CLINICAL SCIENCE

Nitrous Oxide Analgesia: A Psychophysical Evaluation Using Verbal Descriptor Scaling

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*The effect of 33% nitrous oxide/67% oxygen was compared with 100% oxygen and air on verbal reports of either sensory intensity or unpleasantness of sensations associated with painful electrical tooth pulp stimulation. Forty-eight subjects used words describing the sensory intensity (*i.e., *weak, mild, strong) or degree of unpleasantness (*i.e., *annoying, unpleasant, distressing) to assess the sensations produced by a broad range of tooth pulp stimuli. Within the experimental session, a given subject assessed the painful sensations under all three treatments delivered through a nasal inhaler in a double-blind manner. The incorporation of within-subject placebo (nasal inhaler + air) and active placebo (nasal inhaler + oxygen) controls allowed for rigorous assessment of the components of nitrous oxide analgesia. The results of this study suggest that 33% nitrous oxide analgesia reduces the intensity but not the unpleasantness of painful tooth pulp sensations. Further, 100% oxygen provides no analgesic effect.*

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Introduction.

Nitrous oxide is a commonly employed pharmacological agent used therapeutically for pain control. Although nitrous oxide is not a potent anesthetic, it has been used effectively alone as an anti-anxiety agent or as a component of anesthetic combinations. Several advantages of nitrous oxide over other analgesic agents, such as morphine, a narcotic analgesic, are: fewer side-effects, no respiratory depression, limited toxicity, and rapid reversal. Chapman *et al.* (1943) reported that the analgesic potency of 20% nitrous oxide was comparable to 15 mg of morphine for the reduction of experimentally-induced radiant heat pain (threshold increases) and ischemic muscle pain (qualitative verbal reports). In a double-blind study comparing 33% nitrous oxide with 100% oxygen (Thompson and Lown, 1976), nitrous oxide has also been shown to reduce the pain associated with myocardial infarction in 75% of patients.

Although previous studies indicate that 20-33% nitrous oxide is a potent analgesic, they did not assess whether it exerts its major effect on the intensity or the aversiveness of pain sensations. Traditional studies that have evaluated the effects of analgesic agents on clinical and experimental pain have treated pain as either a uni-dimensional experience, or have inferred the dimensions of pain sensation and pain reaction from studies of thresholds and tolerance levels for experimental pain. Critics have argued that these methods are inadequate for assessing pain experience (see Gracely, 1979, for review).

Several investigators have employed more rigorous methodologies in an attempt to quantify both the sensory and the reactive components of the human pain experience. One such method is Sensory Decision Theory (SDT). Chapman *et al.* (1973, 1975) have evaluated the effects of 33% nitrous oxide on the perception of experimentally-induced tooth pulp and thermal pain using SDT. They reported that nitrous oxide reduced both the subject's performance in discriminating between stimuli and the likelihood that the subject would consider electrical tooth pulp stimuli painful. Results with noxious thermal stimuli were different, in that 33% nitrous oxide reduced the likelihood that the subject would consider thermal stimuli painful, whereas the subject's performance in discriminating between suprathreshold stimuli was unaltered.

Recent studies by Heft *et al.* (1980b) and Gracely *et al.* (1978b, 1979, 1982) have used verbal descriptor scales to rate both clinical and experimental pain stimuli. Subjects directly judged their pain with quantified words describing both sensory intensity and unpleasantness, as listed in Table 1. Subjects have reliably used these objective descriptors to assess graded experimental painful stimuli in previous studies (Gracely *et al.*, 1978b, 1979, 1982; Heft *et al.*, 1980b; McGrath *et al.*, 1981, 1983; Wolskee and Gracely, 1980). Since judgments are made on the basis of word meanings, this facilitates within-subject and between-subject comparisons of pain perception and drug effects. Further, subjects have readily been able to match the pain intensity or unpleasantness of their clinical pain to an experimentally-induced pain. These procedures produce objective measures of the clinical pain in units of physical stimulus intensity, which provide a check of the reliability of clinical pain reports (Heft *et al.*, 1980b).

We used these methods in the present study to assess the analgesic effect of 33% nitrous oxide on the report of pain associated with electrical tooth pulp stimulation. The intensity and unpleasantness dimensions of pain were quantified by having subjects select words from verbal descriptor scales developed by Gracely *et al.* (1978a). These verbal descriptors had been previously quantified into standard units of relative magnitude by means of a cross-modality matching procedure which controls for response biases inherent in direct scaling (Gracely *et al.*, 1978a; Tursky, 1976).

TABLE 1
PAIN VERBAL DESCRIPTORS

Sensory Intensity		Unpleasantness	
Faint	1.1	Slightly Unpleasant	2.8
Very Weak	2.3	Slightly Annoying	3.5
Weak	2.8	Unpleasant	5.6
Very Mild	3.9	Annoying	5.7
Mild	5.5	Slightly Distressing	6.2
Moderate	12.4	Very Unpleasant	10.7
Barely Strong	12.6	Distressing	11.4
Slightly Intense	21.3	Very Annoying	12.1
Strong	22.9	Slightly Intolerable	13.6
Intense	34.6	Very Distressing	18.3
Very Intense	43.5	Intolerable	32.3
Extremely Intense	59.5	Very Intolerable	44.8

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Materials and methods.

Subjects. – The 48 subjects were healthy, college-educated men and women who were undergoing dental treatment at the National Institute of Dental Research. Subjects signed a statement of informed consent that explained the procedures and stated that they were free to withdraw from the study at any time. After informed consent was obtained, subjects were assigned randomly to the sensory intensity or unpleasantness verbal descriptor groups.

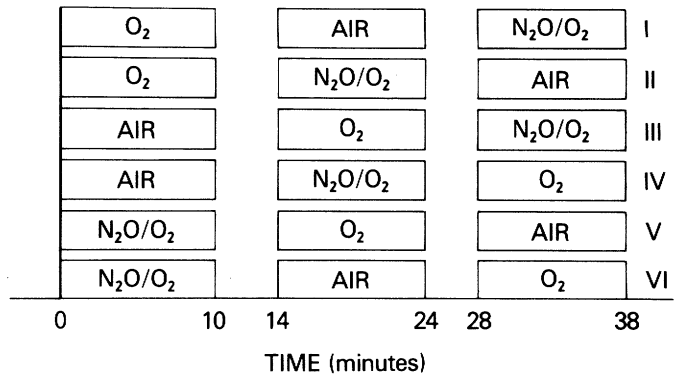
Electrical tooth pulp stimulation. – For convenience and accessibility, caries-free, vital, maxillary anterior teeth were chosen for the experimental electrical tooth pulp stimulation. Cotton rolls kept the selected tooth well-isolated from moisture, and a saliva ejector was placed in the floor of the mouth to prevent shunting of the current through saliva to the gingiva.

The electrical tooth pulp stimuli were one-second trains of monopolar, 1-msec pulses at 100 Hz delivered by a constant current source. The metal electrode was embedded in a polyethylene cylinder modified to adapt easily to the incisal edge of the tooth being stimulated. A silver-plated ear clip served as the indifferent electrode. Toothpaste was applied to couple the electrode to the tooth. Forced air was applied to the tooth through tubing adjacent to the electrode five sec prior to each electrical stimulation, to ensure that the tooth remained dry. Stimulating current was monitored on an oscilloscope, and tooth impedance was determined during each stimulation. Stimulating procedures and parameters were chosen to stimulate only tooth pulp afferents (Fields *et al.*, 1975; Greenwood *et al.*, 1972). The stimulating current of 100 μamp or less is below those values required to stimulate adjacent gingival and periodontal fibers (Greenwood *et al.*, 1972). Although tissue polarization is a known problem with monophasic stimulation, it was not a significant factor with the extremely small currents used. Electrode polarization was not a problem because of the small currents and the coupling of the electrode with paste (Matthews and Searle, 1976).

Treatments. – Subjects received either 33% nitrous oxide (67% oxygen), 100% oxygen, or air through a nasal inhaler. The nasal inhaler remained in place during the experimental session to control for possible placebo effects of the apparatus. The 33% nitrous oxide, 67% oxygen, and 100% oxygen were provided from tanks of compressed oxygen and nitrous oxide. Air was provided by disconnecting the hoses from the apparatus, with the nosepiece remaining in place. Each subject received the three treatment modalities during the 45-minute experimental session, and the orders were counterbalanced over the study population to counteract any order effect (see Table 2). A four-minute time period preceded the beginning of the trial for each treatment modality. In all instances where trial with air was the treatment following nitrous oxide, 100% oxygen was administered for four min before the nosepiece was disconnected, to prevent possible problems of diffusion hypoxia (Fink, 1955).

Procedure. – During a preliminary session, detection threshold, pain threshold, and tolerance level for electrical tooth pulp stimulation were determined for each subject. The thresholds were determined by the Method of Limits (Gescheider, 1976), and the pain tolerance was determined by presenting the subject with an ascending series of stimuli. The maximum stimulus intensity which the subject would accept was considered the tolerance level. Seven stimuli, equal log steps between pain threshold and tolerance, served as the test stimuli.

TABLE 2



The test session occurred prior to a scheduled dental appointment. The 48 subjects were exposed to all three possible treatment modalities during the test session, as summarized in Table 2. During each treatment block, subjects rated their perception of either the pain intensity (n = 24) or unpleasantness (n = 24) of 28 randomly-presented tooth pulp stimuli (four trials of the seven test stimuli) by pointing to words on a random list of descriptors. After each treatment block was completed, the next treatment was administered. Neither the subject nor the observer recording the subject's pain rating was aware of which of the three treatments was being administered at the time.

Individual verbal responses were quantified for each stimulus by substituting a numerical magnitude for each response. These were determined previously by a similar healthy, pain-free, college-educated group of subjects using a cross-modality matching procedure to quantify sensory intensity and unpleasantness words (Gracely *et al.*, 1978a, 1979). The cross-modality matching procedure produced ratio scales of the meanings of the words. Table 1 lists the sensory intensity and unpleasantness descriptors and their relative magnitudes derived previously (Gracely *et al.*, 1979). The unpleasantness words describe aversive perceptions from "slightly unpleasant" until "very intolerable". There are, however, sensations, especially near threshold, which lack an affective or hedonic quality. To allow for such ratings, the additional descriptor "neutral" was inserted. Responses of "neutral" were assigned values of 0.01 to facilitate mathematical treatment of the data. This is the value for "neutral" that was found to maximize the squared Pearson Product Moment correlation coefficient (r^2) relating the current levels and the associated unpleasantness ratings.

Results.

Geometric means of responses were determined for each of the seven test stimuli for each subject during each of the three treatments. The geometric means were then determined for all subjects in the sensory intensity (n = 24) and unpleasantness (n = 24) groups for the three treatment conditions. Figs. 1 and 2 show the group mean log responses plotted as functions of stimulating currents for the two groups with 33% nitrous oxide, 100% oxygen, and air. The squared Pearson Product Moment correlation coefficients, r^2, relating the transformed verbal assessments and the test stimulus intensities, were determined for the group data. This was an index of how reliably the subjects used the verbal descriptors to judge the relative magnitudes of the electrical tooth pulp stimuli. The r^2 values were

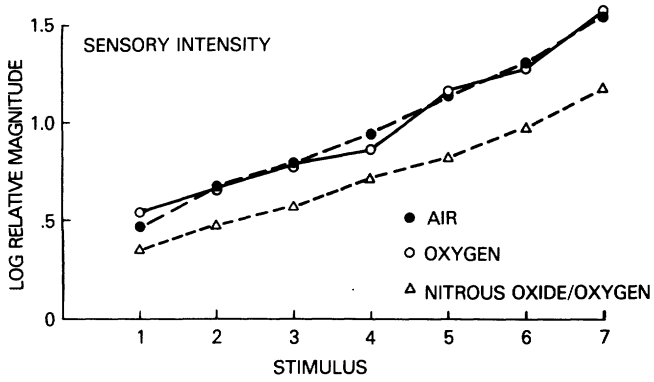


Fig. 1 – Group mean magnitudes of subjects' judgments of the sensory intensity associated with tooth pulp stimulation. Responses are shown for the three treatment conditions: 33% nitrous oxide, 100% oxygen, and air. The ordinate corresponds to the log relative magnitudes of the reported sensory intensity. The abscissa corresponds to the seven log steps of current between pain threshold and tolerance. The geometric mean (n = 24) current intensities for the seven log steps were 9.7 μA, 11.7 μA, 14.1 μA, 16.6 μA, 19.5 μA, 22.4 μA, and 25.7 μA. Each point is the geometric mean of 96 trials.

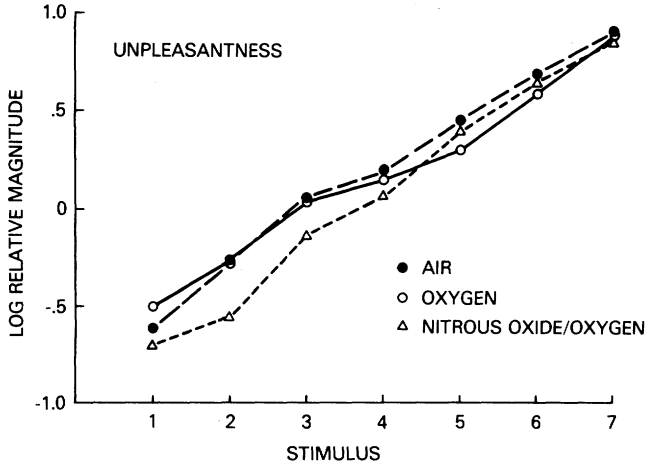


Fig. 2 – Group mean magnitudes of subjects' judgments of the unpleasantness associated with tooth pulp stimulation. Responses are shown for the three treatment conditions: 33% nitrous oxide, 100% oxygen, and air. The ordinate corresponds to the log relative magnitudes of the reported unpleasantness. The abscissa corresponds to the seven log steps of current between pain threshold and tolerance. The geometric mean (n = 24) current intensities for the seven log steps were 11.2 μa, 14.1 μA, 17.2 μA, 20.4 μA, 24.5 μA, 28.8 μA, and 34.4 μA. Each point is the geometric mean of 96 trials.

greater than 0.97 for sensory intensity group data and greater than 0.98 for unpleasantness group data for all treatment conditions. This demonstrates that subjects can reliably judge the experimental stimuli with the pain descriptors, regardless of the experienced treatment regimen.

Effects of the treatments were analyzed by a two-way analysis of variance of the log verbal responses comparing: (1) air *vs.* 100% oxygen for possible analgesic effects of 100% oxygen and (2) 33% nitrous oxide/67% oxygen *vs.* air for drug effects (treatment X subject), for both the dimensions of sensory intensity and unpleasantness. There were no significant effects of 100% oxygen relative to air on the reports of either the pain intensity or unpleasantness associated with electrical tooth pulp stimuli. The group mean log sensory intensity ratings under the 33% nitrous oxide condition shown in Fig. 1 were clearly reduced at all seven stimulus levels [$F(1,288) = 20.36$, $p < 0.01$]. As shown in Fig. 2, there appears to be a reduction in unpleasantness responses with 33% nitrous oxide at the lower stimulus levels; however, this trend was not significant [$F(1,288) = 2.15$, N.S.]. This non-significant reduction in unpleasantness reports seen at the lower stimulus levels results from the inability to measure precisely the unpleasantness of sensations which lack hedonic quality. Since there are more lower intensity sensations judged to lack unpleasantness under the 33% nitrous condition than under the other treatment conditions, the assignment of the 0.01 value to "neutral" judgments tends to exaggerate the reductions in unpleasantness reports seen at the lower stimulus levels under this treatment.

Discussion.

The present study showed that when compared with either air or oxygen, 33% nitrous oxide analgesia reduced the reported sensory intensity associated with electrical tooth pulp stimulation. On the other hand, nitrous oxide failed to reduce the reported unpleasantness of the electrical tooth pulp stimuli in this study. Further, there was no observed analgesic effect of oxygen, a component of balanced nitrous oxide/oxygen analgesia, when compared with air.

The incorporation of within-subject placebo (nosepiece + air) and active placebo (nosepiece + oxygen) controls allowed for rigorous assessment of the analgesic effect of nitrous oxide. No previous studies have utilized a within-subject design to assess separately the effects of nitrous oxide and oxygen in comparison with air. Our findings provide definitive evidence that oxygen had no observable analgesic effect when compared with air, indicating that the effect of 33% nitrous oxide/67% oxygen results from the nitrous oxide alone.

The verbal descriptor scaling procedure provided a direct means of assessing two dimensions of the pain experience: sensory intensity and unpleasantness. The observed reduction in pain intensity independent of effects on the aversiveness of the sensation suggests that nitrous oxide modifies the transmission of neural signals in pain pathways rather than altering transmission in pathways controlling affect and motivation (Melzack and Casey, 1968). Narcotic analgesics have been shown to have a similar effect on the intensity of sensation associated with experimental pain stimuli (Gracely *et al.*, 1979, 1982).

Further features of our experimental design serve to control for response biases. Randomization of the sequencing of stimulus intensities for each trial requires that subjects must attend to the pain intensity or unpleasantness associated with each stimulus presentation. Within-subject cross-over design allows for comparisons of active drug and placebo treatments for each subject. Counter-balancing of the orders of presentation of the three treatments over subjects serves to control for regression tendencies in responding. Finally, the study employs a double-blind design so that neither the subject nor the observer recording the subject's responses knows the identity of the administered drug.

Verbal descriptor scaling procedures provide a method of directly assessing pain in terms of sensory intensity and unpleasantness, because judgments are made on the basis of word meanings. Subjects in previous studies, in which they rated sensations associated with experimental painful stimuli (Gracely *et al.*, 1978b; Heft *et al.*, 1980b; Wolskee

and Gracely, 1980) or clinical pain (Heft *et al.*, 1980a; Wolskee and Gracely, 1980) with the verbal descriptors, reliably assessed their pain experience in terms of these two dimensions. In addition, pain control agents appear to act by reducing pain intensity, unpleasantness, or both. For example, in studies of narcotic analgesia, fentanyl reduced the sensory intensity but not the unpleasantness associated with electrical tooth pulp stimulation in normal subjects (Gracely *et al.*, 1979, 1982). On the other hand, fentanyl reduced both the sensory intensity and unpleasantness of the pain associated with the Myofascial Pain Dysfunction Syndrome (Heft *et al.*, 1980a). This study provides additional evidence that subjects report experimental painful stimuli as a multi-dimensional experience, and that the stimuli can be readily described in terms of pain intensity and unpleasantness.

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REFERENCES

CHAPMAN, C.R.; GEHRIG, J.D.; and WILSON, M.E.: Acupuncture Compared with 33 Per Cent Nitrous Oxide for Dental Analgesia: A Sensory Decision Theory Evaluation, *Anesthesiology* 42:532-537, 1975.

CHAPMAN, C.R.; MURPHY, T.M.; and BUTLER, S.H.: Analgesic Strength of 33 Percent Nitrous Oxide: A Signal Detection Theory Evaluation, *Science* 179:1246-1248, 1973.

CHAPMAN, W.P.; ARROWOOD, J.G.; and BEECHER, H.K.: The Analgetic Effects of Low Concentrations of Nitrous Oxide Compared in Man with Morphine Sulfate, *J Clin Invest* 22:871-875, 1943.

FIELDS, R.W.; TACKE, R.B.; and SAVARA, B.S.: The Origin of Trigeminal Response Components Elicited by Electrical Stimulation of the Tooth Pulp of the Cat, *Arch Oral Biol* 20:437-443, 1975.

FINK, B.R.: Diffusion Anoxia, *Anesthesiology* 16:511-519, 1955.

GESCHEIDER, G.A.: **Psychophysics: Methods and Theory,** Hillsdale, N.J.: Lawrence Erlbaum Associates, 1976, pp. 28-30.

GRACELY, R.H.: Psychophysical Assessment of Human Pain. In: **Advances in Pain Research and Therapy,** Vol. 3, J.J. Bonica, J.C. Liebeskind, and D. Albe-Fessard, Eds., New York: Raven Press, 1979, pp. 805-824.

GRACELY, R.H.; DUBNER, R.; and McGRATH, P.A.: Fentanyl Reduces the Intensity of Painful Tooth Pulp Sensations: Controlling for Detection of Active Drugs, *Anesth Analg* 61: 751-755, 1982.

GRACELY, R.H.; McGRATH, P.; and DUBNER, R.: Ratio Scales of Sensory and Affective Verbal Pain Descriptors, *Pain* 5:5-18, 1978a.

GRACELY, R.H.; McGRATH, P.; and DUBNER, R.: Validity and Sensitivity of Ratio Scales of Sensory and Affective Verbal Pain Descriptors: Manipulation of Affect by Diazepam, *Pain* 5:19-29, 1978b.

GRACELY, R.H.; McGRATH, P.; and DUBNER, R.: Narcotic Analgesia: Fentanyl Reduces the Intensity but Not the Unpleasantness of Painful Tooth Pulp Sensations, *Science* 203: 1261-1263, 1979.

GREENWOOD, F.: HORIUCHI, H.; and MATTHEWS, B.: Electrophysiological Evidence on the Type of Nerve Fibres Excited by Electrical Stimulation of Teeth with a Pulp Tester, *Arch Oral Biol* 17:701-709, 1972.

HEFT, M.W.; GRACELY, R.H.; and DUBNER, R.: Effects of Intravenous Fentanyl on the Assessment of Chronic MPD Pain, *AADR Progr & Abst* 59:No. 1000, 1980.

HEFT, M.W.; GRACELY, R.H.; DUBNER, R.; and McGRATH, P.A.: A Validation Model for Verbal Descriptor Scaling of Human Clinical Pain, *Pain* 9:363-373, 1980b.

MATTHEWS, B. and SEARLE, B.N.: Electrical Stimulation of Teeth, *Pain* 2:245-251, 1976.

McGRATH, P.A.; GRACELY, R.H.; DUBNER, R.; and HEFT, M.W.: Non-pain and Pain Sensations Evoked by Tooth Pulp Stimulation, *Pain* 15:377-388, 1983.

McGRATH, P.A.; SHARAV, Y.; DUBNER, R.; and GRACELY, R.H.: Masseter Inhibitory Periods and Sensations Evoked by Electrical Tooth Pulp Stimulation, *Pain* 10:1-17, 1981.

MELZACK, R. and CASEY, K.L.: Sensory, Motivational and Central Control Determinants of Pain. In: **The Skin Senses,** D.R. Kenshalo, Ed., Springfield, Illinois: C.C. Thomas, 1968, pp. 423-439.

THOMPSON, P.L. and LOWN, B.: Nitrous Oxide as an Analgesic in Acute Myocardial Infarction, *JAMA* 235:924-927, 1976.

TURSKY, B.: The Development of a Pain Perception Profile: A Psychophysical Approach. In: **Pain: New Perspectives in Therapy and Research,** M. Weisenberg and B. Tursky, Eds., New York: Plenum Press, 1976, pp. 171-194.

WOLSKEE, P.J. and GRACELY, R.H.: The Effects of Morphine on Experimental Pain Response in Chronic Pain Patients, *Soc Neurosci Abstr* 6:246, 1980.