pressure were initiated at the beginning of the session. Also, at this time, subjects completed several mood forms and psychomotor tests (see below) while inhaling oxygen through the mask. Subjects were told at this time that the air they were breathing did not contain a drug. Upon completion of baseline testing, subjects began to breathe either nitrous oxide (30%) in oxygen or 100% oxygen. Subjects were told that for the following 35 min they would be inhaling air that may or may not have drug in it. Intravenous injections of naloxone or saline placebo were delivered by the anesthesiologist 10 min after the initiation of nitrous oxide in oxygen or oxygen placebo. Subjects were told that the injection they were receiving may or may not contain a drug. At periodic intervals during and after the inhalation period, mood and psychomotor performance were assessed by a technician who was unaware of the drug and dose being administered. When no test was scheduled, subjects were free to engage in sedentary recreational activities such as reading, listening to the radio or cassette tapes, and watching TV, but studying was not permitted.

Dependent Measures

Subjective and psychomotor effects served as the dependent measures in these studies. Table 1 outlines when the different measures were assessed.

Subjective effects were measured using a visual analog scale (VAS), a subset of questions from the Addiction Research Center Inventory (ARCI), an adjective checklist, and a Drug Effects/Liking Questionnaire. The VAS consisted of 20 100-mm lines, each labelled with the adjectives, "stimulated," "high ('drug' high)," "anxious," "sedated," "dizzy," "tingling," "confused," "drunk," "elated (very happy)," "nauseous," "coasting ('spaced out')," "carefree," "down," "in control of body," "in control of thoughts," "having pleasant thoughts," "having unpleasant thoughts," "having pleasant bodily sensations," "having unpleasant bodily sensations," and "hungry". 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 ARCI is a standardized, true–false questionnaire designed to differentiate among classes of psychoactive drugs (14). Scales are derived from the questions corresponding to different drug effects: particular scales used in this study were the Morphine Benzedrine Group (MBG; measure of euphoria) and the Lysergic Acid Diethylamide (LSD; measure of dysphoric and somatic effects).

The Drug Effects/Liking questionnaire assessed the extent to which subjects currently felt a drug effect, on a scale of 1 to 5 (1 = "I feel no effect from it at all"; 5 = "I feel a very strong effect"), and assessed the extent to which subjects like the drug effect, on a 100-mm line (0 = dislike a lot; 50 = neutral; 100 = like a lot).

In between Experiments 1 and 2 we made the decision to add an adjective checklist to Experiment 2. It consisted of 12 items that the subject rated on a 5-point scale from 0 ("not at all") to 4 ("extremely"). The items in the adjective list are derived from a checklist assessing opiate agonist, agonist–antagonist, and antagonist effects (12,30) and are as follows: "flushing," "skin itchy," "sweating," "upset stomach," "heavy or sluggish feeling," "dry mouth," "headache," "floating," "depressed," "chills," "goose flesh," and "restless."

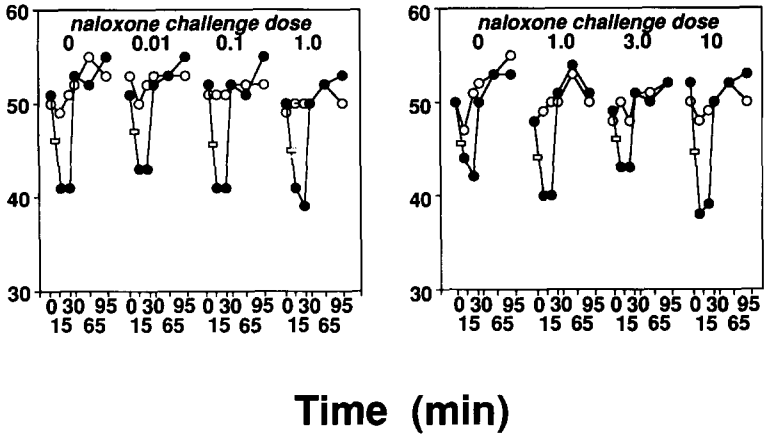

FIG. 1. Effects of nitrous oxide (solid circles) and 100% oxygen (open circles) and naloxone on number of symbols correctly drawn on the Digit Symbol Substitution Test. Each data point represents the mean across nine and eight subjects, respectively, in Experiments 1 and 2. Left frame shows results from Experiment 1 in which naloxone challenge doses of 0.0, 0.01, 0.1, and 1.0 mg/70 kg were given 10 min into the 35-min inhalation period. Right frame shows results from Experiment 2 in which naloxone challenge doses of 0.0, 1.0, 3.0, and 10 mg/70 kg were given 10 min into the 35-min inhalation period. Time point 0 refers to baseline performance when subjects were inhaling 100% oxygen. Next time point is 15 min into the inhalation period, 5 min after naloxone had been injected. Rectangle between time points 0 and 15 denotes when naloxone was given. Remaining time points in which performance was measured were 30 min into the inhalation period, and 5, 30, and 60 min after the inhalation period had ceased.

Psychomotor performance was measured using the Digit Symbol Substitution Test (DSST). In the DSST (36), subjects, for 1 min, replaced a number with a corresponding symbol; the dependent measure was the number of symbols correctly drawn by the subject.

Data Analysis

Repeated-measures analysis of variance (ANOVA) was used for statistical treatment of all data. Factors were antagonist challenge (four levels: three doses of naloxone and saline), drug (two levels: 30% nitrous oxide and 100% oxygen), and time (four–nine levels). F values were considered significant for $p < 0.05$ with adjustments of within-factors degrees of freedom (Huynh-Feldt) to protect against violations of symmetry.

RESULTS

Experiment 1

Subjective effects. Nitrous oxide increased scores on the LSD scale of the ARCI, increased ratings of "feel drug effect," "carefree," "tingling," "elated," "dizzy," "stimulated," and "high," and decreased ratings of "hungry," "in control of body," and "in control of thoughts" (all $p < 0.05$). Ratings that approached significance (i.e., $p < 0.10$) included increases in "drunk," "confused," "coasting," and "sedated." Naloxone had no effects on mood, and there were no significant antagonist challenge × drug interactions.

Psychomotor effects. Nitrous oxide significantly reduced the number of symbols correctly drawn on the DSST ($p < 0.001$). The number of symbols correctly drawn returned to baseline levels within 5 min of recovery from nitrous oxide inhalation. Naloxone had no effects on the DSST, and there was no antagonist challenge × drug interaction (Fig. 1, left frame).

Experiment 2

Subjective effects. Nitrous oxide increased scores on the LSD and MBG scales of the ARCI, increased ratings of "feel drug effect," "carefree," "drunk," "tingling," "confused," "elated," "coasting," "dizzy," "sedated," "stimulated," "nauseous," "anxious," "having pleasant thoughts," "having pleasant bodily sensations," and "high," and decreased ratings of "hungry," "in control of thoughts," and "in control of body" (all $p < 0.05$).

Naloxone had no effects on mood, but there were three antagonist challenge × drug × time interactions. Nitrous oxide decreased hunger ratings ($p < 0.04$) and increased nausea ratings ($p < 0.004$), and a potentiation of these effects was seen only after the 1.0 mg/70 kg naloxone challenge (Fig. 2, right frame). The third significant antagonist challenge × drug × time interaction was strength of drug effect ($p < 0.04$). Naloxone, at the dose of 1.0 mg/70 kg, potentiated the nitrous oxide effect. It is significant to point out that this potentiation of nitrous oxide effects on "hunger," "nausea," and "drug effect" by the 1.0 mg/70 kg naloxone dose was not apparent with the same dose of naloxone in Experiment 1 (compare left to right frames in Fig. 2).

In Experiment 2, significant or near-significant ($p < 0.10$) increases were obtained on the following adjective checklist ratings as a function of nitrous oxide inhalation: "chills" ($p < 0.03$), "floating" ($p < 0.001$), "flushing" ($p < 0.001$), "headache" ($p = 0.08$), "heavy" ($p < 0.03$), and "sweating" ($p = 0.10$). An antagonist challenge × drug × time interaction approached significance on the rating "upset stomach" ($p = 0.10$), and inspection of the data revealed that this rating in-

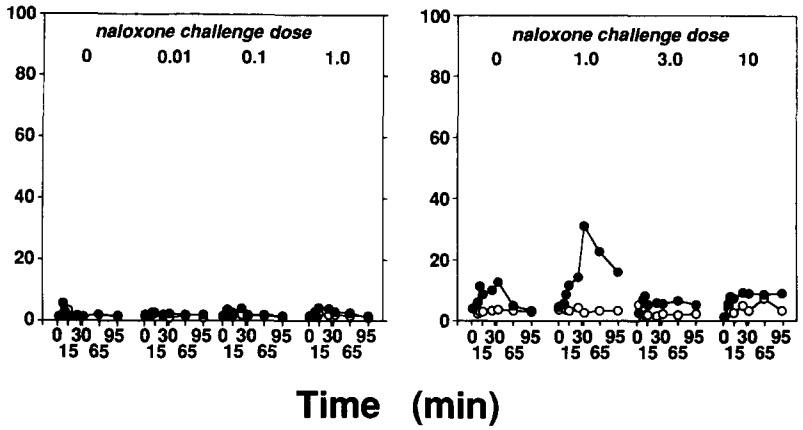

FIG. 2. Effects of nitrous oxide (solid circles) and 100% oxygen (open circles) and naloxone on "nauseous" ratings from the VAS. Each data point represents the mean across nine and eight subjects, respectively, in Experiments 1 and 2. Left frame shows results from Experiment 1 in which naloxone challenge doses of 0.0, 0.01, 0.1, and 1.0 mg/70 kg were given 10 min into the 35-min inhalation period. Right frame shows results from Experiment 2 in which naloxone challenge doses of 0.0, 1.0, 3.0, and 10 mg/70 kg were given 10 min into the 35-min inhalation period. Time point 0 refers to baseline performance when subjects were inhaling 100% oxygen. Next time points are 7 min into the inhalation period (i.e., 3 min prior to injection), and 11 min into the inhalation period (i.e., 1 min after the injection). Remaining time points in which "nauseous" ratings were collected were 15 and 30 min into the inhalation period, and 5, 30, and 60 min after the inhalation period had ceased.

creased after 1.0 mg/70 kg of naloxone was injected when subjects were inhaling nitrous oxide. The increase in this rating persisted during the first 30 min of the 60-min recovery period. An antagonist challenge × drug × time interaction also approached significance on the rating "goose flesh" ($p = 0.08$), but inspection of the data revealed variable effects, that is, increases in this rating after nitrous oxide was inhaled but before 1.0 mg/70 kg naloxone was injected, and increases in this rating both before and after 10 mg/70 kg of naloxone was injected during nitrous oxide inhalation.

Psychomotor effects. As in Experiment 1, nitrous oxide significantly reduced the number of symbols correctly drawn on the DSST ($p < 0.001$). The number of symbols correctly drawn returned to baseline levels within 5 min of recovery from nitrous oxide inhalation. No antagonist challenge × drug interaction was observed (Fig. 1, right frame).

DISCUSSION

We found little evidence that naloxone, at subclinical (Experiment 1), clinical (Experiments 1 and 2), and supraclinical (Experiment 2) doses altered the subjective or psychomotor-impairing effects of nitrous oxide. The antagonist challenge × drug × time effects that were present in Experiment 2 ("nausea," "hunger," and "drug effect") were inconsistent in that we failed to see similar effects in Experiment 1 at the exact same dose of naloxone tested. Further, when being debriefed upon completion of an experiment, subjects could not recall any changes in affect or functioning after any of the naloxone injections.

Our findings, however, do not definitively rule out functional blockade of the opiate receptors as a means of attenuating the subjective or psychomotor consequences of nitrous

TABLE 1

TIME POINTS (MINUTES) WHEN MEASURES WERE COLLECTED.

Measures	0*	7	10†	11	15	30	40	65	95
VAS	X	X		X	X	X	X	X	X
Adj checklist	X	X		X	X	X	X	X	X
ARCI	X				X	X	X	X	X
DSST	X				X	X	X	X	X

*Time point 0 refers to measures collected prior to inhalation period (i.e., baseline).
†Time point 10 refers to when naloxone (or saline) challenge occurred.

oxide. Perhaps even higher doses of naloxone would prove efficacious in affecting the subjective and psychomotor-impairing effects of nitrous oxide. However, as stated earlier, doses up to 25 times the clinical dose needed to reverse respiratory depression (i.e., 10 vs. 0.4 mg) were used. Such a dose (10 mg) has been shown to be effective in reversing nitrous oxide-induced analgesia in humans in a prior study (6). If we had used higher doses of naloxone, these doses may have produced nonspecific effects; that is, naloxone may no longer have behaved as a pure antagonist but as an agonist at an opiate receptor or elsewhere (5,11,21,24,26,38). It is also conceivable that had higher concentrations of nitrous oxide been tested in conjunction with naloxone, interactions would have been obtained. However, the concentration of nitrous oxide that we used was a clinically relevant dose, and higher concentrations than 40% might have oversedated the subject so as to preclude assessment of mood and psychomotor performance.

A somewhat puzzling phenomenon was noted in two of the subjects in Experiment 2 shortly after they were injected with 10 mg of naloxone while inhaling nitrous oxide; the subjects broke into a profuse sweat. We had noticed this also in an earlier pilot study with one of three volunteers. The reason for the sweating and its incidence in only some people is not known. The sweating could have been an effect of naloxone, per se, because other studies have noted this phenomenon, with parenteral supraclinical naloxone doses (7,20). However, in the present study, this phenomenon was never noted in sessions in which naloxone was injected in the presence of oxygen placebo. Sweating is also known to be induced by opiate withdrawal. Could naloxone in the present study be precipitating withdrawal, as manifested by sweating, from an acute administration of a drug with known opiate-like properties, nitrous oxide? Certainly there is evidence in the literature that naloxone can precipitate sweating after an acute administration of morphine in nonopiate-dependent volunteers (4,16,17). However, there is typically a constellation of opiate withdrawal symptoms noted besides sweating, including effects that we could have detected on the adjective checklist and VAS, such as increased restlessness, unpleasant body sensations, anxiety, depression, flushing, chills, goose flesh, and upset stomach (4,16,17). These effects were not noted when 10 mg of naloxone was injected while subjects were inhaling nitrous oxide, suggesting that the sweating was not an EOS-mediated phenomenon. Further, it is not clear why naloxone would precipitate withdrawal symptomatology in the present study without also reversing the effects of nitrous oxide, in the same way that naloxone both reliably reverses opiate effects and induces opiate withdrawal.

One potential criticism of the methodology used in the present study is that subjects were challenged with naloxone during nitrous oxide administration rather than being pretreated with naloxone prior to the administration. There is the notion that the antagonist effects of naloxone are easier to detect when a pretreatment (when the effects of nitrous oxide are not present) rather than a challenge (when the effects of nitrous oxide are present) is used. Certainly, the animal studies that have demonstrated naloxone antagonism of the antinociceptive effects of nitrous oxide involved pretreating with the narcotic antagonist (2,3,22,28,33). However, a naloxone challenge can be a sensitive assay in detecting opioidergic effects of nitrous oxide in humans: in two studies (6,37), naloxone [0.4 mg in (6) and 4 or 8 mg in (37)] injected during nitrous oxide (33%) inhalation antagonized the analgesic effects of the gas in healthy volunteers. Future studies, though, might compare naloxone pretreatment to naloxone challenges to determine if there are any differences in how or whether nitrous oxide effects are altered by these two different administration regimens.

Our negative findings for naloxone in these studies suggest that the subjective and psychomotor effects of nitrous oxide may be mediated via other neurochemical systems. Animal studies have demonstrated involvement of benzodiazepine receptors in mediating some of the behavioral effects of nitrous oxide (31,32). Mice administered nitrous oxide made significantly more entries and spent more time in the open arms of an elevated plus maze than control mice administered room air (indicative of reduced "anxiety"), but this behavior was antagonized by pretreatment with the benzodiazepine antagonist, flumazenil (10). Other neurotransmitters that have been demonstrated as mediating the effects of nitrous oxide include dopamine (9,18), serotonin (29), *N*-methyl-D-aspartic acid (NMDA) (35), and nitric oxide (25). It is conceivable that any one of these systems may play a role in the subjective and psychomotor-impairing effects of nitrous oxide.

In conclusion, at the concentrations of nitrous oxide and naloxone tested, our findings suggest that the mood-altering and psychomotor-impairing effects of nitrous oxide are not mediated via the EOS. Our findings are consistent with those studies that have demonstrated the anesthetic effects of nitrous oxide are altered little, if at all, by opiate blockade (15,34). Our findings are inconsistent with those studies that have indicated the analgesic effects of nitrous oxide may be mediated, at least in part, by the EOS (2,3,22,28,37). Further studies investigating the underlying mechanisms mediating the subjective and psychomotor effects of nitrous oxide are necessary and perhaps should focus on the benzodiazepine, monoamine, and NMDA receptors.

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REFERENCES

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders—revised, third edition. Washington, DC: American Psychiatric Association; 1987.
2. Berkowitz, B.; Ngai, S. H. Nitrous oxide "analgesia": Resemblance to opiate action. Science 194:967–968; 1976.
3. Berkowitz, B. A.; Finck, A. D.; Ngai, S. H. Nitrous oxide analgesia: Reversal by naloxone and development of tolerance. J. Pharmacol. Exp. Ther. 203:539–546; 1977.
4. Bickel, W. K.; Stitzer, M. L.; Liebson, I. A.; Bigelow, G. E. Acute physical dependence in man: Effects of naloxone after brief morphine exposure. J. Pharmacol. Exp. Ther. 244:126–132; 1988.
5. Blumberg, H.; Dayton, H. B. Naloxone and related compounds. In: Kosterlitz, H. W.; Collier, H. O. J.; Villarreal, J. E., eds. Agonist and antagonist actions of narcotic analgesic drugs. Baltimore: University Park Press; 1973.

6. Chapman, C. R.; Benedetti, C. Nitrous oxide effects on cerebral evoked potential to pain: Partial reversal with a narcotic antagonist. Anesthesiology 51:135–138; 1979.
7. Cohen, M. R.; Cohen, R. M.; Pickar, D.; Weingartner, H.; Murphy, D. L.; Bunney, W. E. Behavioural effects after high dose naloxone administration to normal volunteers. Lancet 2:1110; 1981.
8. Derogatis, L. R.; Lipman, R. S.; Cozi, L. HSCL-90: An outpatient psychiatric rating scale—a preliminary report. Psychopharmacol. Bull. 9:13–17; 1973.
9. Dorris, R. L.; Smith, G. Further studies on the mechanism of the behavioral effects of nitrous oxide. FASEB J. 6:A1282; 1992.
10. Emmanouil, D.; Quock, R. M. Possible involvement of benzodiazepine receptors in the anxiolytic effect of nitrous oxide in the elevated plus maze. Third IBRO World Cong. Neurosci. Abstr.; 1991:211.
11. Frank, G. B. Opiate drug receptors on excitable cell membranes. Arch. Int. Pharmacodyn. 217:4–17; 1975.
12. Fraser, H. F.; van Horn, G. D.; Wolbach, A. B.; Isbell, H. Methods for evaluating addiction liablility. (a) "attitude" of opiate addicts toward opiate-like drugs, (b) a short-term "direct" addiction test. J. Pharmacol. Exp. Ther. 133:371–387; 1961.
13. Goldstein, A.; James, I. F. Multiple opioid receptors. Criteria for identification and classification. Trends Pharmacol. Sci. 5:503–505; 1984.
14. Haertzen, C. A. Development of scales based on patterns of drug effects, using the Addiction Research Center Inventory (ARCI). Psychol. Rep. 18:163–194; 1966.
15. Harper, M. H.; Winter, P. M.; Johnson, B. H.; Eger, E. I. Naloxone does not antagonize general anesthesia in the rat. Anesthesiology 49:3–5; 1978.
16. Heishman, S. J.; Stitzer, M. L.; Bigelow, G. E.; Liebson, I. A. Acute opioid physical dependence in postaddict humans: Naloxone dose effects after brief morphine exposure. J. Pharmacol. Exp. Ther. 248:127–134; 1989.
17. Heishman, S. J.; Stitzer, M. L.; Bigelow, G. E.; Liebson, I. A. Acute opioid physical dependence in humans: Effect of varying the morphine-naloxone interval. J. Pharmacol. Exp. Ther. 250: 485–491; 1989.
18. Hynes, M. D.; Berkowitz, B. A. Catecholamine mechanisms in the stimulation of mouse locomotor activity by nitrous oxide and morphine. Eur. J. Pharmacol. 90:109–114; 1983.
19. Iwamoto, E. T.; Martin, W. R. Multiple opioid receptors. Med. Res. Rev. 1:411–440; 1981.
20. Jones, R. T.; Herning, R. Naloxone-induced mood and physiological changes in normal volunteers. In: Usdin, E.; Bunney, W. E., Jr.; Kline, N., eds. Endorphines in mental health research. New York: Oxford University Press; 1979:484–491.
21. Kumor, K. M.; Haertzen, C. A.; Jasinski, D. R.; Johnson, R. E. The psychopharmacologic and prolactin response after large doses of naloxone in man. Pharmacol. Biochem. Behav. 30:967–975; 1988.
22. Lawrence, D.; Livingston, A. Opiate-like analgesic activity in general anaesthetics. Br. J. Pharmacol. 73:435–442; 1981.
23. Levine, J. D.; Gordon, N. C.; Fields, H. L. Naloxone fails to antagonize nitrous oxide analgesia for clinical pain. Pain 13:165–170; 1982.
24. Lynch, W. C.; Libby, L.; Johnson, H. F. Naloxone inhibits intermale aggression in isolated mice. Psychopharmacology (Berlin) 79:370–371; 1983.
25. McDonald, C. E.; Ellenberger, E. A.; Tausman, S. A.; Quock, R. M. Antagonism of nitrous oxide antinociception in mice by inhibitors of nitric oxide synthesis. FASEB J. 7:A488; 1993.
26. McMillan, D. E.; Wolf, P. S.; Carchman, R. A. Antagonism of the behavioral effects of morphine and methadone by narcotic antagonists in the pigeon. J. Pharmacol. Exp. Ther. 175:443–458; 1970
27. Miller, R. J. Multiple opiate receptors for multiple opioid peptides. Med. Biol. 60:1–6; 1982.
28. Moody, E. J.; Mattson, M.; Newman, A. H.; Rice, K. C.; Skolnick, P. Stereospecific reversal of nitrous oxide analgesia by naloxone. Life Sci. 44:703–709; 1989.
29. Mueller, J. L.; Quock, R. M. Contrasting influences of 5-hydroxytryptamine receptors in nitrous oxide antinociception in mice. Pharmacol. Biochem. Behav. 41:429–432; 1992.
30. Preston, K. L.; Bigelow, G. E.; Liebson, I. A. Antagonist effects of nalbuphine in opioid-dependent human volunteers. J. Pharmacol. Exp. Ther. 248:929–937; 1989.
31. Quock, R. M.; Emmanouil, D. E.; Vaughn, L. K.; Pruhs, R. J. Benzodiazepine receptor mediation of behavioral effects of nitrous oxide in mice. Psychopharmacology (Berlin) 107:310–314; 1992.
32. Quock, R. M.; Wetzel, P. J.; Maillefer, R. H.; Hodges, B. L.; Curtis, B. A.; Czech, D. A. Benzodiazepine receptor-mediated behavioral effects of nitrous oxide in the rat social interaction test. Pharmacol. Biochem. Behav. 46:161–165; 1993.
33. Quock, R. M.; Curtis, B. A.; Reynolds, B. J.; Mueller, J. L. Dose-dependent antagonism and potentiation of nitrous oxide antinociception by naloxone in mice. J. Pharmacol. Exp. Ther. 267:117–122; 1993.
34. Smith, R. A.; Wilson, M.; Miller, K. W. Naloxone has no effect on nitrous oxide anesthesia. Anesthesiology 49:6–8; 1978.
35. Vaughn, L. K.; Pruhs, R. J. The NMDA receptor antagonist dizocilpine blocks nitrous oxide withdrawal seizures. FASEB J. 6:A1281; 1992.
36. Wechsler, D. The measurement and appraisal of adult intelligence. Baltimore: Williams and Wilkens; 1989.
37. Yang, J. C.; Clark, W. C.; Ngai, S. H. Antagonism of nitrous oxide analgesia by naloxone in man. Anesthesiology 52:414–417; 1980.
38. Zilm, D. H. Naloxone response in nondependent man: Effect on six physiological variables. Neuropharmacology 19:591–595; 1980.